MAYO CLINIC

Mayo Clinic Rheumatology Update

April 17-18, 2015

Sawgrass Marriot
Ponte Vedra Beach, Florida

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Disputes

Table of Contents

CME Activity Description

This two-day course provides internists and general practitioners with an up-to-date focus on rheumatologic disorders. This course aims to help participants gain a better understanding of how to recognize and diagnose common rheumatologic disorders, as well as identify which patients can be managed within their own practice and which need referral to a specialist. Residents and fellows will have the opportunity to participate by submitting original studies for poster presentations. This course is seeking to offer optional CME and self-assessment credits available online after the course.

CME Activity Objectives

Upon conclusion of this program, participants should be able to:
• Review basic clinical and therapeutic aspects of rheumatologic conditions
• Improve interpretation skills for common rheumatology laboratory testing
• Identify patients that can be managed in primary care practices and patients that need to be referred to rheumatology
Attendance at this Mayo course does not indicate nor guarantee competence or proficiency in the performance of any procedures which may be discussed or taught in this course.

Intended Audience

This course aims to educate primarily internists and general practitioners, but will be applicable to Rheumatologists, as well as allied health staff working in the afore mentioned areas.

Continuing Education Credit

Mayo Clinic College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Mayo Clinic College of Medicine designates this live activity for a maximum of 13.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACPE
This course is eligible for Accreditation Council for Pharmacy Education (ACPE) credits. The exact number of credits has yet to be determined. Additional CME and self-assessment credits toward Part 2 Maintenance of Certification will be offered.

AAFP
This Live activity, Rheumatology Update 2015, with a beginning date of 04/17/2015, has been reviewed and is acceptable for up to 14.50 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME Record of Attendance

A Record of Attendance is provided to you during on-site registration. The Record of Attendance allows attendees to calculate their own credits of participation in the educational activity.

The total number of credits participants can earn per day is noted on the Record of Attendance. Below each day is a line to record the actual number of credits during which you participated in the educational

activity. It is recommended that you record your actual credits daily as you proceed through the CME activity.

Upon conclusion of the CME activity, please total the number of credits you have recorded on the top half of the form, sign it, and return it with your evaluation to the registration desk.

The bottom half of the form represents your Record of Attendance, which **you must retain** for your records. Please make sure the number of credits claimed in both sections coincide. No other documentation is provided to you after this CME activity. The Record of Attendance has replaced the certificate.

The Record of Attendance can be used for requesting credits in accordance with state licensing boards, specialty societies, or other professional associations.

CME Activity Evaluation

The overall CME activity evaluation will be emailed following the activity to the email address that was provided when you registered. The CME activity evaluation is brief and will only take a few minutes to complete.

Faculty evaluation forms were offered to a sampling of the registrants. Completed faculty evaluation forms should be returned to the registration desk at the conclusion of the CME activity. If you wish to participate in evaluating the faculty, please stop at the registration desk to inquire if extra evaluation forms are available.

Your feedback is very important to us and will be used for planning future programs, as well as identifying faculty strengths and opportunity for growth.

Syllabus and Internet Access

An electronic syllabus will be provided to all attendees. Participants are invited to bring their laptops to the meeting room(s). Due to copyright issues or revisions, some slides may be shown during a presentation, but not provided within the syllabus.

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Electronic Devices

Please turn all electronic devices (cellular telephones, pagers, etc.) to silent mode. As a courtesy to the presenters and other participants, phone calls should be taken outside of the general session.

Faculty

Course Director(s)

Andy Abril, M.D.; Benjamin Wang, M.D.

Guest

Guest Faculty
Gurjit S. Kaeley, M.D.
University of Florida Health
Jacksonville, Florida

Mayo Clinic

Andy Abril, M.D.
Florentina Berianu, M.D.
Ronald R. Butendieck, Jr., M.D.
Kenneth T. Calamia, M.D.
John M. Davis, III, M.D.
W. Leroy Griffing, M.D.
Thomas G. Mason, II, M.D.
Lester E. Mertz, M.D.
Clement J. Michet, M.D.
Kevin G. Moder, M.D.
Thomas D. Rizzo, Jr., M.D.
Jason C. Sluzevich, M.D.
Benjamin Wang, M.D.
Kenneth J. Warrington, M.D.

Faculty, Planning Committee and Provider Disclosure Summary

Mayo Clinic Rheumatology Update
April 17-18, 2015

As a provider accredited by ACCME, Mayo Clinic College of Medicine (Mayo School of CPD) must ensure balance, independence, objectivity and scientific rigor in its educational activities. Course Director(s), Planning Committee Members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of these relevant financial relationships will be published in activity materials so those participants in the activity may formulate their own judgments regarding the presentation.

Listed below are individuals with control of the content of this program who have disclosed…

Relevant financial relationship(s) with industry:

Name	Nature of Relationship	Company
John M. Davis, III, M.D.	Grant/ Research	Roche, Genentech, Pfizer
Leroy Griffing, M.D.	Grant/ Research	Bayer HealthCare

No relevant financial relationship(s) with industry:

Name	
Florentina Berianu, M.D.	Clement J. Michet, M.D.
Ronald Butendieck, M.D.	Kevin G. Moder, M.D.
Kenneth T, Calamia, M.D.	Thomas D. Rizzo, Jr., M.D.
Gurjit S. Kealey, M.D.	Jason Sluzevich, M.D.
Thomas G. Mason, M.D.	Benjamin Wang, M.D.
Lester Mertz, M.D.	Kenneth J. Warrington, M.D.

References to off-label and/or investigational usage(s) of pharmaceuticals or instruments in their presentation:

Name	Manufacturer/Provider	Product/Device
Kenneth T. Calamia, M.D.	Anti TNF agents	Multiple

Rheumatology Update

Marriott Sawgrass, Ponte Vedra Beach, Florida

April 17-18, 2015

Friday, April 17, 2015	
7:15 a.m.	Continental Breakfast and Registration
7:45	Introductions/Pre-Test
8:00	Approach to the Patient with MSK Symptoms Kevin G. Moder, M.D.
8:30	Fibromyalgia Benjamin Wang, M.D.
9:00	Rheumatoid Arthritis-Preventive Care for RA Patients John M. Davis, III, M.D.
9:30	Questions and Answers
9:45	Break
10:00	Crystaline Arthropathies Benjamin Wang, M.D.
10:30	Gout Management W. Leroy Griffing, M.D.
11:00	Back Pain Thomas D. Rizzo, Jr., M.D.
11:30	Questions and Answers
11:45	Lunch
12:45 p.m.	Rheumatoid Arthritis-Update on Treatment John M. Davis, III, M.D.
1:15	Autoantibodies in Rheumatology Kevin G. Moder, M.D.
1:45	Scleroderma W. Leroy Griffing, M.D.
2:15	Questions and Answers
2:30	Break
2:45	Systemic Lupus Gen. Concepts Ronald R. Butendieck, Jr., M.D. ACPE UAN: 0853-0000-15-048-L01-P Contact hours: 0.5
3:15	Polymyalgia Rheumatica Florentina Berianu, M.D.
3:45	Sjögren's Syndrome Ronald R. Butendieck, Jr., M.D. ACPE UAN: 0853-0000-15-049-L01-P Contact hours: 0.5
4:15	Questions and Answers
4:30	Adjourn
4:30 – 6:00 p.m.	Poster Presentation

Program schedule is subject to change without notice.

Rheumatology Update

Marriott Sawgrass, Ponte Vedra Beach, Florida

April 17-18, 2015

Saturday, April 18, 2015

7:30 a.m.	Continental Breakfast
7:45	Announcements
8:00	Vasculitis Overview Andy Abril, M.D. ACPE UAN: 0853-0000-15-047-L01-P Contact hours: 0.5
8:30	Primary Raynaud's Phenomenon Thomas G. Mason, II, M.D.
9:00	Inflammatory Myopathies Lester E. Mertz, M.D.
9:30	Questions and Answers
9:45	Break
10:00	Update on GCA Andy Abril, M.D.
10:30	Juvenile Inflammatory Arthritis Thomas G. Mason, II, M.D.
11:00	Cutaneous Manifestations of Rheumatologic Disorders Jason C. Sluzevich, M.D.
11:30	Questions and Answers
11:45	Lunch
12:45 p.m.	Psoriatic Arthritis Gurjit S. Kaeley, M.D.
1:15	Spondyloarthropathies Clement J. Michet, M.D.
1:45	Hip Pain Thomas D. Rizzo, Jr., M.D.
2:15	Questions and Answers
2:30	Break
2:45	Musculoskeletal Ultrasound in Rheumatology Gurjit S. Kaeley, M.D.
3:15	Behcet's Disease Kenneth T. Calamia, M.D.
3:45	Auto Inflammatory Syndromes Lester E. Mertz, M.D.
4:15	Questions and Answers
4:30	Post-Test
4:45 p.m.	Closing Remarks/Adjourn

Program schedule is subject to change without notice.

Commercial Support

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This activity is supported in part by educational grants from the following companies in accordance with ACCME Standards:
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April, 17-18, 2015

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Vasculitis Overview

Mayo Clinic Rheumatology Update

April 2015

Kenneth J. Warrington MD

Associate Professor of Medicine

Division of
RHEUMATOLOGY

DISCLOSURE

Relevant Financial Relationship(s)

None

Off Label Usage

Limited FDA-approved therapy

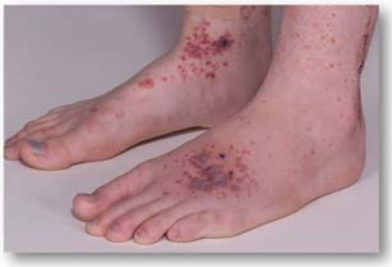
Return to Program Schedule

Objectives

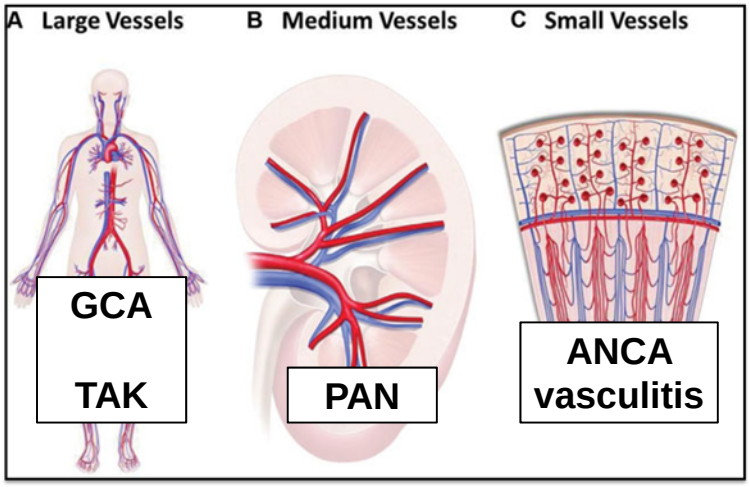
- Describe vasculitis nomenclature and classification
- Discuss clinical features and cases pertaining to large, medium and small vessel vasculitis
- Explain treatment options

Vasculitis

- Group of diseases
  - Vascular inflammation
- Clinical features
  - Highly variable
- Multisystem disease
- Rapidly progressive organ dysfunction

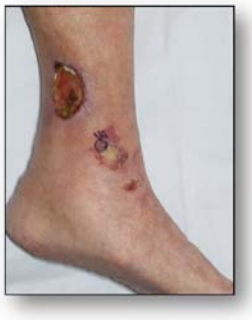


2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides



Arthritis & Rheumatism Vol. 65, No. 1, January 2013, pp 1–11

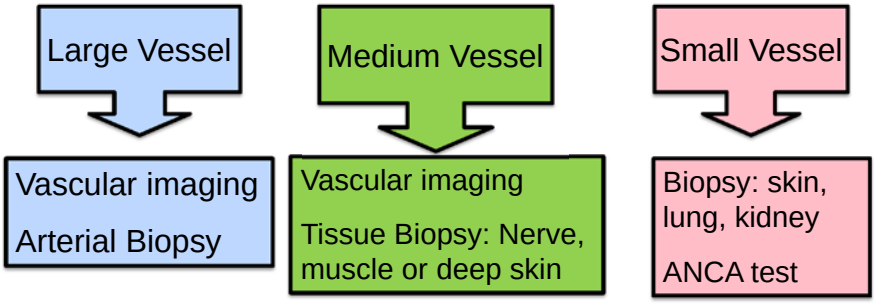
- Variable Vessel Vasculitis
  - Behçet's disease
- Single Organ Vasculitis
  - e.g. CNS vasculitis
- Vasculitis with Rheumatic Disease
  - e.g. RA, SLE
- Vasculitis associated with probable etiology
  - Hepatitis (B, C)
  - Drug-induced (Antibiotics, others)
  - Malignancy - heme



Arthritis & Rheumatism Vol. 65, No. 1, January 2013, pp 1–11

High Clinical Suspicion

Systemic Inflammatory Process



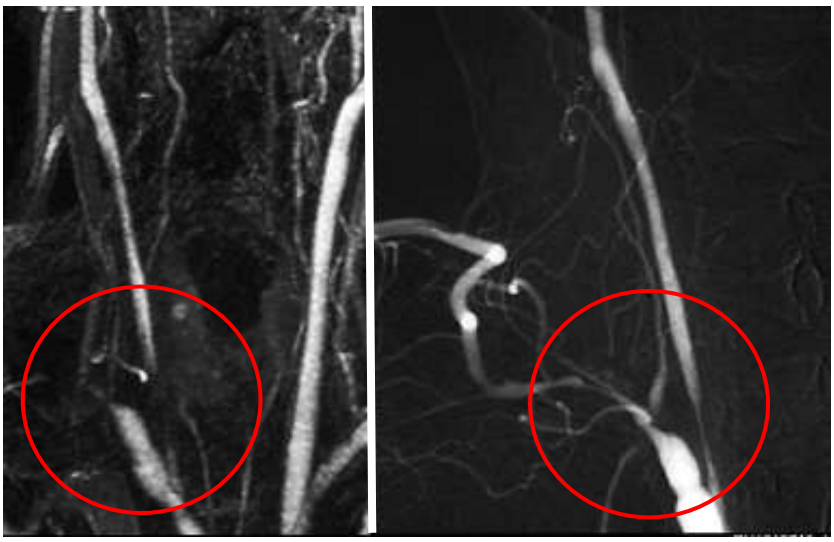
ANCA: Antineutrophil Cytoplasmic Antibodies

Case

- 29 year-old F; difficult to control HTN
- 6 months of malaise, myalgias and fatigue
- R upper extremity claudication
- Exam: BP 80/- mmHg R arm; 156/80 mmHg L arm
  - R radial pulse absent
  - R carotid and R subclavian bruit; abdominal bruit
- Lab: Hb 10.5 g/dl, ESR 22 mm/hr; CRP 12 mg/L.
  - Autoimmune serologies all negative

MRA

Angiogram



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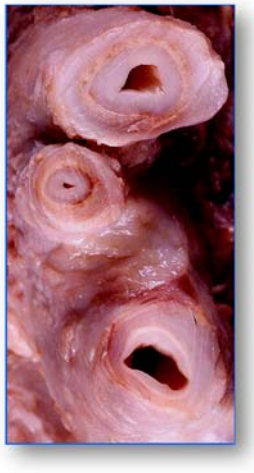
Takayasu Arteritis

- Women (80-90% of cases)
  - Young (< 40 yrs)
- Very rare: 1-2/million/yr
- No specific lab test
  - ESR, CRP *may be normal*
- Age at diagnosis: 31 years
- Delay in diagnosis: ~18 months
  - Imaging: MRA, CTA, PET



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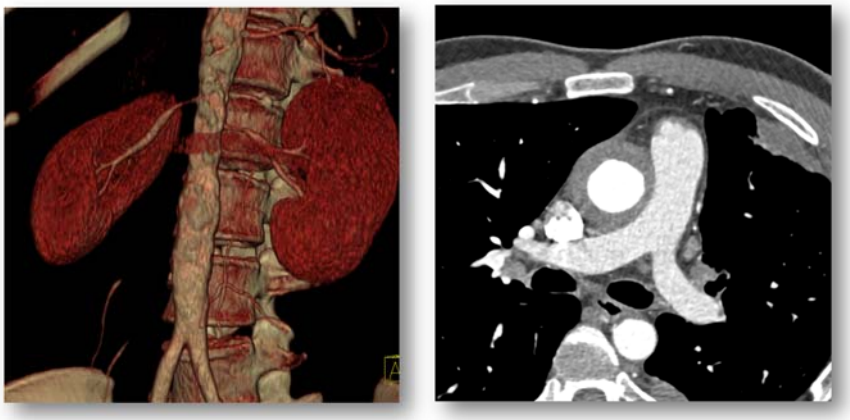
Takayasu Arteritis



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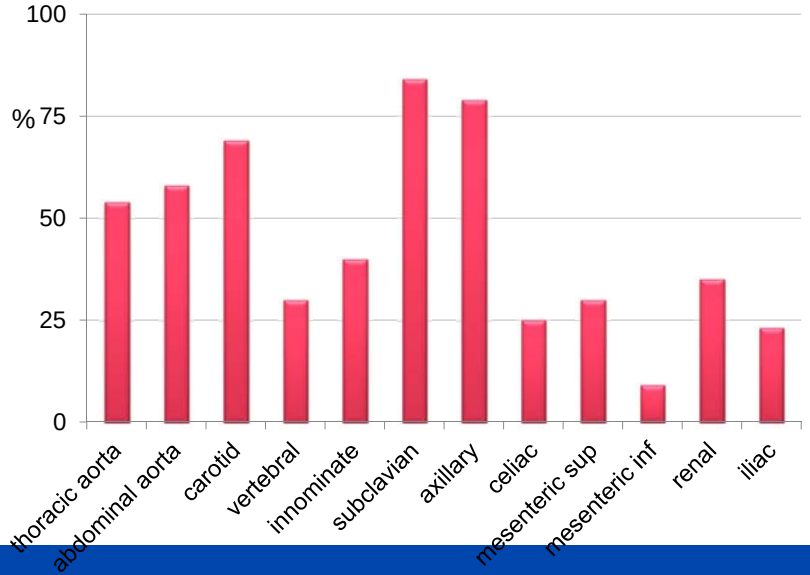
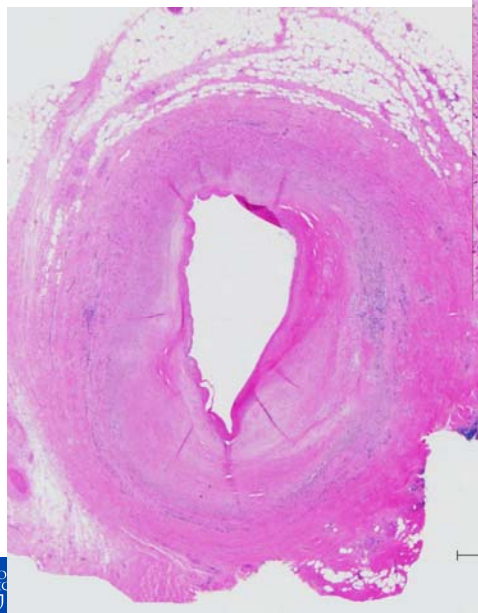
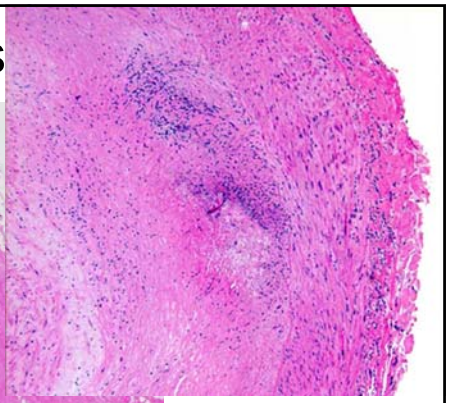
Imaging - Distribution of arterial involvement

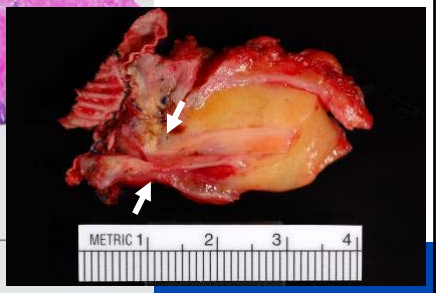


Mayo Clin Proc. 2013;88(8):822-830

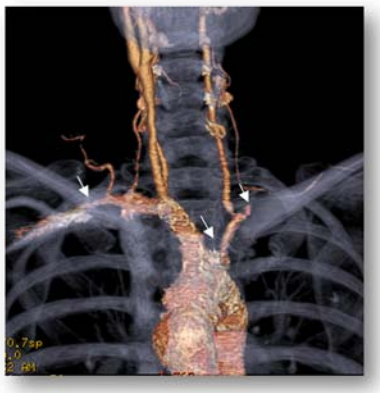
Coronary Vasculitis







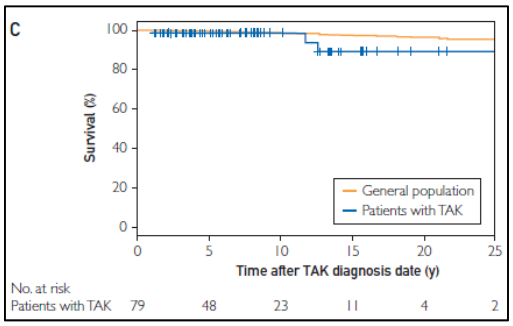
Takayasu Arteritis



- Assessment of disease activity
  - Challenging
  - Serial imaging essential
- Treatment
  - Steroids
  - Immunosuppressives: MTX, AZA, MMF
  - Refractory cases: TNF inhibitors
  - Vascular intervention

Takayasu Arteritis - Survival

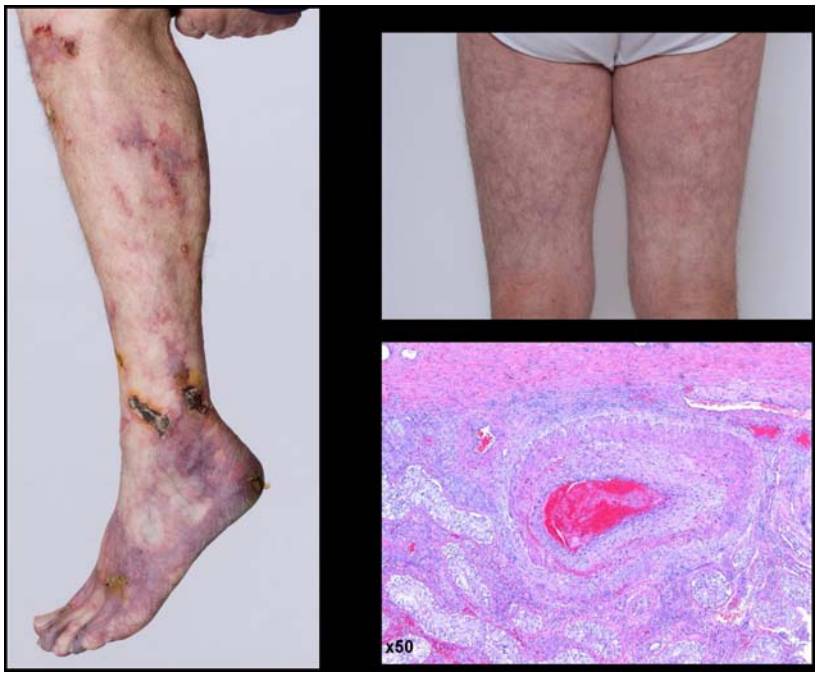
- 10 years – 97%
- 15 years – 86%
- Median age at death
  - 45.5 years
- SMR 3.0 (1-8.9)



Schmidt J et al. Mayo Clin Proc. 2013;88(8):822-830

Case

- 36 year-old male hx of iv drug use
- Constitutional symptoms
- Post-prandial abdominal pain; testicular pain & necrotic leg ulcers
- BP is 200/110 mmHg.
- ESR is 112 mm/hr
- Creat is 2.3 mg/dL. Urine: protein, no blood
- HBsAg is positive and viremia present

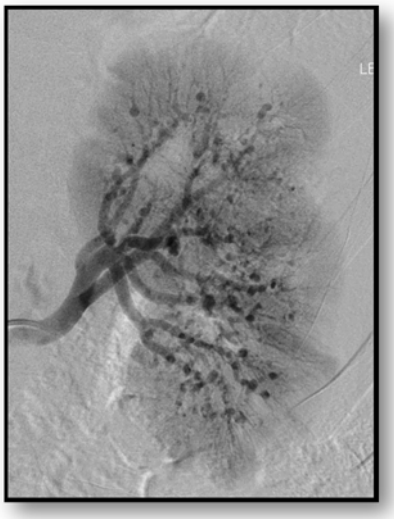


Polyarteritis Nodosa

- Vasculitis of medium-sized arteries
  - Rare: 5-10 / million / yr
  - Incidence declining
- More common in men
  - mainly age 40 to 60 years
- Associated conditions
  - Hepatitis B infection (third); HIV
  - Hematologic: Hairy cell leukemia
  - Medications: Minocycline

Watts RA, et al. Ann Rheum Dis 2001;60(12):1156-7.
Guillevin L, et al. Medicine (Baltimore) 2005;84(5):313-22.

PAN Diagnosis: Biopsy or Angiography



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Classification Criteria (3/10)

1. HTN – new onset
2. Renal insufficiency
3. Mononeuritis multiplex/ polyneuropathy
4. Hepatitis B
5. Aneurysms or occlusions on angiogram
6. Biopsy – Vasculitis
7. Weight loss >4kg
8. Livedo reticularis
9. Testicular pain
10. Muscle weakness/myalgia

No Lung Involvement
No active urine sediment
No ANCA

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Lightfoot RW et al. Arthritis Rheum. 1990 Aug;33(8):1088-93

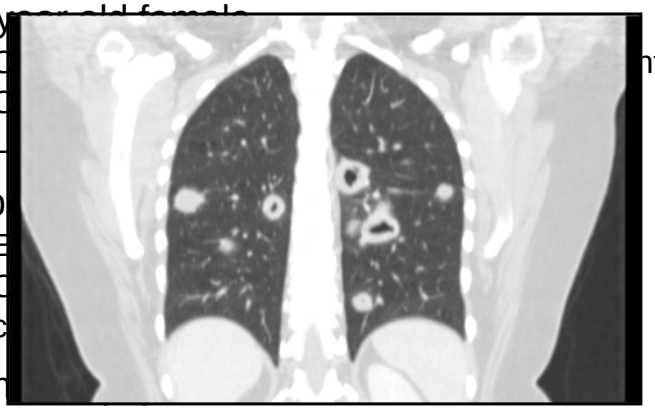
Polyarteritis Nodosa
Treatment

- Corticosteroids
  - Prednisone 1 mg/kg per day for 4 weeks with taper over 9 to 12 months
- Cyclophosphamide
  - Poor prognostic features: renal insufficiency, GI, cardiac or neuro involvement
- Hep-B associated PAN
  - Limit immunosuppression
  - Early use of anti-viral Rx

Guillevin L, et al. Arthritis Rheum 2003;49(1):93-100.

Case

- 25 y
  - C
  - C
  - L
- Lab
  - E
  - C
  - c
- Ren
  - Necrotizing glomerulonephritis, no immune-complexes



ANCA-associated Vasculitis

Granulomatosis with Polyangiitis

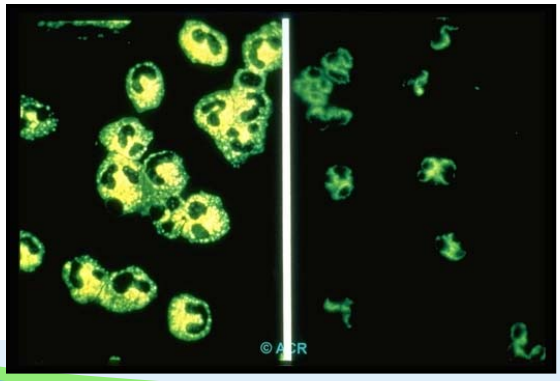
C-ANCA

Proteinase-3 (PR-3)

Microscopic Polyangiitis

P-ANCA

Myeloperoxidase (MPO)



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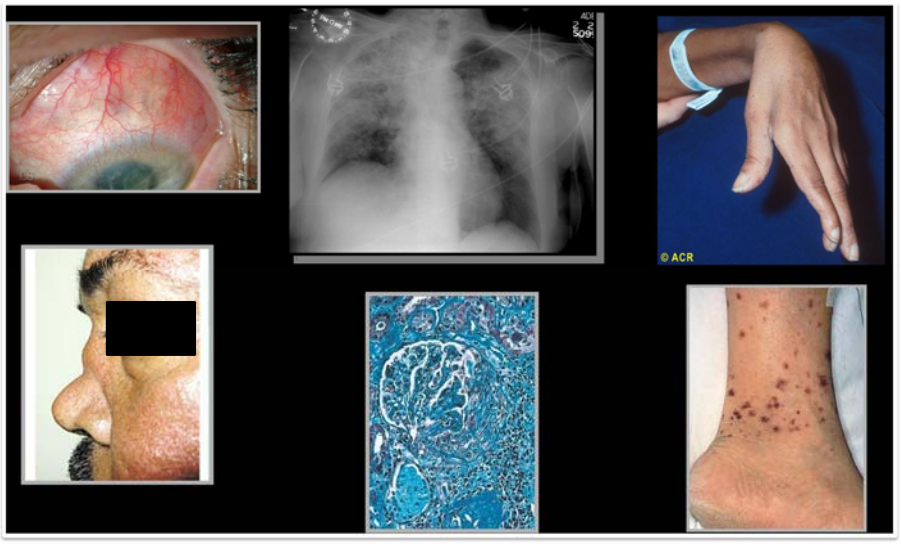
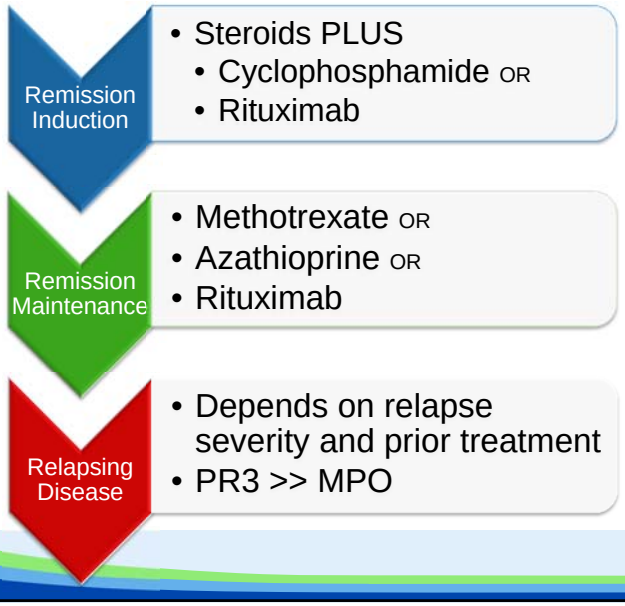
ANCA-associated Vasculitis



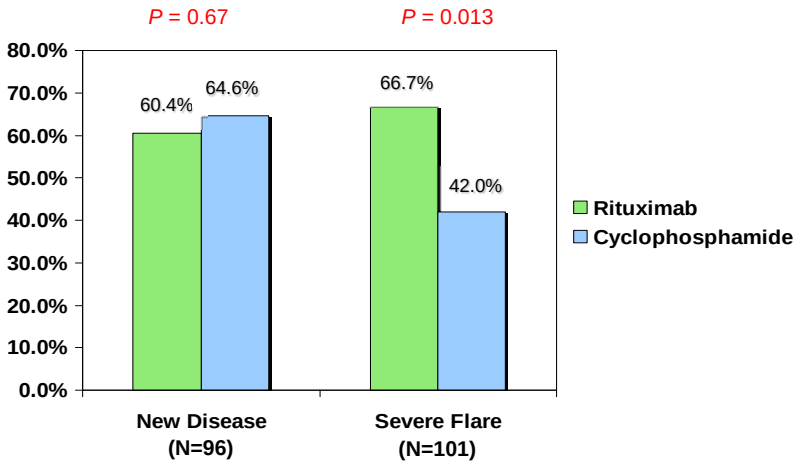
Treatment - principles

- Early intervention essential
- Tailored to the type and severity of vasculitis
  - Co-morbidities
- Remission achievable in almost all patients
  - Relapses common
- Close monitoring
  - Damage
  - Treatment toxicity

Treatment of ANCA Vasculitis



Treatment Response by Disease Status at Baseline – data from the RAVE trial

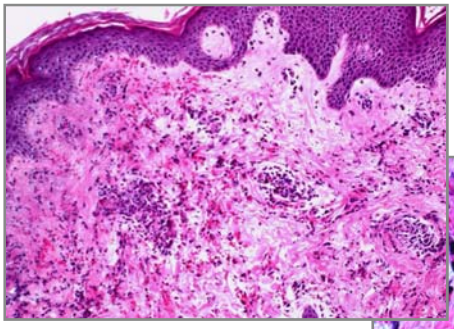


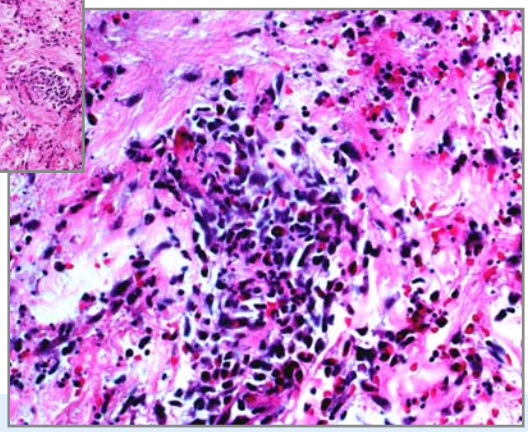
Stone JH et al. N Engl J Med 2010;363:221-232

Case 6

- 47 year old M; history of asthma, nasal polyposis and recurrent sinusitis
- 8 weeks of cough & dyspnea
- Weight loss, low grade fevers
- Recent onset purpuric rash and bilateral foot drop
- ESR 72 mm/1hr; Creat 1.0 mg/dL
- Eosinophils – 40% of WBC
- P-ANCA and MPO positive

Skin biopsy





Vascular necrosis with nuclear dust and perivascular lymphocytes and eosinophils. Many PMN's are fragmented.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

ACR Classification Criteria

1. Asthma
2. Eosinophilia >10% WBC
3. Mononeuropathy or Polyneuropathy
4. Transitory Pulmonary Infiltrates
5. Paranasal sinus abnormality
6. Biopsy with extravascular eosinophils

*4/6 Criteria (sensitivity of 85% and specificity of 99.7%)

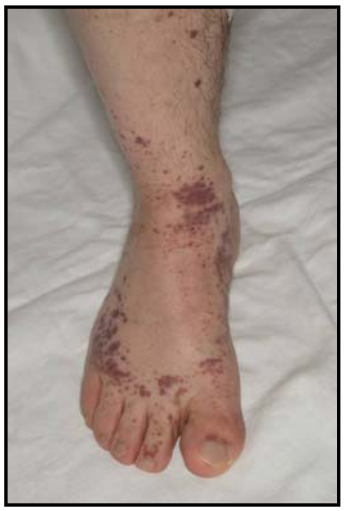
Masi AT et al Arthritis Rheum. 1990 Aug;33(8):1094-100

ANCA-associated Vasculitis

	GPA	MPA	EGPA
Small-Vessel Vasculitis	+	+	+
ANCA	C-ANCA (PR-3)	P-ANCA (MPO)	P-ANCA (MPO)
Necrotizing granulomas	+	-	-
Asthma & Eosinophilia	-	-	+

Cryoglobulinemic Vasculitis

- Small-vessel vasculitis
  1. Cutaneous vasculitis
  2. Glomerulonephritis
  3. Neuropathy
- Labs
  - Positive RF,
  - Cryoglobulins (II)
  - Low complement
  - Hepatitis C

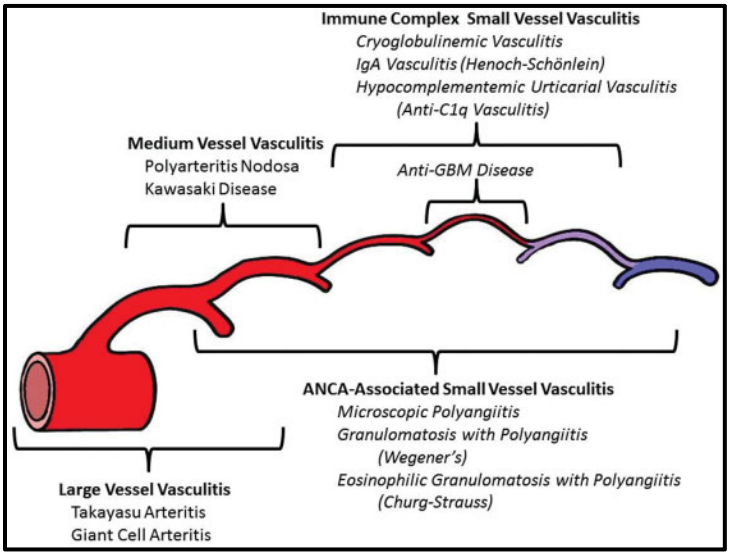


TAKE HOME MESSAGES
Vasculitis

1. Progressive multi-organ disease
   - Unexplained systemic inflammation
2. Multi-specialty evaluation
   - Exclude mimics
3. Prompt diagnosis essential
   - Corticosteroids initial therapy
4. Chronic illness
   - Treatment-related morbidity

MAYO CLINIC

Summary



MAYO CLINIC

Arthritis & Rheumatism Vol. 65, No. 1, January 2013, pp 1–11

Resources

www.vasculitisfoundation.org

http://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Vasculitis/

http://my.clevelandclinic.org/disorders/vasculitis/hic_vasculitis.aspx

http://rarediseasesnetwork.epi.usf.edu/vcrc/

www.clinicaltrials.gov

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Assessment Question #1

- True or False
  - Lupus vasculitis is considered to be a secondary form of vasculitis related to a rheumatic disease.

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Assessment Question #2

- True of False
  - Relapses of ANCA vasculitis are common

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Assessment Question #3

- Which of the following medications is appropriate for refractory Takayasu arteritis?
  - A. Steroids
  - B. Azathioprine
  - C. TNF inhibitors
  - D. Methotrexate

MAYO CLINIC

Return to Program Schedule

Primary Raynaud's Phenomenon

T. G. Mason, MD
Associate Professor of Medicine and Pediatrics, Mayo Clinic College of Medicine

Disclosures

- Financial
  - none
- Other
  - Member, test-writing committee for rheumatology, American Board of Internal Medicine (ABIM)

Return to Program Schedule

Disclosure of ABIM Service: Thomas Mason, MD

- I am a current member of the Rheumatology Board Exam Committee.
- To protect the integrity of certification, ABIM enforces strict confidentiality and ownership of exam content.
- As a current member of the Rheumatology Board Exam Committee, I agree to keep exam information confidential.
- As is true for any ABIM candidate who has taken an exam for certification, I have signed the Pledge of Honesty in which I have agreed to keep ABIM exam content confidential.

No exam questions will be disclosed in my presentation.

MAYO CLINIC

Goals

- Recognize the clinical features of primary Raynaud's phenomenon (RP)
- Understand the relationship of RP to rheumatic diseases
- Develop an approach to patients with RP
- Recall initial management strategies for RP

MAYO CLINIC

Historical background

- Maurice Raynaud in 1862 labelled as "local asphyxia of the extremities"
- Result of "increased irritability of the central parts of the cord presiding over the vascular innervation"

Raynaud, M. New researches on the nature and treatment of local asphyxia of the extremities 1874. Translated by Barlow London: New Sydenham Society,1888

Historical background

- Reflex vasodilation produced by warming the body could be overcome by putting the hands in cold water, resulting in vasospasm
- Conversely, that vasospasm could not be produced by body cooling if the hands were kept warm
- Sir Thomas Lewis concluded that Raynaud phenomenon (RP) was due to a "local fault" rather than a defect in the central nervous system

Lewis, T. Heart. 1929;14:7

Which of the following are associated with primary Raynaud's phenomenon?

- Age of onset of 40-50 years
- Men affected as often as women
- Normal peripheral pulses
- Antinuclear antibodies in a nucleolar pattern
- Gastro-esophageal reflux (GERD)

MAYO CLINIC

Which of the following are associated with primary Raynaud's phenomenon?

- Age of onset of 40-50 years
- Men affected as often as women
- **Normal peripheral pulses**
- Antinuclear antibodies in a nucleolar pattern
- Gastro-esophageal reflux (GERD)

MAYO CLINIC

Raynaud's physiology

- Poiseuille's law
- Flow is proportional to radius to the 4th power
- Small changes in radius have huge impact on blood flow

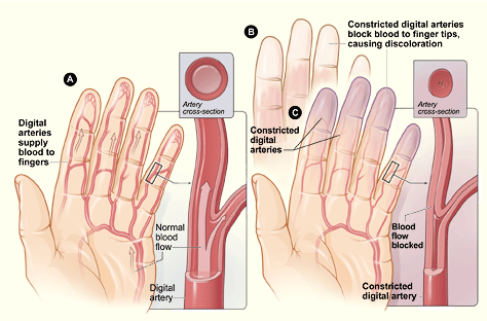

Image from Encyclopedia of Science

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Raynaud's color changes

- Initially, pallor, from increased vasoconstriction
- Eventually, cyanosis from relative ischemia
- Frequently, hyperemia with re-warming (e.g. "over dilation")

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Screening questions: Raynaud's

- *Are your fingers unusually sensitive to cold?*
- *Do your fingers change color when they are exposed to cold temperatures?*
- *Do your fingers turn white, blue, or both*?
  - Dx is made if 3/3 are +

Wigley FM. NEJM. 2002;347(13):1001.

Screening questions: Raynaud's

- Occupational issues: (repetitive trauma, etc.)
- Neuropathies
- Medications
  - Nicotine
  - Stimulants
  - Ergotamine derivatives

Which of the following is the primary mechanism for primary RP?

- Fixed, obstructive arterial lesions
- Thrombotic/embolic vasculopathy
- Small vessel vasculitis
- Overactive vasoconstriction
- Fibrosis of vascular endothelium

MAYO CLINIC

Which of the following is the primary mechanism for primary RP?

- Fixed, obstructive arterial lesions
- Thrombotic/embolic vasculopathy
- Small vessel vasculitis
- **Overactive vasoconstriction**
- Fibrosis of vascular endothelium

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RP mechanisms

- RP is an exaggerated vascular response to cold or stress
- Abnormal vasoconstriction of digital arteries and cutaneous arterioles
- In primary RP, evidence suggests the defect is an increase in alpha-2 adrenergic responses in the digital and cutaneous vessels.

Flavahan NA, et al. J Pharmacol Exp Ther. 1987;241(2):361

Other variables impacting RP

- Sensory (over) reactivity
  - Alpha-2 receptor mediated, esp. primary RP
- Vessel (over) reactivity
  - Endothelial cells
  - Circulating factors
- Vessel structure
  - Fibrosis (scleroderma, etc.)

RP: primary vs. secondary

Primary

- No associated illness
- Onset in adolescence, early adulthood
- Mostly female
- Symmetric attacks

Secondary

- Associated condition/CTD (scleroderma, etc)
- Onset associated with CTD (+/- 2-3 yrs.)
- Male and female
- Attacks can be asymmetric/digital

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Rheumatologic conditions with RP

Rheumatic condition (CTD)	Clinical features
Systemic lupus erythematosus (SLE)	Photosensitivity, mucositis, serositis, arthritis, renal, CNS, hematologic, autoantibodies
Inflammatory muscle disease (IIM)	Proximal muscle weakness, skin findings, lab and bx evidence of myopathy
Scleroderma*	Skin changes, GERD/dysphagia, ILD, pulmonary HTN, calcinosis

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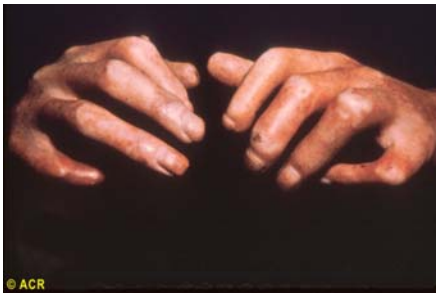
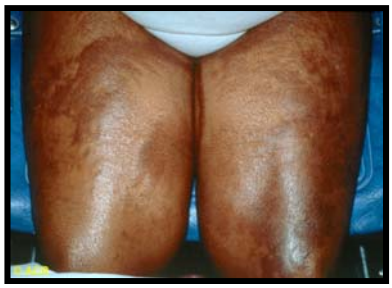
Scleroderma

- Tight skin
- 90% or more have RP
- A common cause of secondary RP
- RP may precede dx of scleroderma by years

Scleroderma





Scleroderma means “tight skin”. The skin tightness can be peripheral, and seen in the image of the hands/fingers, or more central, as shown by the “shininess” of the skin of the thigh area.

Rheumatologic conditions with RP: scleroderma

Diffuse: (PSS)

- RP
- Wide spread skin fibrosis
- Some esophageal disease
- Interstitial lung ds (ILD)
- Anti-Scl-70 Ab

Localized: CREST

- Cutaneous calcinosis
- RP
- Esophageal fibrosis
- Sclerodactyly
- Telangiectasia
- Centromere Ab
- Pulmonary HTN

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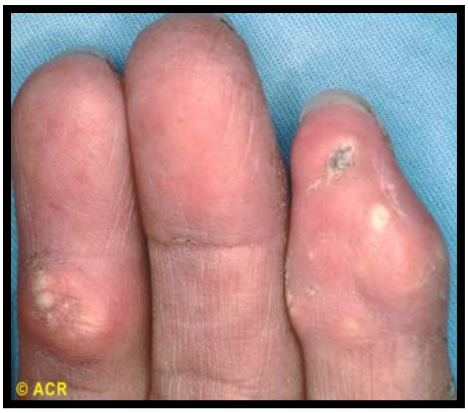
Clinical features of scleroderma



Cutaneous calcinosis

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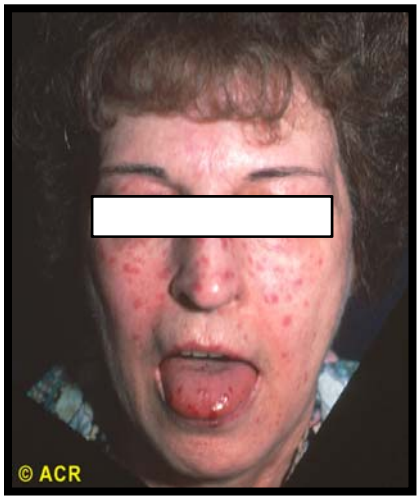
Clinical features of scleroderma



Telangiectasias

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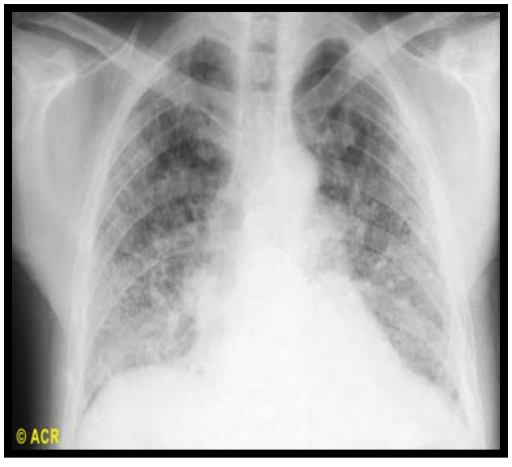
Clinical features of scleroderma



CXR showing pulmonary fibrosis from PSS

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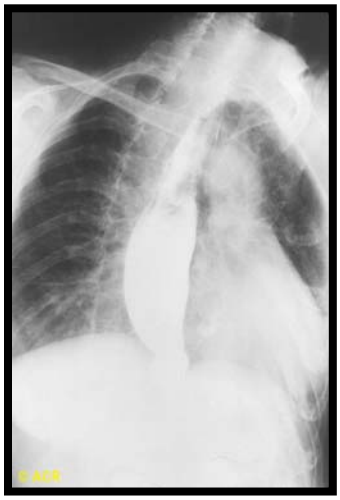
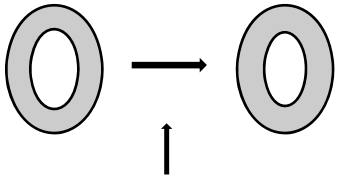
Clinical features of scleroderma



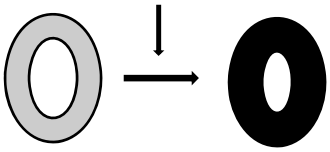
Esophagram showing
decreased peristalsis
in distal 2/3 of esophagus

Physiology of Primary RP



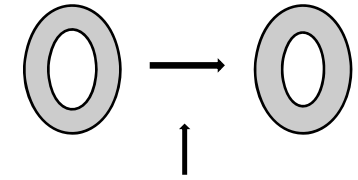
Normal vasoconstriction

Cold exposure, psychologic stress, etc.



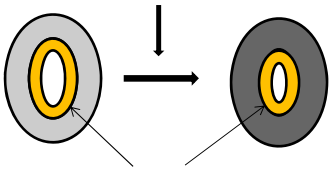
Raynaud's phenomenon

Physiology of Secondary RP



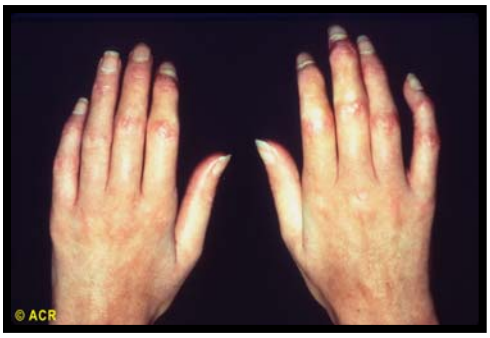
Normal vasoconstriction

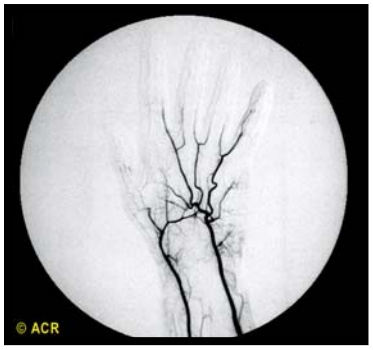
Cold exposure, psychologic stress, etc.



Raynaud's phenomenon in scleroderma

Small vessel disease in scleroderma





Chronic ischemia leads to "tapering" of the digits

Which RP patients will get scleroderma?

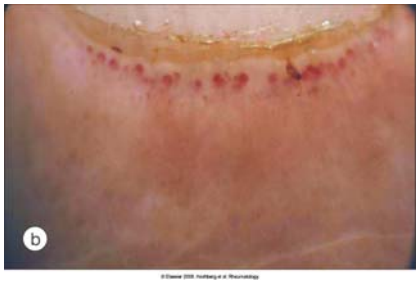
- 784 consecutive RP pts 1984-1999 (Montreal)
- All had nailfold capillary microscopy
- All had stored sera for autoAb testing
- Most were Caucasian, women, dx at age 40
- Duration of RP 2-3 yrs. at dx

Koenig M, et. al. Arthritis Rheum 2008

Nailfold capillaroscopy

baseline

scleroderma



Just proximal to the cuticle, dilated capillary loops can be seen adjacent to “bare areas” that can be indicative of the vasculopathy of scleroderma

Bolster et al, In Hochberg et al, 2008

Which RP patients will get scleroderma?

Tests	Number	5 yr. f/u	10 yr. f/u
No nail changes, no autoAb	446	6 (1.3%)	7 (1.6)
(+) nail changes, no AutoAb	31	7 (22.6%)	7 (22.6%)
No nail changes, (+) AutoAb	65	14 (21.5%)	21 (32.3%)
(+) nail changes and (+) AutoAb	44	29 (65.9%)	32 (72.7%)
Total	**586**	**56 (9.5%)**	**67 (11.4%)**

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Koenig M, et. al. Arthritis Rheum 2008

RP work-up: history

- Confirm typical color change
- Review exposures
- Features of secondary RP
  - Rashes, serositis, arthritis, etc. for SLE
  - Proximal muscle weakness, rashes for IIM
  - Skin changes, GERD, ILD, etc. for scleroderma

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RP work-up: exam

- Vascular exam
- Skin exam
  - Nail changes
  - Early scleroderma changes
  - Livedo
- Strength assessment
- MSK exam

RP work-up: lab studies

- Acute phase reactants: ESR or CRP
- Organ screening: CBC with diff, U/A, creatinine, etc.
- Autoantibodies:
  - Anti-nuclear (ANA)
  - Extractable nuclear antigens (ENA)
    - Scl-70
    - RNP
  - Centromere

Which of the following Rx is best initial treatment for primary RP?

- Diltiazem
- Lisinopril
- ASA
- Nifedipine
- Sympathetic nerve block

Which of the following Rx is best initial treatment for primary RP?

- Diltiazem
- Lisinopril
- ASA
- **Nifedipine**
- Sympathetic nerve block

Primary RP: Rx treatment

- Education
- Exposure avoidance
- Keeping core temperature up
- Consider vasodilatory Rx

Calcium channel blockers for primary Raynaud's phenomenon

- N = 7 trials, 296 pts
- Nifedipine primary Rx
- About 2 fewer attacks/wk
- "… that oral calcium channel blockers are minimally effective in the treatment of primary Raynaud's phenomenon as measured by the frequency of attacks."

Cochrane reviews 2014

Primary RP: Rx treatment

- Watch for orthostasis
- Calcium channel blockers:
  - Nifedipine
- Alpha-blockers
  - Doxazosin
  - Prazosin

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Summary

- Primary RP is generally a problem of over-vasoconstriction
- It generally starts in adolescence
- Some CTD, particularly scleroderma, can present with Raynaud's (secondary RP)
- Exclusion of CTD can be done by clinical and laboratory assessments
- Treatment of RP includes vasodilatory Rx

MAYO CLINIC

Return to Program Schedule

Inflammatory Myopathies

Rheumatology Update 2015
L.E. Mertz MD
Rheumatology Division
Mayo Clinic Arizona

Disclosure statement

There are no financial conflicts to disclose.

Return to Program Schedule

Learning Objectives

- List common disorders that cause muscle weakness.
- Name five common inflammatory myopathies.
- Recall the clinical use of biological markers in the diagnosis of muscle disorders.
- Recognize the value of electromyography.
- Order autoantibody testing to confirm and categorize inflammatory myopathies.
- List typical treatments used for inflammatory myopathies.

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Inflammatory Myopathies

<u>Disorders causing true muscle weakness</u>

- Inflammatory myopathies.
- Genetic/metabolic myopathies.
- Drug/toxin induced myopathies.
- Endocrinopathy induced myopathies.
- Paraneoplastic myopathies.
- Central neurologic disorders.
- Peripheral nerve disorders.

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Inflammatory Myopathies

- Polymyositis
- Dermatomyositis
  - Clinically amyopathic dermatomyositis
- Overlap syndromes
  - RA, SLE, Scleroderma, MCTD, SjS
- Necrotizing autoimmune myopathy
  - Drug induced, paraneoplastic
- Inclusion body myositis
- Vasculitis
- Sarcoidosis
- Chronic viral myositis: HIV, Echovirus
- Graft versus host disease
- Eosinophilic myositis

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Inflammatory Myopathies

- Incidence PM + DM: 20/million
- Prevalence PM + DM: 50-220/million
  - 80% have an autoantibody/30-40% have a MSA.
  - 20-80% have interstitial lung disease
  - Dysphagia in 1/3-1/2 of patients
  - Myocarditis is rare
  - Malignancy relative risk: 2.4 for DM, 1.8 for PM
- Incidence IBM: 1-8/million
- Prevalence IBM: 5-70/million
  - Most have no autoantibodies(5' nucleotidase 1A)
  - No interstitial lung disease
  - Dysphagia 1/3-1/2 of patients.
  - Myocarditis not seen.
  - Malignancy: no increased risk.

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Inflammatory Myopathies

Malignancy and Myositis

- DM: relative lifetime risk 2.4 times normal.
  - Applies to amyopathic DM presentation as well.
- PM: relative lifetime risk 1.8 times normal.
- 4.4 1st year, 3.4 yrs1-3, 2.2 years 3-5, 1.6 > 5 yrs
- Type of cancer-adenocarcinoma
  - Cervix, lung, ovary, pancreas, stomach, bladder.
- Malignancy workup
  - Age appropriate cancer screening.
  - HRCT chest, standard CT abdomen, pelvis
  - Possibly transvaginal US in women.

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Inflammatory Myopathies

Worrisome features

- Positive urine hemoglobin without RBCs
  - Suggests myoglobinuria: check urine myoglobin.
    - Increases risk of renal toxicity if CK >15,000-20,000 U/L
    - IV fluids.
- Dyspnea
  - Respiratory muscle weakness, diaphragmatic weakness.
  - Intrinsic lung disease: ILD, DAD.
    - PFTs with inspiratory and expiratory pressures.
    - HRCT
  - Inflammatory cardiomyopathy/myocarditis
    - Cardiac ultrasound or MRI.
- Dysphagia
  - Aspiration, pneumonia.
    - Swallowing study
    - Gastrostomy tube feedings

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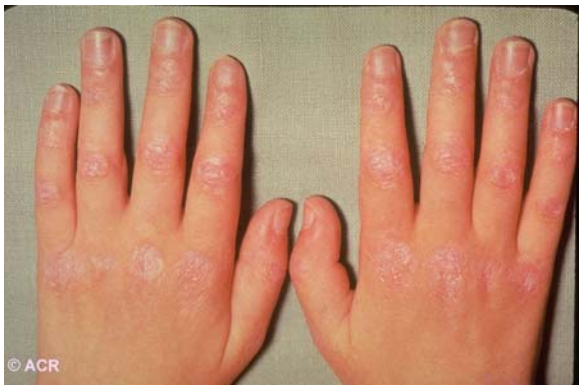
Inflammatory Myopathies

Dermatomyositis



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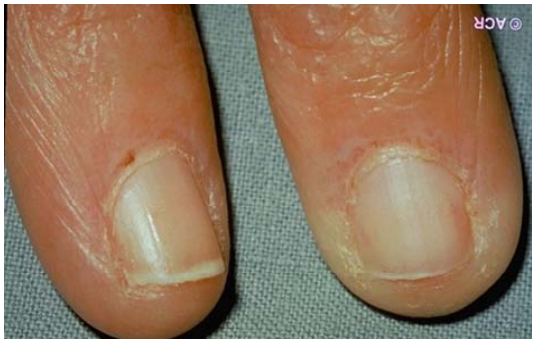
Inflammatory Myopathies

Dermatomyositis

MAYO CLINIC

Inflammatory Myopathies

Dermatomyositis



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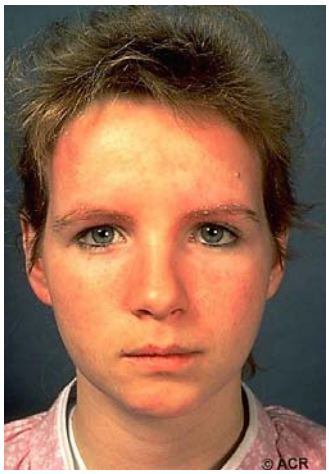
Inflammatory Myopathies

Dermatomyositis

MAYO CLINIC

Inflammatory Myopathies

Dermatomyositis



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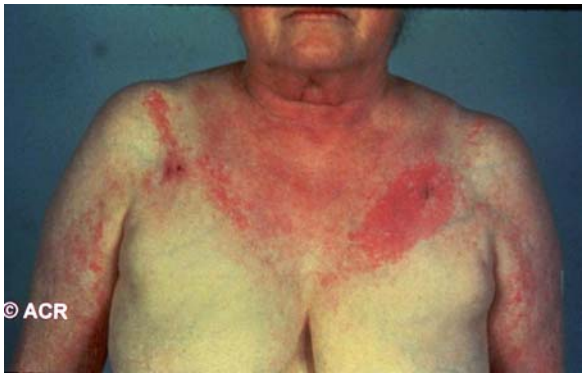
Inflammatory Myopathies

Dermatomyositis



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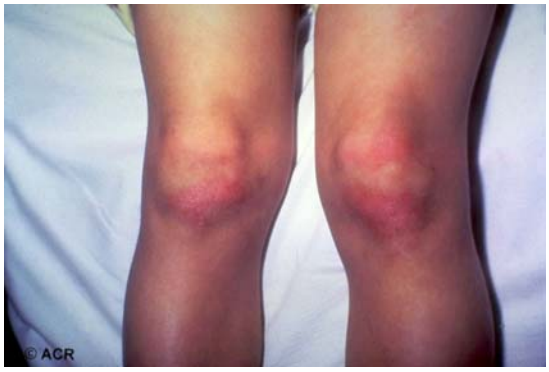
Inflammatory Myopathies

Dermatomyositis



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Inflammatory Myopathies

- Overlap syndrome
  - Myositis occurring in association with a well defined rheumatologic disorder:
    - Scleroderma>MCTD>SjS, RA, SLE
- Necrotizing autoimmune myopathy
  (Immune-mediated necrotizing myopathy)
  - Drug or malignancy related.
    - Statins
  - Easily confused with PM (no rash)
  - Little or no inflammation on biopsy
    - Macrophages not lymphocytes
  - Autoantibodies: anti-HMG CoA R, anti-SRP
  - Statin assoc: requires immunosuppressive tx.

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Inflammatory Myopathies

The spectrum of statin myopathy

Curr Opin Rheumatol 2013, 25:747–752

Table 1. A comparison of toxic statin myopathy with statin-associated autoimmune myopathy

	Toxic statin myopathy	Statin-associated autoimmune myopathy
Symptoms	Myalgias common; Weakness infrequent	Myalgias common; Weakness common
Maximum creatine kinase (IU/l)	Normal (with mild disease) to >100 000 (with rhabdomyolysis)	1000–50 000 IU/l
Muscle biopsy	Mild disease: cytochrome oxidase negative fibres, vacuolization; Severe disease: myofiber necrosis and regeneration with minimal inflammation	Myofiber necrosis and regeneration with minimal inflammation; MHC class I up-regulation; MAC deposition on nonnecrotic fibers
Genetic risk factors	SNP in *SLCO1B1* gene	HLA-DRB1*11:01
Anti-HMGCR antibody	Absent	Present
Clinical course after statin discontinuation	Improvement	Persistent/progressive weakness and CK elevation
Appropriate therapy	Statin withdrawal (or dose reduction)	Statin withdrawal and immunosuppressive therapy

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Inflammatory Myopathies

- Inclusion body myositis
- Defined clinically and histopathologically
  - Slowly progressive weakness proximal>distal
  - Closely resembles PM
  - Distal involvement of wrist and interosseous muscles characteristic.
  - No lung or cardiac involvement.
  - Dysphagia is common.
  - Severe quadriceps weakness often first visit
  - CK often $\leq$ 2,000-3,000 U/L.
  - EMG: similar to DM and PM, however with neuropathic abnormalities.
  - Muscle biopsy
    - Inflammatory infiltrate similar to PM
    - Inclusion bodies, amyloid deposits

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Inflammatory Myopathies

Myositis associated antibodies

(usually Hep2 ANA positive)

- Anti-SS-A Sjs, SLE, RA overlap
- Anti-U1 snRNP MCTD
- Anti-Sm SLE overlap
- Anti-KU PM/Scleroderma overlap
- Anti-PM/Scl PM/Scleroderma overlap
- Anti-U2 snRNP PM/Scleroderma overlap

Inflammatory Myopathies

Myositis specific antibodies

(May be ANA negative-cytoplasmic, not nuclear)

- Anti-Jo-1 Ab
- Anti-PL-7
- Anti-PL-12
- Anti-EJ
- Anti-OJ

common anti-synthetase antibodies

- Anti-MI-2 DM-like, good prognosis.
- Anti-SRP PM-like, necrotizing autoimmune myopathy, little inflam, poor prog
- Anti-HMGCoAR Statin related necrotizing autoimmune myopathy, little inflammation.

Inflammatory Myopathies

Anti-synthetase Syndrome

Clinical manifestation	+	Anti tRNA synthetase ab	
*Inflammatory myopathy		Jo-1	15-30%
*Interstitial lung disease		PL-7	2-5%
Inflammatory arthritis	PL-12		2-5%
Raynaud's phenomenon		EJ	2-5%
*Mechanic's hands		OJ	<2%
Fever, weight loss		KS	<2%
(one or more in combination)	Ha		<1%
		Zo	<1%

Inflammatory Myopathies

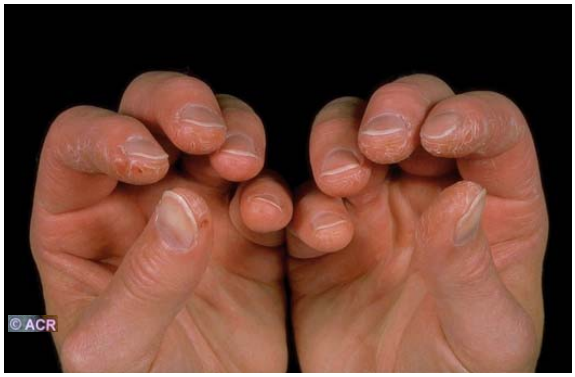
Autoantibodies

- Polymyositis
  - Anti-synthetase syndrome 45%
  - Anti SRP 11%
  - Anti Mi-2 1%
- Dermatomyositis
  - Anti-synthetase syndrome 14%
  - Anti SRP 0%
  - Anti Mi-2 18%
- Overlap syndromes
  - Anti-synthetase syndrome 16%
- Inclusion body myositis(sporadic)
  - Generally no autoantibodies
- Necrotizing autoimmune myopathy
  - Anti SRP antibodies,
  - Anti HMGCoA reductase antibodies.

Inflammatory Myopathies

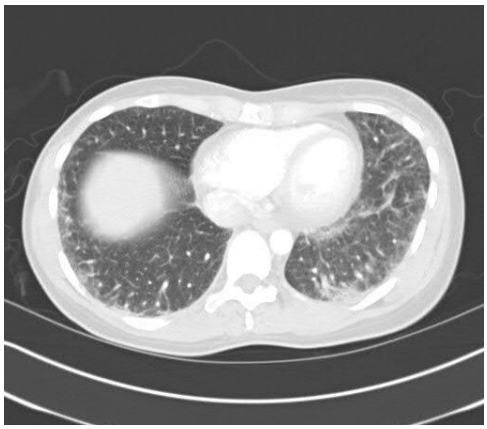
Anti-synthetase syndrome

Mechanic's Hands



Inflammatory Myopathies

Interstitial Lung Disease



Inflammatory Myopathies
Muscle Biopsy

- Dermatomyositis
  - Perifascicular and capillary inflammation
  - CD4+ Tcells present
  - Complement activation products present.
- Polymyositis
  - Intra-fascicular inflammation present
  - CD8+ T cells present
  - No complement activation.
- Inclusion body myositis
  - Intra-fascicular inflammation present
  - CD8+ T cells present
  - Filamentous inclusions, vacuoles, amyloid deposits
- Necrotizing autoimmune myopathy
  - Similar to PM but necrosis with little or no inflammation.
- Overlap syndrome
  - Like PM

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Inflammatory myopathies

MRI Scanning

- Not routinely done.
- May be helpful in specific circumstances:
  - Identifying muscle edema/inflammation
    - Guide muscle biopsy.
    - Clarify persistent inflammation during treatment.
  - Identifying muscle atrophy/fat replacement
    - Clarify absence of inflammation and opportunity to reduce treatment in end stage myopathy.

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Inflammatory Myopathies
Muscle Enzymes

	Skeletal muscle	Cardiac muscle	Brain	Intestine	Bladder	Lung	Liver	RBCs
CK-MM	99%	80%	10%	+/-	+/-	+/-	-	-
CK-MB	1%	20%	0%	-	-	-	-	-
CK-BB	0%	0%	90%	-	-	-	-	-
Aldolase	+	-	+	-	-	-	+	-
AST	+	+	+	+	+	+	+	+
ALT	+	+	+	+	+	+	+	+
LDH	LDH 5	LDH 1	+	+	+	+	LDH 5	+
Trop T	+/-	+	-	-	-	-	-	-
Trop I	-	+	-	-	-	-	-	-

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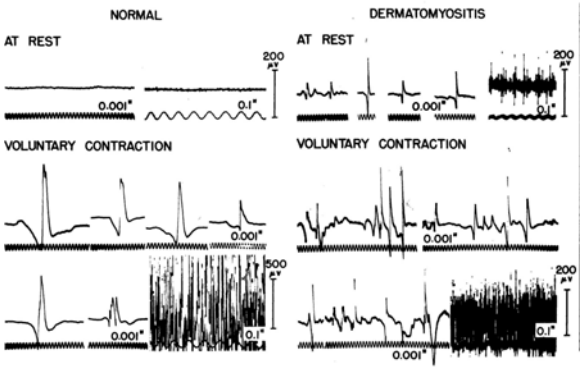
Inflammatory Myopathies
EMG-CMUP



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Inflammatory Myopathies

Treatment Considerations for DM and PM

- Most patients require lifelong treatment.
- Severe muscle weakness can be incapacitating
- Extra skeletal involvement can be life threatening.
  - Pulmonary
    - ILD, respiratory muscle weakness
  - Myocarditis, CHF
  - Severe dysphagia
    - Aspiration pneumonitis
- Infectious complications of treatment can be life threatening.
  - PJP pneumonitis
  - Other infections

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Inflammatory Myopathies

Basic approach to drug treatment of DM and PM

- Minimal treatment duration is approximately 2 years.
- Most patients will relapse on solo corticosteroid tx.
- Initial treatment includes corticosteroids plus a second immune suppressing agent.
  - Most immunosuppressives require months to become beneficial
- Slowly reduce prednisone to the 10 mg/day range over 6 months.
- Attempt to eliminate prednisone between 6-12 months while continuing the immunosuppressive.
- If an excellent response, slowly reduce and eliminate the immunosuppressive over the next year.
- Observe for relapses.

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Inflammatory Myopathies

Basic approach to drug treatment of IBM,NAM, Overlap

- IBM
  - Generally treatment resistant.
  - Supportive care and physical therapy important.
  - CK often normalizes with treatment but no long term benefit.
  - Treat as for DM and PM in specific circumstances
    - Measurably progressive disease.
    - Progressive dysphagia (IVIG)
- NAM
  - Treat identically to DM and PM.
- Overlap syndrome
  - Usually milder muscle inflammation than DM, PM, NAM, IBM
  - Treatment is usually dictated by the primary rheumatologic condition (SSc, MCTD, RA, SLE, etc)
  - Intensification of ongoing treatment often sufficient.

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Inflammatory Myopathies

Drug Treatment options for DM and PM

- Corticosteroids
  - Prednisone p.o. 1-2 mg/kg daily or higher.
  - Methylprednisolone IV 500-1000 mg daily X 3-5 days.
- Immunosuppressive/corticosteroid sparing
  - Methotrexate s.c. or p.o.
  - Azathioprine
  - Mycophenolate mofetil (ILD)
  - Methotrexate + AZA or MPM
  - Cyclophosphamide (severe ILD)
  - IVIG (add on)
  - Rituximab (refractory or ILD).
  - Tacrolimus
  - Hydroxychloroquine, chloroquine: rash of DM.

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Inflammatory Myopathies

Summary of important points

- Statins cause both toxic and autoimmune myopathies which are treated differently.
- Inclusion body myositis is often associated with distal upper extremity weakness.
- CK-MB and troponin T may be elevated in inflammatory myopathies without cardiac involvement.
- Myositis specific antibodies identify subsets of inflammatory myopathies not found by ANA testing.
- The anti-synthetase syndrome may be seen in association with PM, DM and the Overlap syndrome.
- Treatment of DM and PM will usually require both corticosteroids and an immunosuppressant agent.

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The End

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Inflammatory Myopathies

Which disorder is not an inflammatory myopathy?

1. Polymyositis.
2. Inclusion body myositis.
3. Dermatomyositis.
4. Mixed connective tissue disease.
5. Polymyalgia rheumatica.

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Inflammatory Myopathies

Which disorder is not a known endocrinologic cause of muscle weakness?

1. Hypothyroidism.
2. Hyperparathyroidism.
3. Hypercortisonism.
4. Fibromyalgia.
5. Hypovitaminosis D.

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Inflammatory Myopathies

Which drug is not a known cause of muscle weakness:

1. Methotrexate.
2. Colchicine.
3. Hydroxychloroquine.
4. HMG-CoA reductase inhibitors (statins).
5. Ethanol.

Inflammatory Myopathies

Which two neurologic conditions may result in an elevated creatine kinase :

1. Amyotropic lateral sclerosis.
2. Myasthenia gravis.
3. Sensory motor peripheral neuropathy.
4. Guillian-Barre syndrome.
5. Critical illness myopathy.

Inflammatory Myopathies

Case(49955610)

- 59 year old nurse reports a 4 month history of mild progressively worsening myalgia beginning in the calves then thighs then upper arms.
- Eventually develops weakness and could not walk stairs from the 1st floor to the second floor surgical suites or hang a 3 L irrigation bag on the IV pole.
- Primary care lab: AST 259 U/L, ALT 262 U/L, Alk Phos 58 U/L. Creatinine, CMP, sTSH, CBC normal.
- Urine: normal.

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Inflammatory Myopathies

Case

- CK 13,845 U/L (38-176)
- CK-MB 416.7 ng/ml (<3.8)
- Troponin T 1.330 ng/ml (<0.01)
- ESR = 21 mm/hr, CRP <3.0 mg/L.

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Inflammatory Myopathy

Case

- Medications
  - Amlodipine, ranitidine, lisinopril, estrogen vaginal cream, calcium + vitamin D, ASA 81 mg, fish oil supplement, MVI, kidney bean extract
- PMH
  - HPTN, hyperlipidemia, osteopenia, colon cancer resected 2004, hyst and BSO
  - Recent colonoscopy and mammography normal.

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Inflammatory Myopathies

Case

- ROS
  - No family history of inflammatory rheumatologic disorders or muscle disorders
  - No fever but had lost 15 lbs. Mild alopecia.
  - No rash, dyspnea, dysphagia, abdominal pain, changes in B or B habits.
  - No diplopia, jaw or facial diplegia.
  - Recent onset of Raynaud's phenomenon.

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Inflammatory Myopathies

Case

- Physical Examination
  - No distress. Vital signs normal.
  - No rash, sclerodactyly, synovitis, rales, murmurs, abdominal masses, lymphadenopathy.
  - Could rise from a chair unassisted by arms.
  - Could squat and rise with mild difficulty.
  - Could easily stand on toes and heels
  - Gait was normal.
  - DTRs were normal.

Inflammatory Myopathies

Muscle Group	Left	Right
Cervical flexors	4+	
Cervical extensors	5	
Trapezius	5	5
Deltoids	4	4
Pectoralis	5	5
Biceps	5	5
Triceps	4	4
Wrist flexors	5	5
Wrist extensors	5	5
Interosseous	5	5

Muscle Group	Left	Right
Hips flexors	4-	4-
Hip adductors	4+	4+
Hips abductors	4+	4+
Quadriceps	5	5
Hamstring	5	5
Ankle dorsi flexors	5	5
Ankle plantar flexors	5	5

0 No muscle contraction
1 Trace muscle contraction
2 Moves through ROM horizontally
3 Moves through ROM vertically
4 Holds against moderate pressure
5 Normal

Inflammatory Myopathies

AutoAbs to Proteinase 3	**<0.2 Units**
AutoAbs to Myeloperoxidase	**<0.2 Units**
C3 Complement	**86 mg/dL**
C4 Complement	**19 mg/dL**
Complement Total Serum	**49 U/mL**
ANA	**2.6 Units HI**
ENA Scrn	**<1**
(SSA, SSB, Sm, RNP, Scl-70, Jo-1)	
ds-DNA Ab IgG	**<12.3 IU/mL**
CRP Quant	**<3.0 mg/L**
RF Quant	**<15 IU/mL**

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Inflammatory Myopathies

Case

- EKG normal
- Chest x ray normal
- Cardiac ultrasound normal
- Urinalysis repeated negative for Hgb
- Urine myoglobin negative
- Troponin I ordered, not reported

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Inflammatory Myopathies

EMG

- **SUMMARY**
  - Nerve conduction studies were normal. The needle examination showed fibrillation potentials in all muscles examined, and small, morphologically simple appearing motor unit potentials with rapid recruitment in these muscles.
- **INTERPRETATION**
  - There is EMG evidence of a moderately severe myopathy with electrodiagnostic features that would predict an underlying pathological substrate of necrosis, inflammation, fiber splitting, or vacuolar change. A left deltoid muscle biopsy would be appropriate.

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Inflammatory Myopathies

Deltoid Muscle Biopsy

- A sparse inflammatory exudate is present at one or two perivascular sites.
- Mild increase in perimysial fibrous and fatty connective tissue
- Dx: myopathy, slight.
- Insufficient evidence to diagnose dermatomyositis.

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Inflammatory Myopathies

Myositis Antibody Panel
(RDL Laboratory)

Myositis Ab Panel PM/SCL	**Negative**
Myositis Ab Panel JO-1	**Negative**
Myositis Ab Panel MI-2	**Negative**
Myositis Ab Panel PL-7	**Negative**
Myositis Ab Panel PL-12	**Negative**
Myositis Ab Panel EJ	**Negative**
Myositis Ab Panel OJ	**Negative**
Myositis Ab Panel SRP	**Weak Positive**
Myositis Ab Panel KU	**Negative**
Myositis Ab Panel U2 SN RNP	**Negative**

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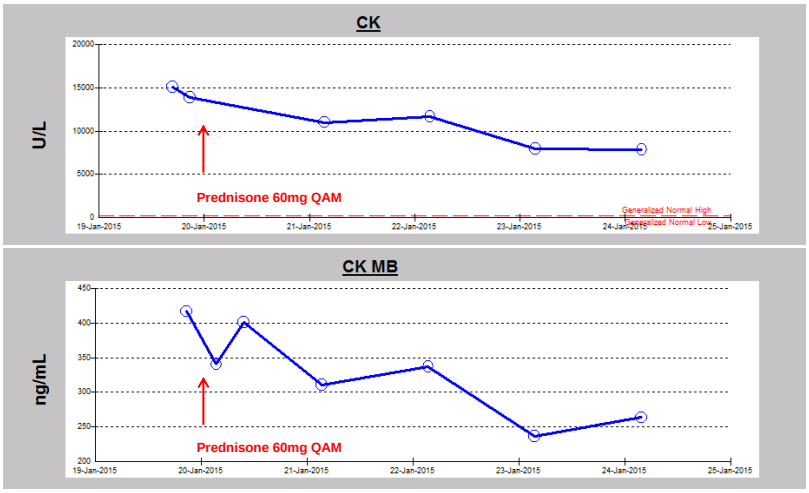
Inflammatory Myopathies



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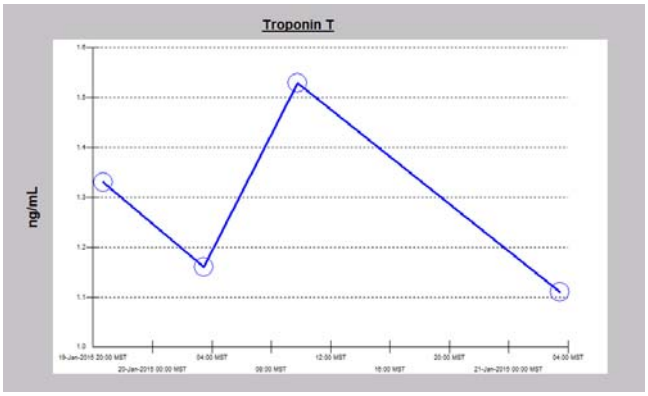

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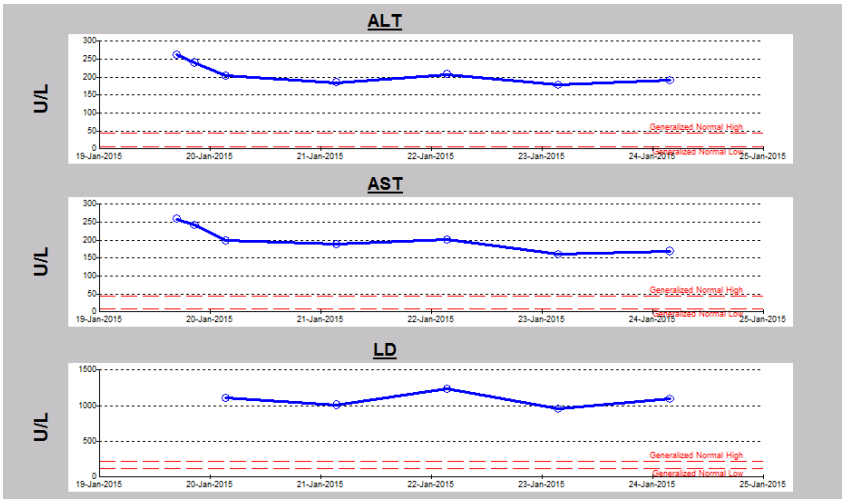

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Inflammatory Myopathies

Case

- Discharged on 60 mg prednisone QAM.
- Outpatient evaluation and treatment plan:
  - HRCT chest
  - Contrast CT abdomen and pelvis
  - Add methotrexate 0.6 ml SC weekly + folic acid
  - Slowly reduce prednisone once CK is normal.
  - Eliminate prednisone and continue methotrexate.
  - Reduce and eliminate methotrexate over several years if possible.

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Inflammatory Myopathies

EMG

MUSCLE	Insertional Activity	SPONTANEOUS Fibrillation	SPONTANEOUS Fasciculation	VOLUNTARY MOTOR UNIT POTENTIALS: MUP Normal	RECRUITMENT Activation	RECRUITMENT Reduced	RECRUITMENT Rapid	DURATION Long	DURATION Short	AMPLITUDE High	AMPLITUDE Low	PHASES %	PHASES turns	OTHER
R. tibialis anterior	↑	++	0				+	+	+		++			
R. medial gastrocnemius	↑	++	0	Normal			+		+		+			
R. vastus medialis	↑	+	0						+		+/-			
R. tensor fasciae latae	↑	++	0				+		+		+		++	
R. deltoid	↑	++	0				++		++		++		+	
R. triceps brachii	↑	++	0				+							
R. biceps brachii	↑	++	0				+		+		+			
R. first dorsal interosseous	↑	+	0				+		++		++			

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Return to Program Schedule

Giant Cell Arteritis

Andy Abril MD
Chair, Division of Rheumatology
Mayo Clinic
Jacksonville, Florida

- No disclosures

Return to Program Schedule

GOALS

- 1- General Concepts
- 2- Clinical Presentation
  - Craneal symptoms
  - Extracraneal symptoms
- 3- Treatment

GCA

- Most common form of systemic vasculitis in adults
  - Incidence: ~ 1/5,000 persons > 50 yrs/year
  - Lifetime risk: 1.0% (F) 0.5% (M)
  - Women > men
  - Northern European ancestry
  - Average age at onset ~73 years

GCA:
2 main components

- Vessel wall inflammation
  - Arterial Stenosis and occlusion
    - Ischemic symptoms
      - Headaches
      - Jaw and limb claudication
- Systemic Inflammation
  - Myalgias
  - Anemia
  - Malaise

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Deng J et al: *Circulation*. 2010;121:906-915

Clinical Case

- 72 year old female presenting with:
  - Malaise for 1 month
  - Low grade fever
  - Right temporal headache for 3 weeks
  - Pain in the jaw when chewing steak
  - Stiffness in the shoulders worse in the mornings
  - ESR : 52 mm/hr

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ACR Classification Criteria

- Age at onset of disease >50 years
- New headache
- Temporal artery abnormality (Tenderness to palpation or decreased pulse)
- Elevated ESR >50 mm/1hr
- Abnormal findings on biopsy of the temporal artery
  - Vasculitis with predominant mononuclear cells or granulomatous inflammation usually with multinucleated giant cells

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Biomarkers for GCA

- ESR
  - 11% have ESR < 50 mm/h[1]
- C-Reactive Protein

– Biopsy proven GCA (2000-2008; 177 cases) [2]
  - Sens 86%; Spec 30%; NPV 88%
    - Outperformed the ESR
    - 4% had normal ESR and CRP

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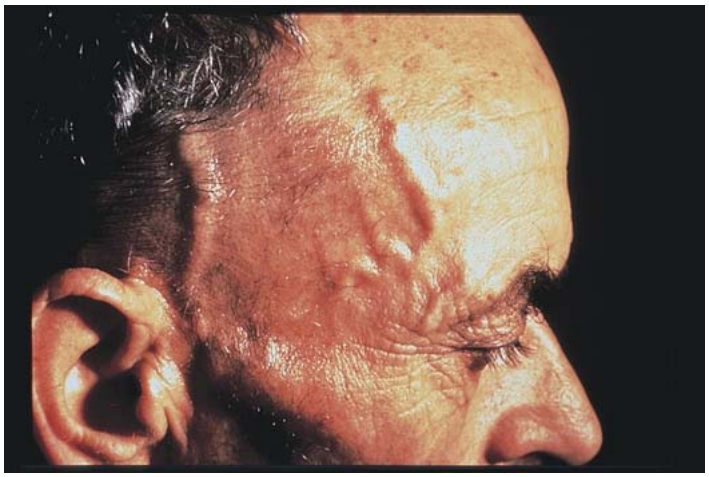
[1] Salvarani C et al. Arthritis Rheum. 2001 Apr;45(2):140-5
[2] Kermani TA et al. Semin Arthritis Rheum. 2011 Nov 23

Temporal arteritis



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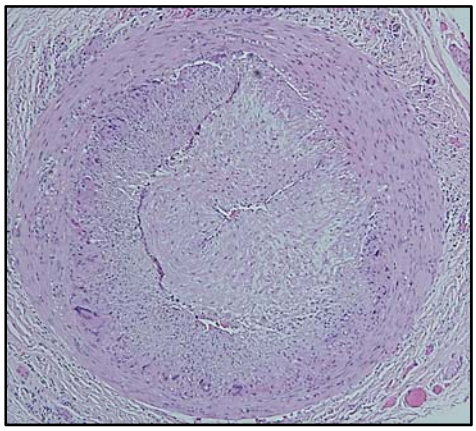
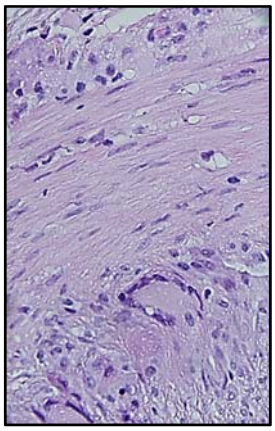
Temporal Artery Biopsy





Weyand CM, Warrington KJ. Giant Cell Arteritis. (in Vasculitis 3rd Ed; Ball & Bridges)

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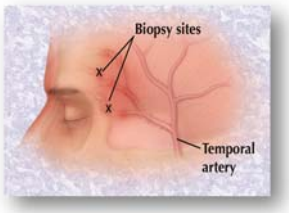
Temporal Artery Biopsy

- Mayo data [1]
  - Rate of positive biopsy: 26.8%
- Positive predictors
  - Weight loss
  - Jaw claudication
  - Clinically abnormal artery[2]
- Referral area didn't matter



1. Rieck KL et al; J Oral Maxillofac Surg. 2011 Jan;69(1):36-40

2. Smetana GW, Shmerling RH. JAMA 2002;287(1):92-101

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TAB- one or both sides ?

- Higher yield with bilateral biopsies
  - Range: 3% - 13%
- Length
  - Generally 1-2 cm; 'skip lesions'
  - Lower yield if <0.5 cm
- Corticosteroids
  - 2-4 weeks - no change in yield

Pless M et al. *J Neuroophthalmol* 2000; 20: 216-8
Mahr A, et al. Ann Rheum Dis. 2006 Jun;65(6):826-8
Achkar, A.A., et al., Annals of internal medicine, 1994. . 120(12): p. 987-92.

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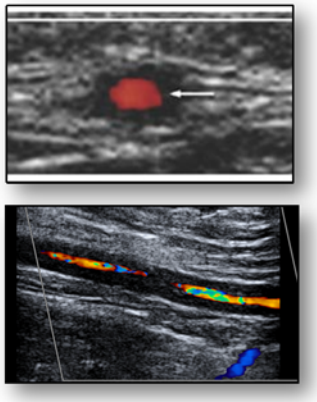
Non-invasive diagnosis of GCA

- Ultrasound
  - Hypoechoic 'halo' surrounding the lumen (edema)
  - Disappears promptly with treatment
  - Highly operator-dependent



Schmidt WA. Nature Clinical Practice Rheumatology (2007) 3, 35-42

Bley TA et al. AJNR Am J Neuroradiol. 2007 Oct;28(9):1722-7

'Temporal arteritis' is not always GCA

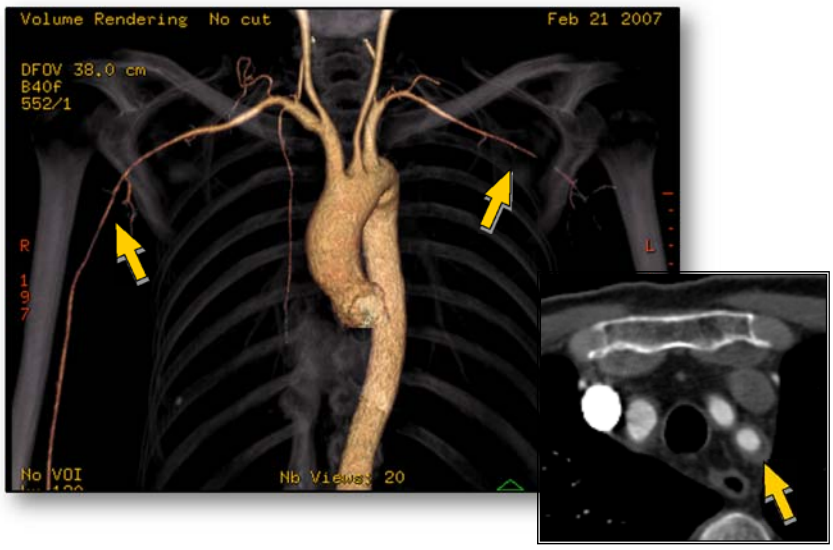
- TA with Hematologic Malignancy
  - Leukemia:
    - Hairy Cell, CLL, CMML, AML[1]
  - Lymphoma [2, 3, 4]
    - Rare
  - Amyloidosis
- TA with Systemic Vasculitis[5]
  - PAN
  - ANCA-Associated Vasculitis
  - Cryoglobulinemic Vasculitis

1 Warrington K et al. J Rheumatol 2003;30:846–8
2 Webster E et al J Rheumatol. 1986 Dec;13(6):1163-6
3 Wooten MD et al Semin Arthritis Rheum. 1996 Oct;26(2):564-74
4 Hutson TE, Hoffman GS. Arthritis Care Res. 2000 Dec;13(6):417-23
5 Genereau T et al. Arthritis Rheum 1999; 42:2674-81.

Clinical Case 2

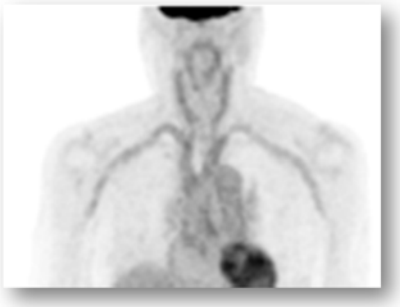
- 66 year old female
- Polymyalgia Rheumatica
  - Prednisone taper for 10 months
  - No cranial symptoms or signs
- Past month
  - Weight loss, malaise, left arm claudication
  - BP: (R) 136/82 (L) 90/
  - Left radial pulse: absent
  - ESR 85 mm/hr

GCA - Arterial Stenoses



GCA
Upper Extremity Arterial Involvement

- Frequency by imaging:
  - PET - 74%
  - CT angio - 42%
  - Ultrasound - 30%
- Symptoms < 10%
- Isolated PMR
  - PET – 31%

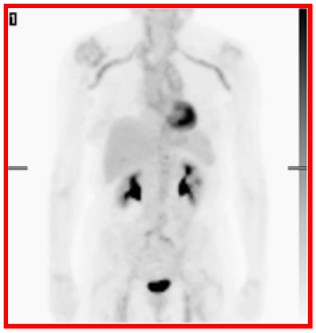


Blockmans D et al. Rheumatology (Oxford) 2007; 46: 672–77

Schmidt WA et al. Rheumatology (Oxford). 2008 Jan;47(1):96-101

Ghinoi A et al. Rheumatology (Oxford). 2012 Apr;51(4):730-4

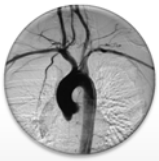
Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6



Trejo-Gutierrez, JF. Larson, JM. Abril, A. Lancet. 2008 Jan 12; 371(9607): 176

Clinical Features

Older
Cranial symptoms
Vision loss



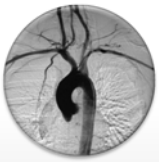
Younger
Often absent
Arm Claudication
Vascular findings

Schmidt WA Rheumatology (Oxford). 2008 Jan;47(1):96-101 c
Muratore F et al. Arthritis Rheum. 2012 Oct; 64(10):S994. # 2358
Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6

MAYO CLINIC

Diagnosis

ACR ‘90 Criteria (95%)
Earlier Diagnosis
TAB



ACR ‘90 Criteria (40%)
Delayed Diagnosis
Vascular Imaging

Schmidt WA Rheumatology (Oxford). 2008 Jan;47(1):96-101 c
Muratore F et al. Arthritis Rheum. 2012 Oct; 64(10):S994. # 2358
Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6

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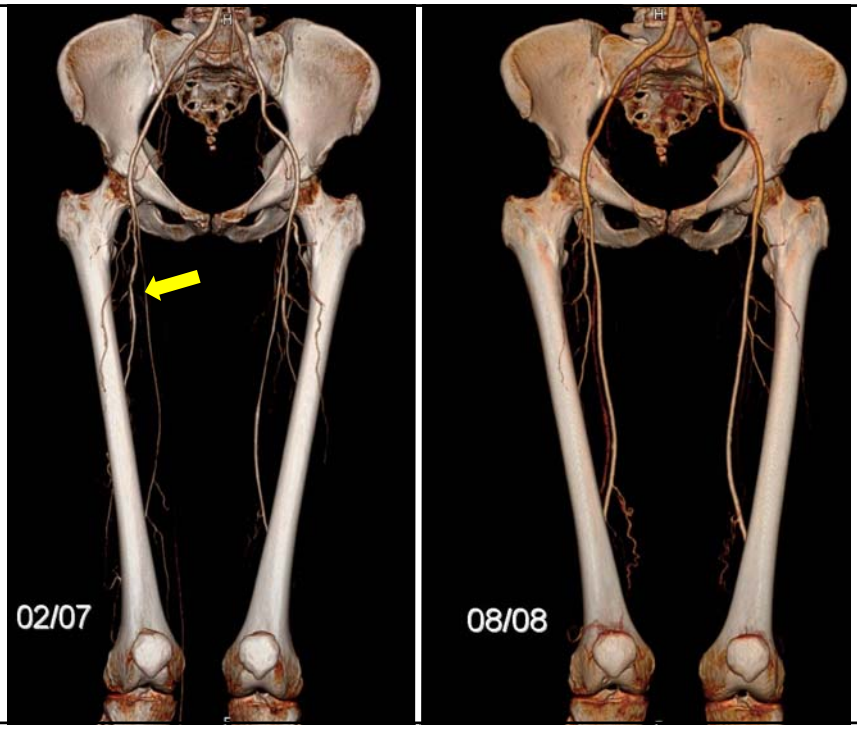
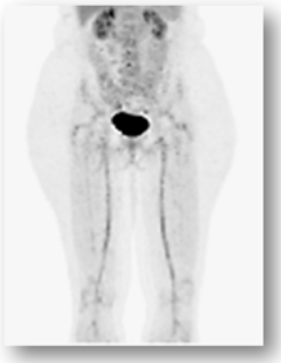


GCA
Lower Extremity Arterial Involvement

- Imaging
  - PET - 37%
  - Ultrasound - 12-50%
- Clinical manifestations
  - Leg Claudication 1-20%
  - Often presenting feature
  - 15-30% critical leg ischemia



Blockmans D et al. Arthritis Rheum. 2006 Feb 15;55(1):131-7
Aschwanden M et al. Ann Rheum Dis 2010; 69:1356–1359
Czihal M et al. J Rheumatol. 2012 Feb;39(2):314-21
Kermani TA et al. J Rheumatol. 2009 Oct;36(10):2277-83

Key Points

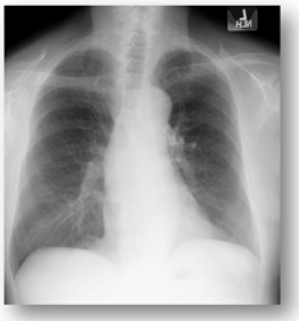
- Extent of vasculitis is under-recognized[1]
- Careful history and examination
  - Vascular system: pulses, bruit
  - BP measurement
  - Vascular Laboratory studies
- Vascular Imaging

MAYO CLINIC

1. Grayson PC, et al, VCRC. J Rheumatol. 2012 Feb;39(2):303-9

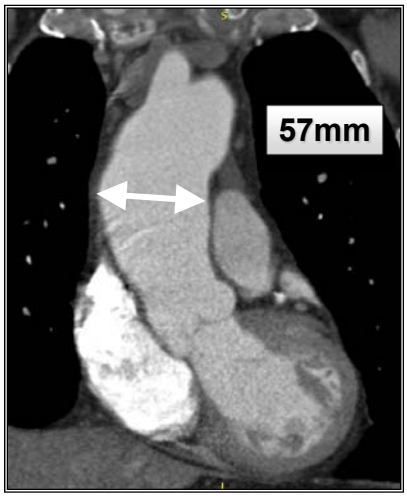
Case

- 67 year-old female; healthy
  - Never smoked
- GCA
  - CRP 130 mg/L
  - Positive TA Biopsy
  - Prednisone (2 yrs)
- 5 years later . . .
  - Asymptomatic
  - Normal exam
  - Normal ESR & CRP



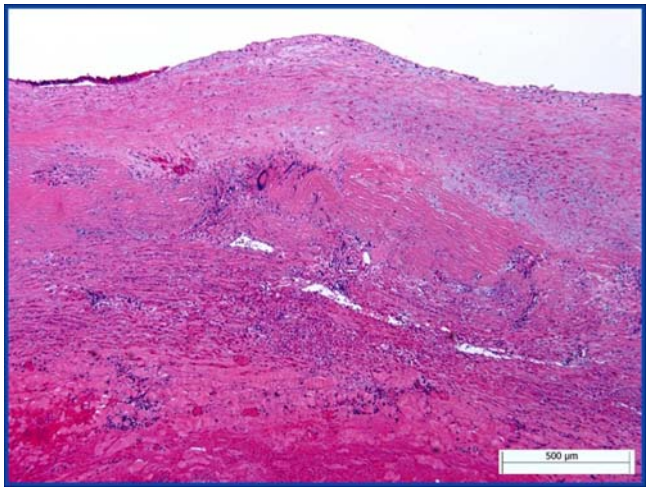
MAYO CLINIC

Aneurysm of the Ascending Aorta



MAYO CLINIC

Active Giant Cell Aortitis



MAYO CLINIC

Slide courtesy of DV Miller, MD

GCA
Aortic Aneurysm

- Thoracic Aortic Aneurysms
  - 6.6-17.3 – fold increased risk[1,2]
  - 12% - 33% incidence at 10 years of F/U[3]
- No consistent clinical predictors
  - Aortic Regurgitation

Evans JM et al. Ann Intern Med 1995;122(7):502-7

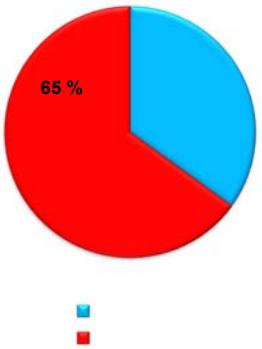
Robson JC. Ann Rheum Dis. 2013 Oct 4

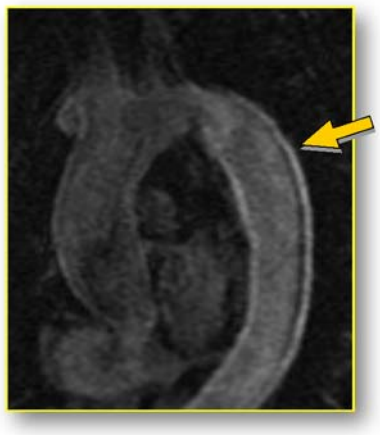
Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.

MAYO CLINIC

Aortitis at Onset of GCA

CT Angio (thickening)





Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6

Kermani TA, Warrington KJ. Curr Neurol Neurosci Rep. 2012 Apr;12(2):138-44

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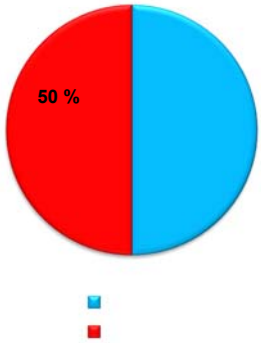
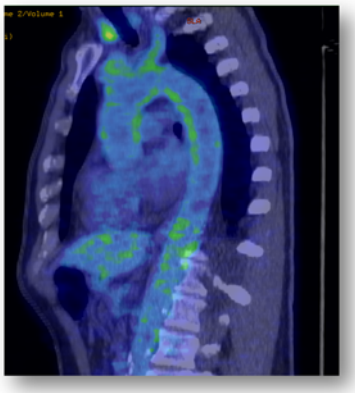
Aortitis – no focal symptoms

PET scan (FDG uptake)



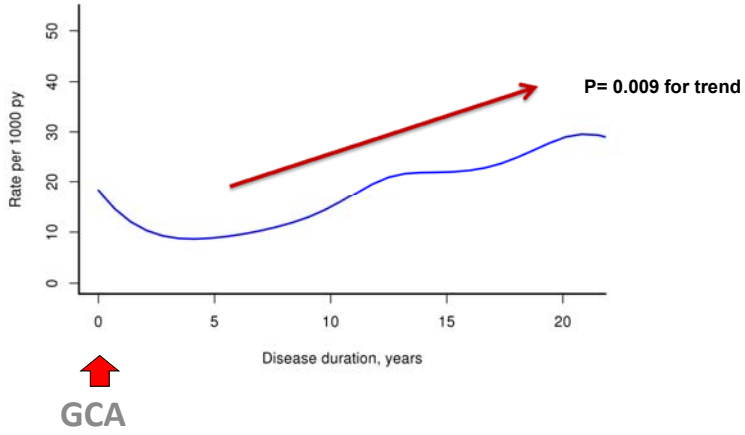


Blockmans D Rheumatology (Oxford). 2008 Aug;47(8):1179-84.

Blockmans D et al. Arthritis Rheum. 2006 Feb 15;55(1):131-7

MAYO CLINIC

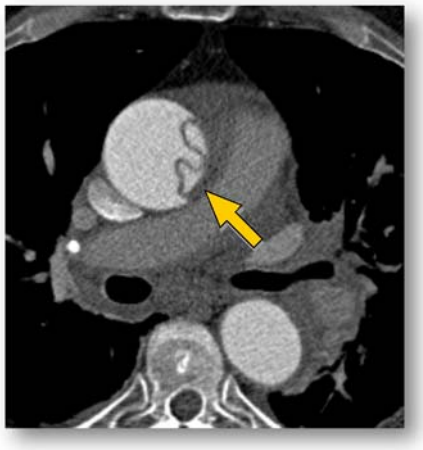
Aortic Aneurysm - A late complication after remission



Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.

MAYO CLINIC

Aneurysm/Dissection - Increased Mortality



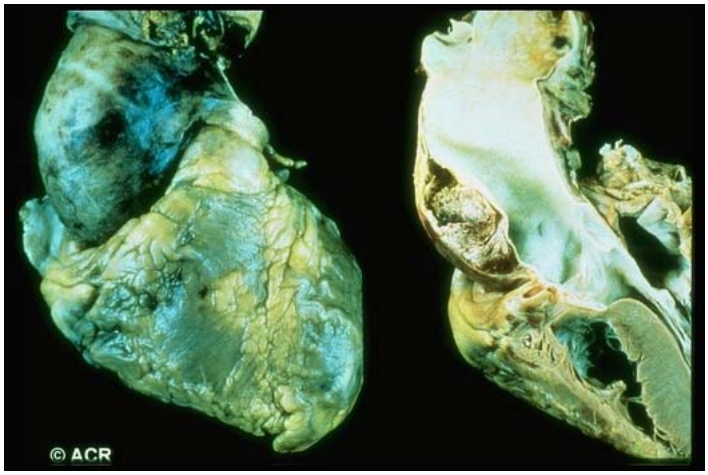
Unknown:

- **Rate of progression**
- **Optimal timing of repair**

MAYO CLINIC

Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.

Temporal arteritis



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Aneurysm screening

- Expert recommendations:
  - Yearly Chest X-ray
  - Cardiac Echocardiogram
  - Baseline CT scan or MRI (ACC/SVM)
- To detect one previously unknown TAA/TAD
  - 5 to 10 patients with GCA would need aortic imaging

Salvarani C et al Lancet. 2008 Jul 19;372(9634):234-45

Bongartz, Matteson. Curr Opin Rheumatol 2006;18:10–17

Mackie SL et al. Ann Rheum Dis. 2012 Dec 22

Hiratzka LF, et al. J Am Coll Cardiol 2010;55:e27–129

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Treatment

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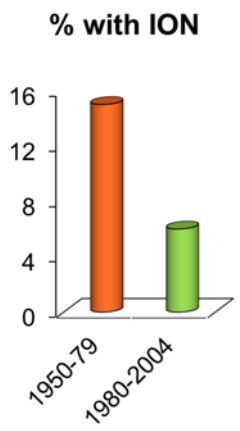
Ischemic Optic Neuropathy

- Vision loss in the pre-steroid era: 60%
- Corticosteroids
  - Treat early
  - Do not reverse ION
  - Beyond the 1st 2 weeks, risk is *very low*
    - about 1% risk of vision loss over 5 years



Cid M Rheum Dis Clin N Am 33 (2007) 819–834
Aiello PD et al Ophthalmology. 1993 Apr;100(4):550-5
Singh AG et al. Arthritis Rheum, 2012; Vol 64 Supp p: S993-S993

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Corticosteroids

- Efficacy
  - Symptoms
  - Inflammatory markers
  - Prevent ION
- Limitations
  - Vascular complications
  - Relapses ('flares') occur in 50-80% of patients
  - Median duration of CS: 2.1 years

    75% off CS after 5 years

Udayakumar, Kermani, Warrington et al. (Manuscript in preparation)

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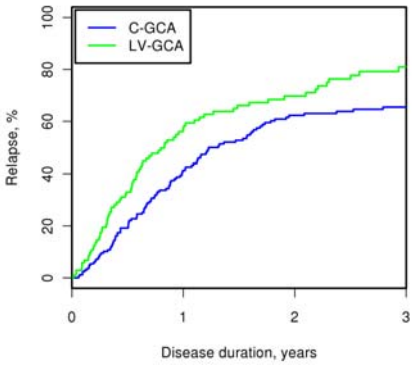
Patients with Large-Vessel GCA are more refractory to therapy

- Mayo cohort (n=103)
  - More relapses
  - Higher cumulative dose of CS
  - Median time to stop CS: 4.5 years (vs 2.2 yrs)

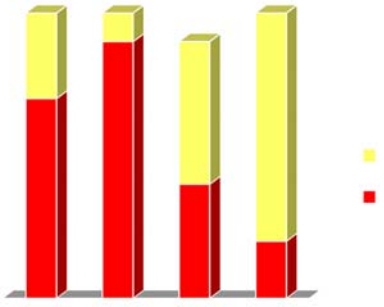


MAYO CLINIC

Muratore F et al. Arthritis Rheum. 2012 Oct; 64(10):S994. # 2358

The patient on corticosteroids

Contralateral TAB in patients with treated GCA – the 'second biopsy' study

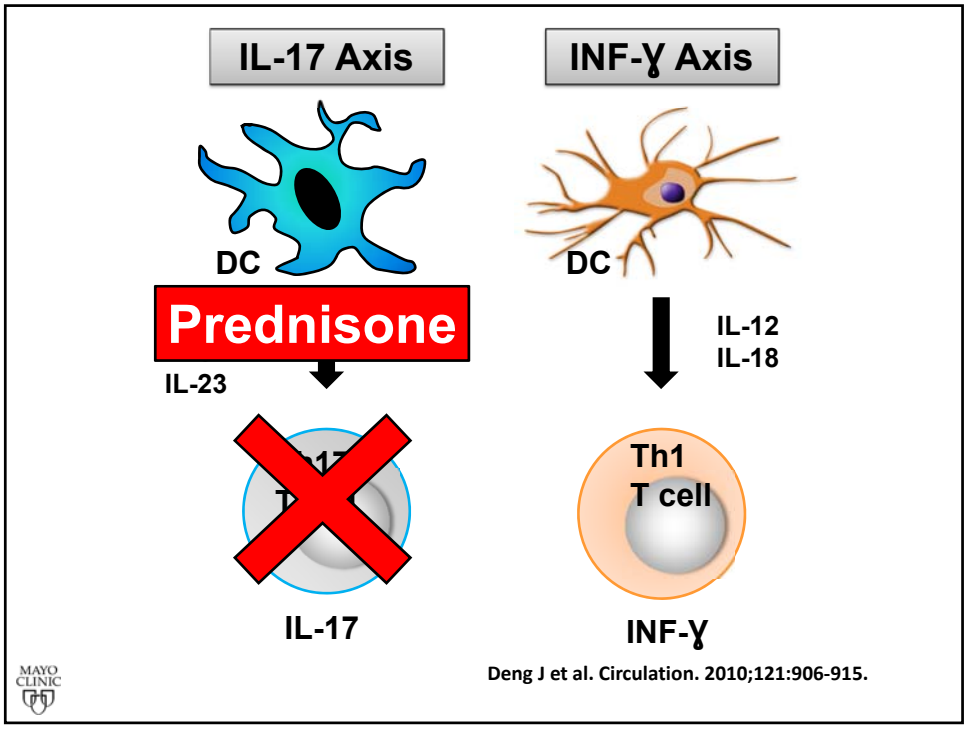


MONTHS

Slide courtesy of Brian Younge MD

Deng J Circulation. 2010 Feb 23;121(7):906-15

MAYO CLINIC



Deng J et al. Circulation. 2010;121:906-915.

Limitations of corticosteroids

- Adverse effects ~ 90%
- Infection risk increased 50%[1]
  - First 6 months
  - No increase in H. Zoster risk in pts with GCA[2]

Pneumocystis pneumonia
Mean hospital stay – 21 days
Mortality 30 %[3]

[1]*Durand M et al. Arthritis Care Res (Hoboken). 2012 Apr;64(4):581-8*
[2]*Schafer V et al Rheumatology (Oxford). 2010 Nov;49(11):2104-8*
[3]*Kermani TA et al. Arthritis Care Res (Hoboken). 2011 Jan 14*

Methotrexate

- Meta-analysis (3 randomized trials)
  - 84 on MTX
  - 77 on placebo
- MTX reduced:
  - Risk of 1st relapse by 35%
  - Risk of 2nd relapse by 51%
  - Exposure to steroids

MAYO CLINIC

Mahr A et al Arthritis Rheum. 2007 Aug;56(8):2789-97.

Biologics for GCA

- Infliximab
  - No evidence of efficacy
- Abatacept
  - Randomized withdrawal multi-center pilot study
- Tocilizumab
  - Antibody to Interleukin-6 receptor
  - Reported efficacy in case reports & small series
  - Randomized, double-blind, placebo-controlled study: GiACTA www.gca-study.com

Hoffman G et al, Ann Int Med 2007:146:56
Salvarani C et al. Rheumatology (Oxford). 2012 Jan;51(1):151-6

Oliveira, F et al, 2014 May-Jun; 32(2 Suppl 82): S76-8

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Adjunctive therapy

- Aspirin
  - May reduce ischemic events
  - Generally recommended
  - Retrospective data
    - Conflicting evidence
- Statins
  - No evidence of benefit

Salvarani C, et al. Rheumatology (Oxford). 2009 Mar;48(3):250-3
Schmidt et al. J Rheumatol. 2013 Jun;40(6):910-5.

MAYO CLINIC

Conclusion

- Giant Cell Arteritis
  - Variable clinical presentation
  - Chronic Vasculopathy
    - Vascular Damage
- Unmet therapeutic need
  - Targeted, more effective therapy
  - Less toxicity

MAYO CLINIC

Return to Program Schedule

Diagnosing Childhood Arthritis

T. G. Mason, MD
Associate Professor of Medicine and Pediatrics,
Mayo Clinic College of Medicine

Disclosures

- Financial
  - none
- Other
  - Member, test-writing committee for rheumatology, American Board of Internal Medicine (ABIM)

Return to Program Schedule

Disclosure of ABIM Service: Thomas Mason, MD

- I am a current member of the Rheumatology Board Exam Committee.
- To protect the integrity of certification, ABIM enforces strict confidentiality and ownership of exam content.
- As a current member of the Rheumatology Board Exam Committee, I agree to keep exam information confidential.
- As is true for any ABIM candidate who has taken an exam for certification, I have signed the Pledge of Honesty in which I have agreed to keep ABIM exam content confidential.

No exam questions will be disclosed in my presentation.

MAYO CLINIC

Goals/objectives

- Recall the classification criteria for the diagnosis of juvenile idiopathic arthritis (JIA)
- Recognize the articular and extra-articular features associated with the various forms of JIA
- To be able to diagnose children with JIA

MAYO CLINIC

Which of the following children is most likely to have JIA:

- 14 y/o girl with 10 months of widespread musculoskeletal pain & RF of 17 (< 15)
- 9 y/o boy with 3 weeks of severe ankle and shin pain that wakes him from sleep
- 5 y/o boy who for the last 18 months gets a sore throat with adenopathy and fever every 2 months
- 3 y/o girl with a painless limp for 3 months

MAYO CLINIC

Which of the following children is most likely to have JIA:

- 14 y/o girl with 10 months of widespread musculoskeletal pain & RF of 17 (< 15)
- 9 y/o boy with 3 weeks of severe ankle and shin pain that wakes him from sleep
- 5 y/o boy who for the last 18 months gets a sore throat with adenopathy and fever every 2 months
- **3 y/o girl with a painless limp for 3 months**

MAYO CLINIC

What is childhood arthritis?

- JRA
  - Swelling, or 2 of these:
    - decreased ROM, painful ROM, tenderness or warmth
  - At least six week duration
  - No other cause
  - Onset before age 16 yrs.

MAYO CLINIC

What is childhood arthritis?

- JIA
  - Swelling, or 2 of these:
    - decreased ROM, painful ROM, tenderness or warmth
  - At least six week duration
  - No other cause
  - Onset before age 16 yrs.

MAYO CLINIC

Other causes:

- Infection related
  - Septic
  - Lyme
  - Rheumatic fever
  - Reactive
- Structure related
  - Joint hypermobility
  - Other (increased Q-angle, etc.)

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Joint hypermobility

- Aspects of benign joint hypermobility:
  - hyperflexion at hips/back, thumb
  - hyperextension of knee, elbow, fingers
  - No other features (cardiac, ocular, etc.)

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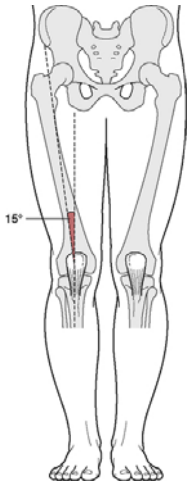
ACR website 2014

Patellofemoral knee pain

- Pes planus
- Foot pronation
- Increased Q-angle
- Wide hips



What is childhood arthritis?

JIA

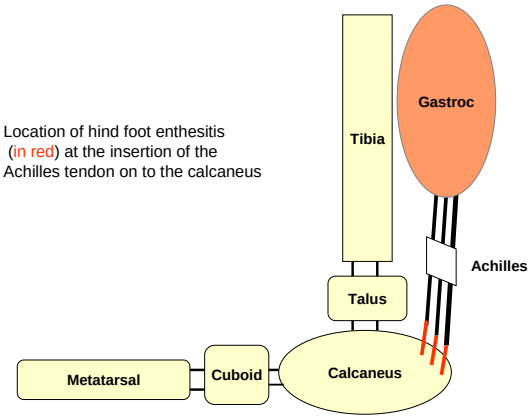
- **9 types**
  - **Systemic-onset**
  - **Polyarticular (+RF/ -RF)**
  - **Pauciarticular**
    - **Persistent**
    - **Extended**
  - **Psoriatic**
  - **Enthesitis-related**
  - **Undifferentiated**

JRA

- **3 types**
  - **Systemic-onset**
  - **Polyarticular**
  - **Pauciarticular**
- **Doesn't include early spondyloarthropathy**

Enthesitis

Location of hind foot enthesitis (in red) at the insertion of the Achilles tendon on to the calcaneus



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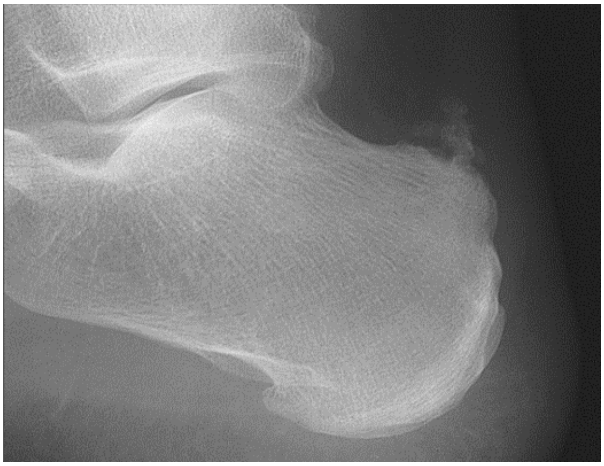
Calcaneal enthesitis



MAYO CLINIC

The prevalence (rate) of JIA is …

- 1/100 children
- 1/1,000 children
- 1/10,000 children
- 1/100,000 children

The prevalence (rate) of JIA is …

- 1/100 children
- **1/1,000 children**
- 1/10,000 children
- 1/100,000 children

JIA: pathologic concepts

- JIA is an autoimmune condition
- Prevalence is about 1/1,000
- Incidence is about 1/10,000 per yr.
- Damage is done when misguided immune mechanisms are directed at joint structures
- Many of these mechanisms can be leveraged by various degrees on immunosuppression

MAYO CLINIC

Which of the following is most likely found in a 3 y/o girl with pauci-JIA?

- Elevated serum rheumatoid factor (RF)
- Subcutaneous nodules
- Asymptomatic uveitis
- Decreased ROM of spine
- Spiking afternoon fevers

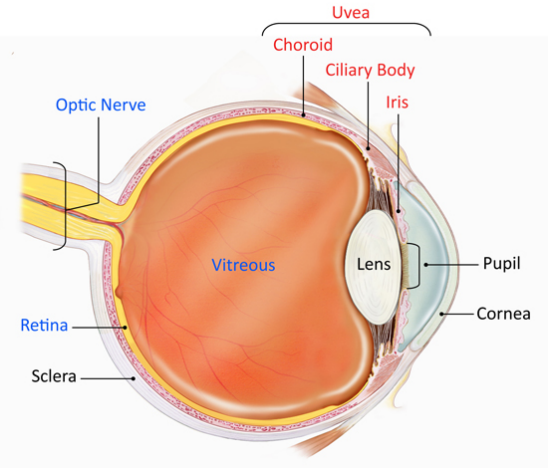
MAYO CLINIC

Which of the following is most likely found in a 3 y/o girl with pauci-JIA?

- Elevated serum rheumatoid factor (RF)
- Subcutaneous nodules
- **Asymptomatic uveitis**
- Decreased ROM of spine
- Spiking afternoon fevers

MAYO CLINIC

Human eye: uveitis

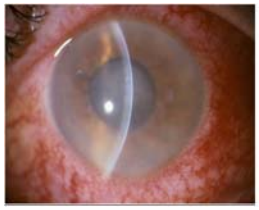


MAYO CLINIC

From national Eye Institute Website, 2014

Uveitis

Anterior uveitis



Posterior uveitis

Uveitis

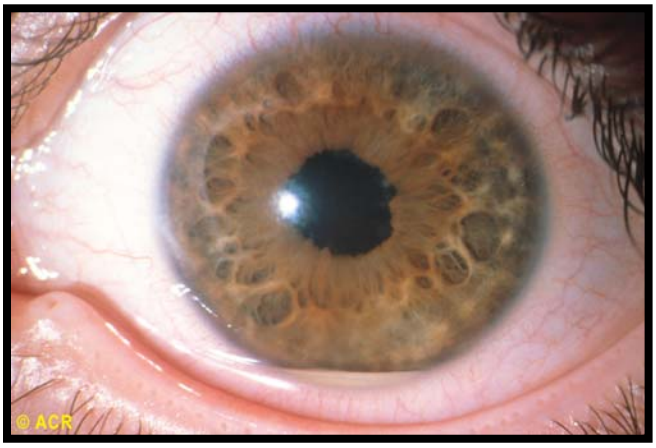
Anterior

- Red eye
- Painful
- Photophobic
- Slit lamp exam optional
- Associated with spondyloarthropathies like AS, IBD, ReA

Posterior

- Not red
- Not painful
- Not usually photophobic
- Slit lamp exam required
- Seen in pauci-JIA, occasionally PsA

Hypopyon form uveitis



JIA: uveitis-risk factors

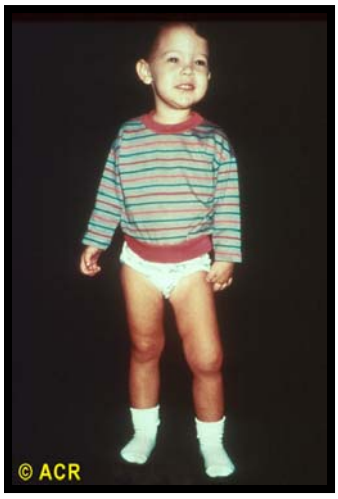
- Girls (4X)
- Pauciarticular >> polyarticular > PsA
- ANA + (80% of uveitis with + ANA)
- Under age 7 yrs.
- Highest risk group need every q 3-4 month evaluations

Pauciarticular JIA: up to 65%

- Fever & rash absent
- Four or fewer joints involved
- Increased risk for chronic uveitis
- Typically LE joints
- Chance for “extension” (-> poly) = 10-20%
  - Increased if UE involvement
- Prognosis is good
- Tx = NSAIDs, IA injections, MTX

MAYO CLINIC

Left knee involvement with pauciarticular JIA (pauci JIA)

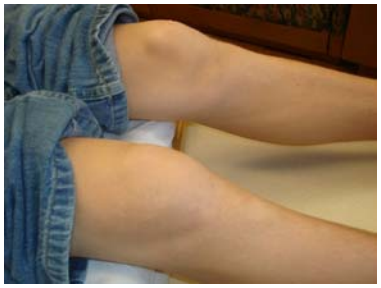


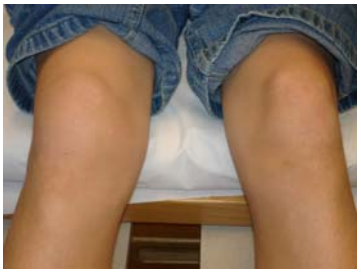
MAYO CLINIC

Left ankle effusion

MAYO CLINIC

Right knee effusion





MAYO CLINIC

Limb length discrepancy in pauci JIA

- Note the difference in length & girth of the right LE, compared to left. The right knee is effected, resulting in increased growth rate of the right leg

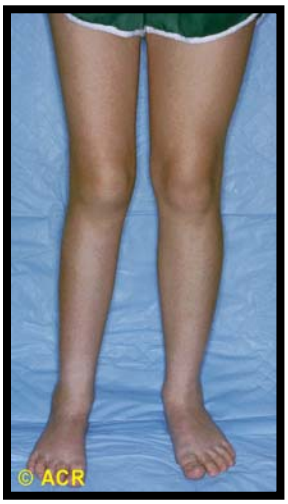
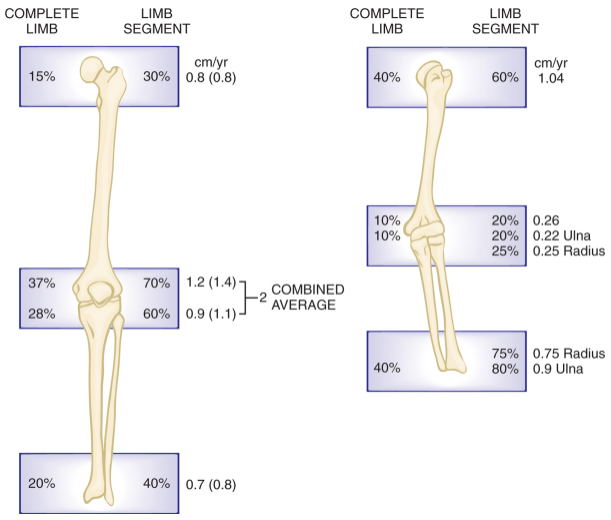


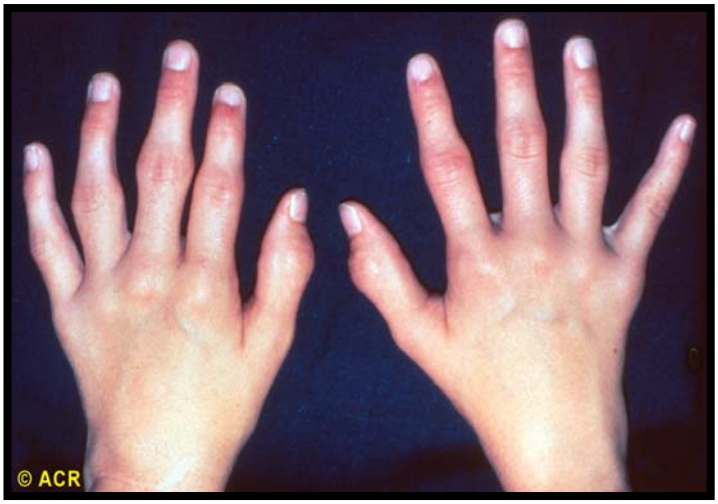
Figure 671-1 The contribution (%) of each physis to the overall length of the extremities. *(From Morrissy R, Weinstein S [editors]: Lovell and Winter's Pediatric Orthopedics, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2001.)*



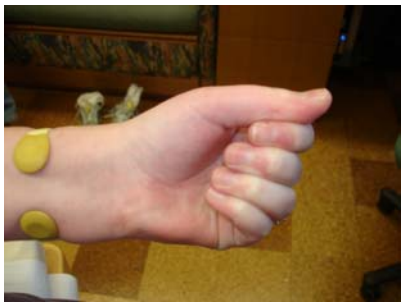
Polyarticular JIA: up to 25%

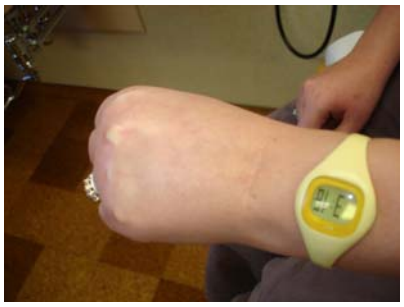
- Fever & rash absent
- Five or more joints involved
- Increased risk joint damage
- Typically UE joints/small joints
- Associated with nodules, autoantibodies
- “Premature RA”
- Tx = NSAIDs, IA injections, MTX, biologics

Synovitis of MCP, PIP and wrist joints, bilaterally in polyarticular JIA (poly JIA)



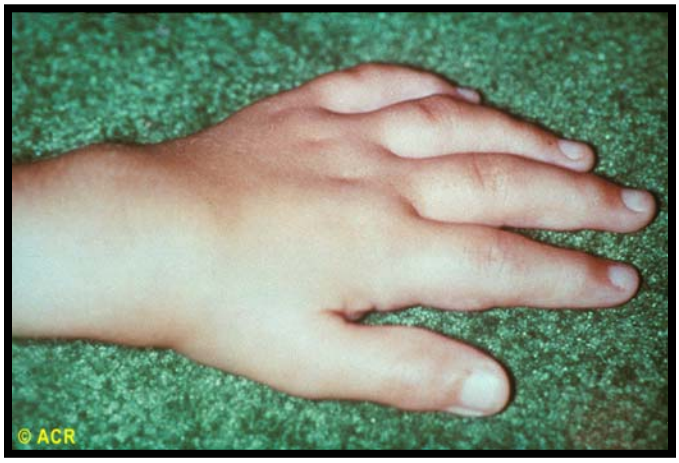
Incomplete fist



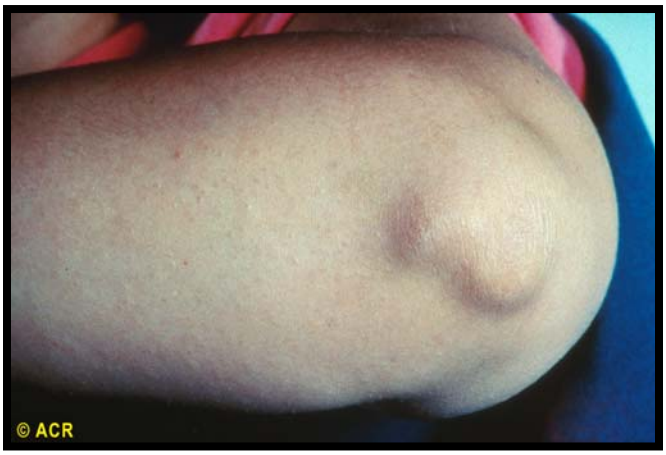


Decreased wrist extension

Synovitis of MCP , PIP and wrist joints in poly JIA



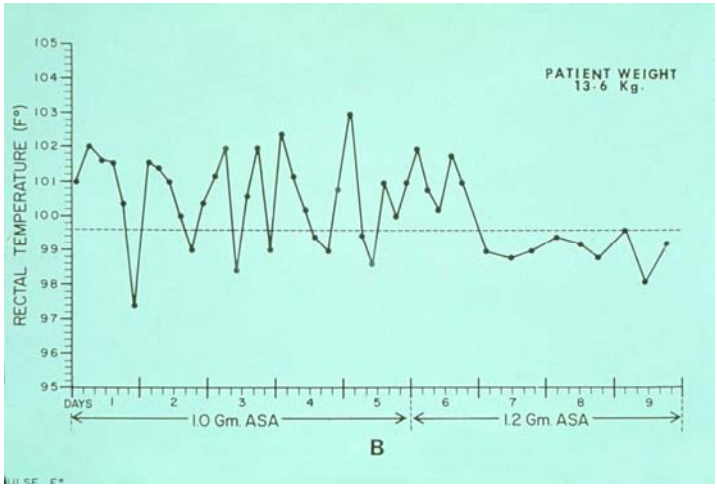
Olecranon nodule with poly JIA



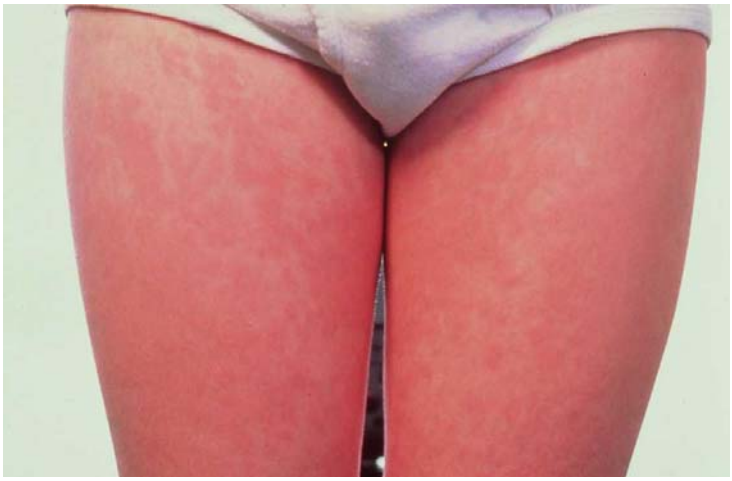
Systemic-onset JIA: about 10%

- Fever & rash major features
- Variable number of joints involved
- Increased risk joint damage
- Not associated with autoantibodies
- Elevated acute phase reactants, ferritin
- “Two processes”
  - Articular
  - Extra-articular

Fever pattern in soJIA



Rash from systemic onset JIA (soJIA)



Systemic-onset JIA

- Often seen in hospital/FUO work-up
- Worst prognosis (some related to tx)
- Increased risk joint damage
- Tx now with IL-1 and IL-6 blocker, & MTX, steroids
- Risk of macrophage activation (MAS)
  - Continuous fever, cytopenias, liver dysfunction
  - High mortality risk

Laboratory Studies: Rheumatology

- Acute phase reactants
- Autoantibodies
- Organ assessment
  - Articular: Imaging
  - Extra-articular: Imaging, blood tests, physiologic testing, etc

Suggested laboratory studies: JIA

- Acute phase reactants
  - CBC with diff, ESR, CRP
- Autoantibodies
  - ANA, RF, CCP
- Organ assessment
  - Articular: Imaging: x-rays
  - Other: chemistry, “rule-out” tests

Closing comments

- Is not an acute condition
- Particularly in smaller children is a problem with function, not pain
- Is not associated with night time pain/pain that awakes from sleep
- Is frequently seen with no autoantibodies
- Is often seen with normal acute phase reactants

Closing comments

- Pauci-JIA: associated with *asymptomatic* uveitis
  - + ANA increases risk for uveitis
- Poly-JIA: associated with high risk of joint damage, "precocious RA"
  - + RF (or CCP) increased risk for damage
- soJIA: associated with quotidian fever pattern, elevated acute phase reactants, transient rash
- Remember that CTD can "start out" as JIA, especially in teenagers

Return to Program Schedule

Cutaneous Manifestations of Rheumatologic Disorders

Jason Sluzevich M.D.

Assistant Professor of Dermatology
Department of Dermatology
Mayo Clinic Florida

April 18, 2015

Skin Findings in Connective Tissue Disease

Acquired

Specific	Lupus
	Dermatomyositis
	Scleroderma & Morphea
	MRH, RA, Sjogren's
Non-Specific	Alopecia
	Vasculitis
	Raynaud's
	Calcinosis cutis

Return to Program Schedule

Lupus Erythematous

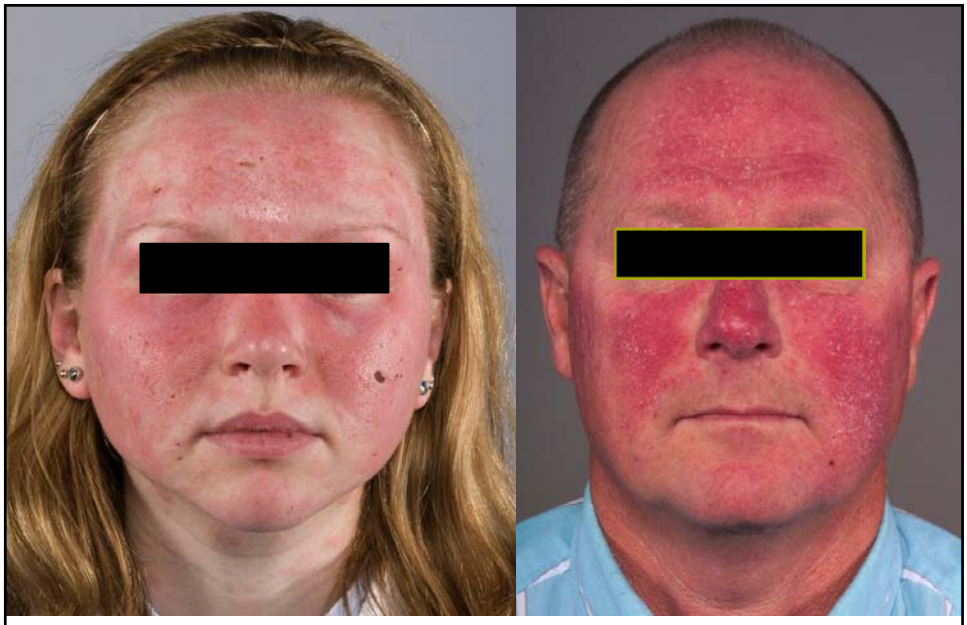
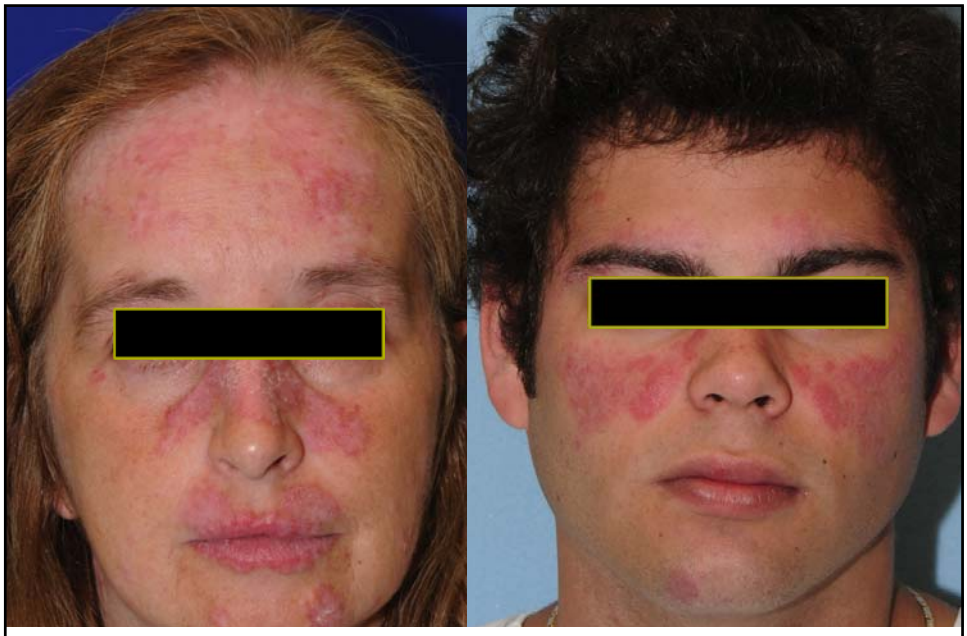


Photo distributed erythematous patches/thin plaques

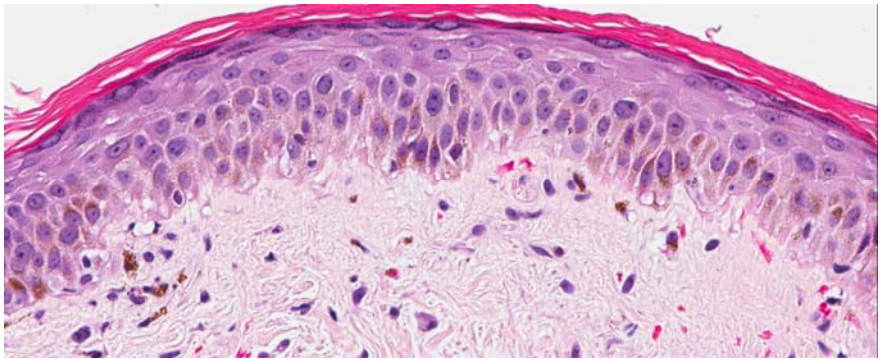
Malar Distribution aka "*Butterfly Rash*"



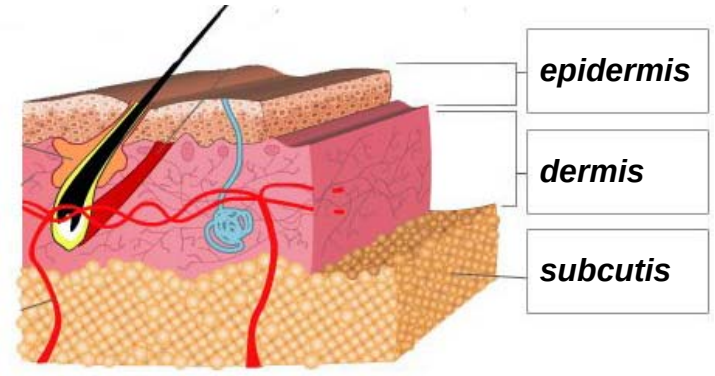
Systemic or Skin Limited?

Skin Biopsies in Lupus

- No difference between skin limited lupus and systemic lupus
- Common pattern: Vacuolar Interface



Forms of Cutaneous Lupus



"Inflammatory Sandwich"

Degree and localization of inflammation produces different forms of skin lupus that are distinctive

Forms of Cutaneous Lupus

Epidermal predominate

- Discoid Lupus

Dermal predominate

- Tumid Lupus

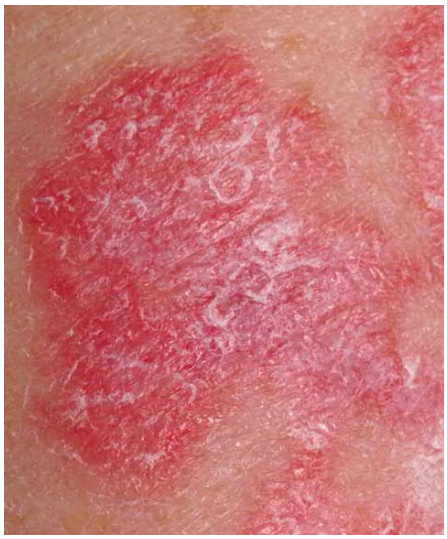
Subcutis (pannicular) predominate

- Lupus Profundus

Sometimes combined patterns are seen.

Discoid Lupus

- Most common form of cutaneous lupus
- Face, ears, scalp preferentially
- Ovoid or round shape
- Scarring and alopecia



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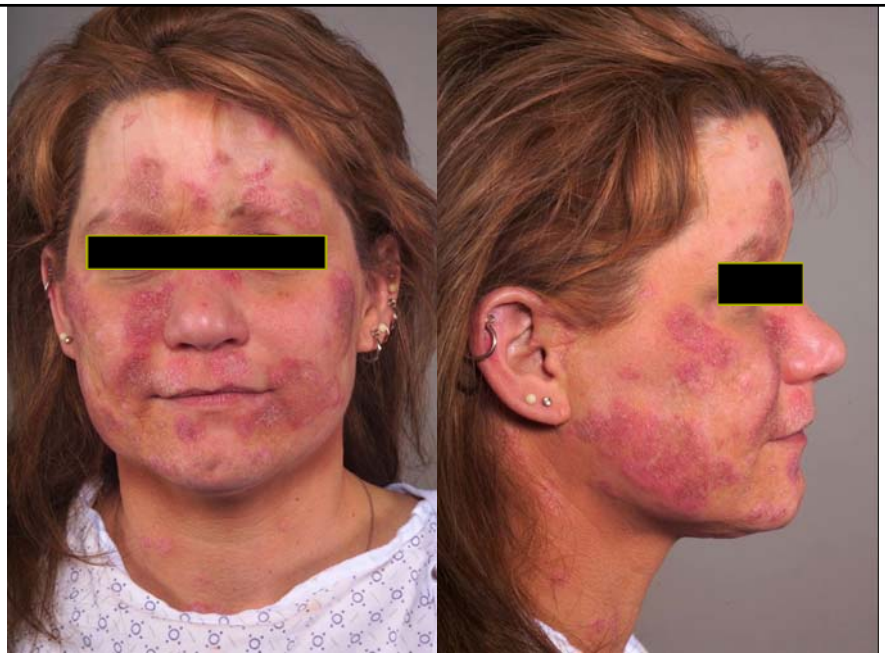

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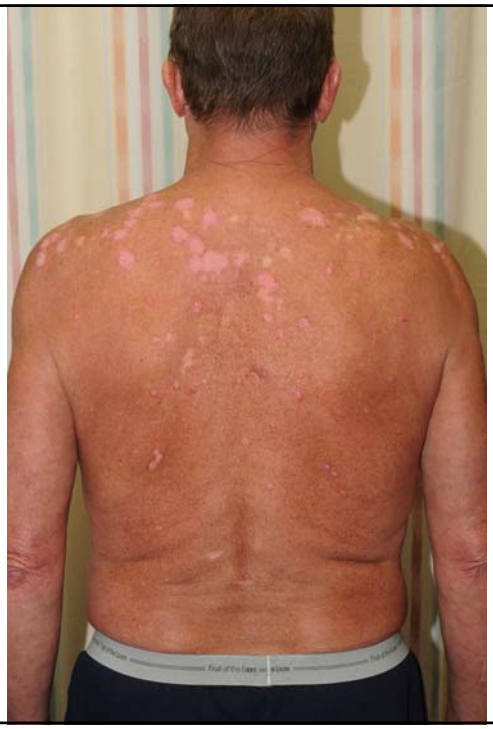
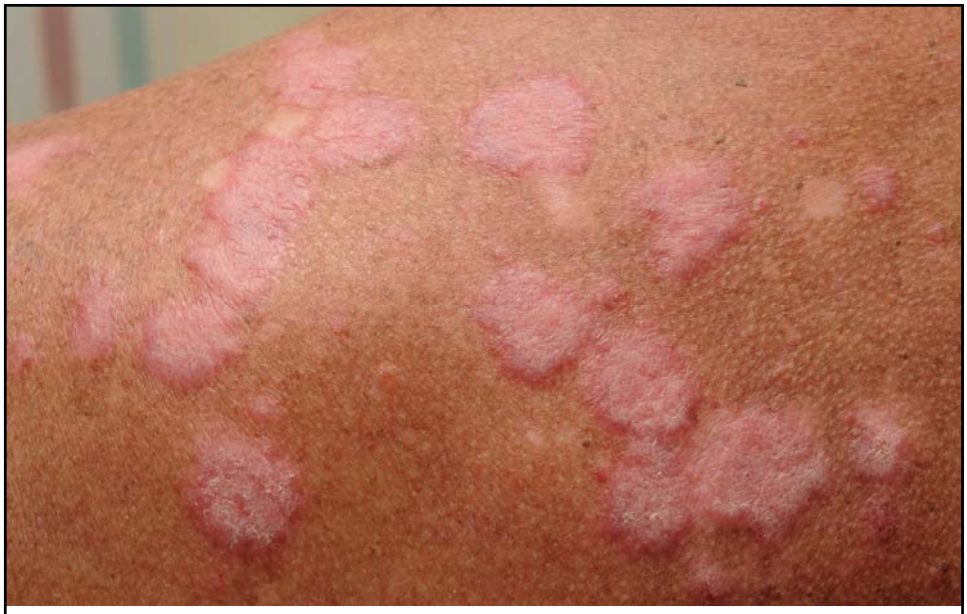
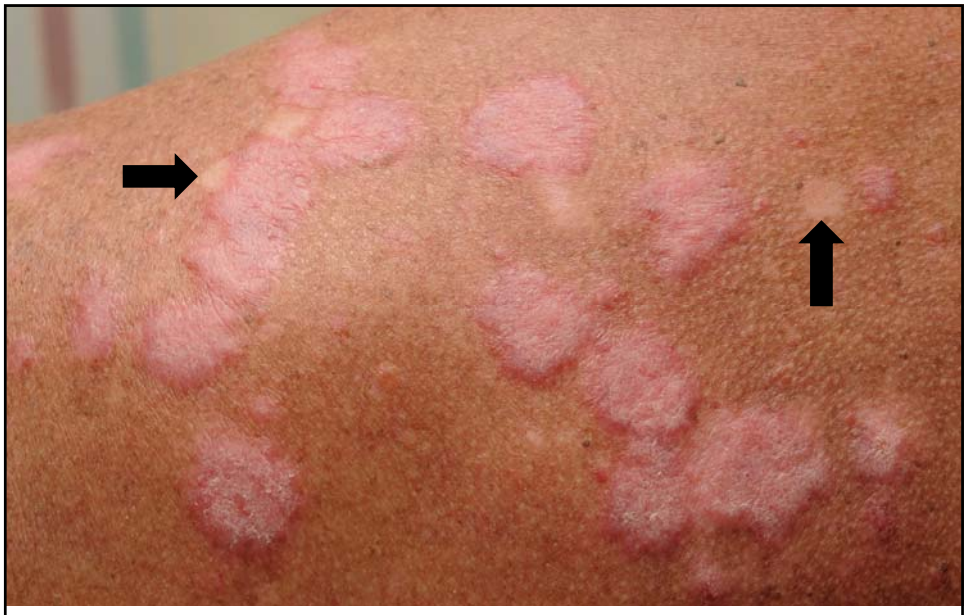
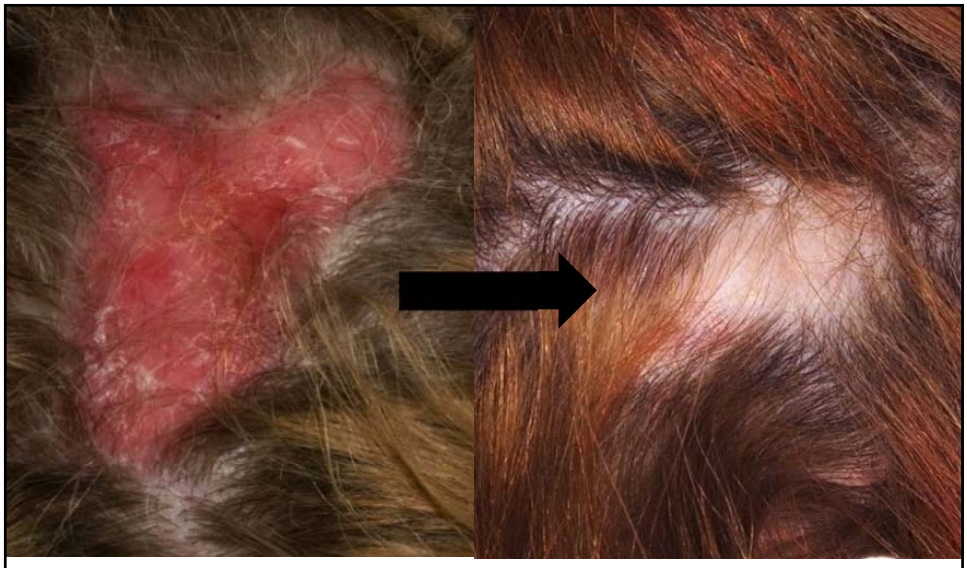




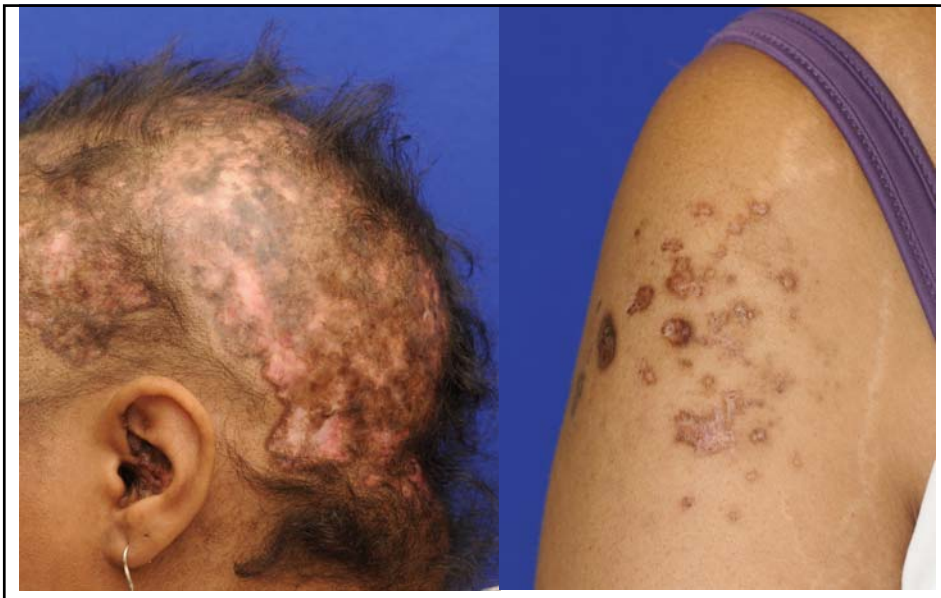
Discoid Lupus: Active lesions.
Ovoid erythematous scaling plaques. The erythema and scale are signs of active disease.



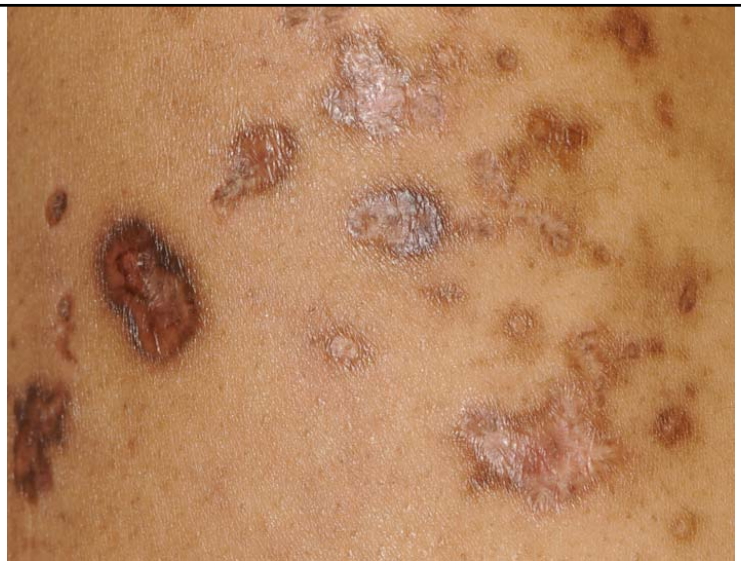
Discoid Lupus : burns out with time and or treatment. Produces ovoid hypopigmented smooth patches with scarring



ACTIVE DLE	INACTIVE DLE
Scaling red scaling alopecic plaque	Smooth white scarred alopecic patch

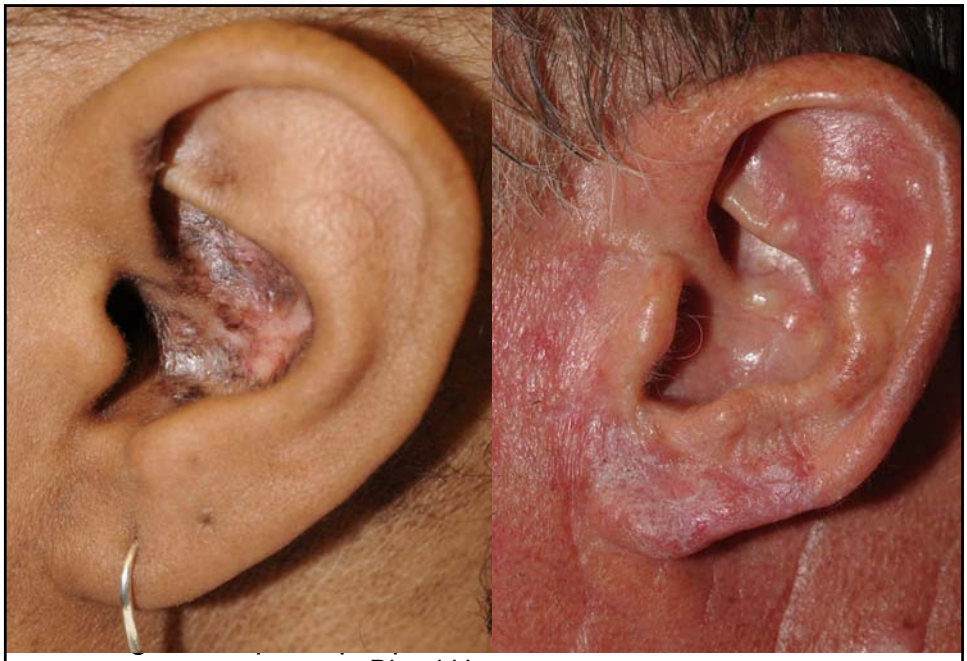


In patients of color, hyperpigmentation and hypopigmentation predominate. Erythema is generally less prominent.



ACTIVE DLE: hyperpigmented, scaling, scarring

INACTIVE DLE: centrally hypopigmented, peripherally hyperpigmented, scarring



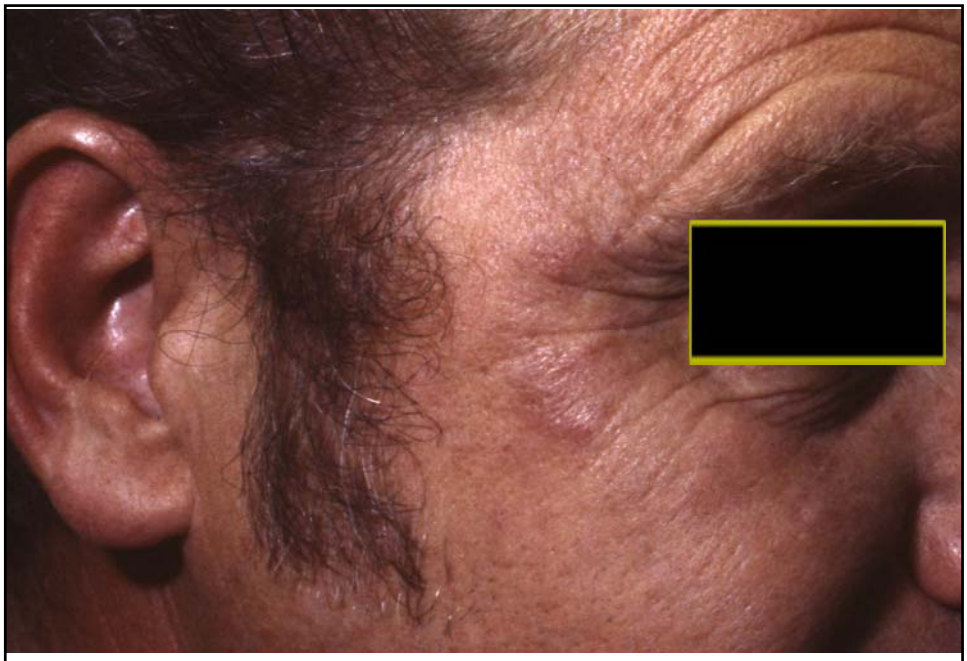
Discoid Lupus
Characteristic Ear Involvement

Tumid Lupus

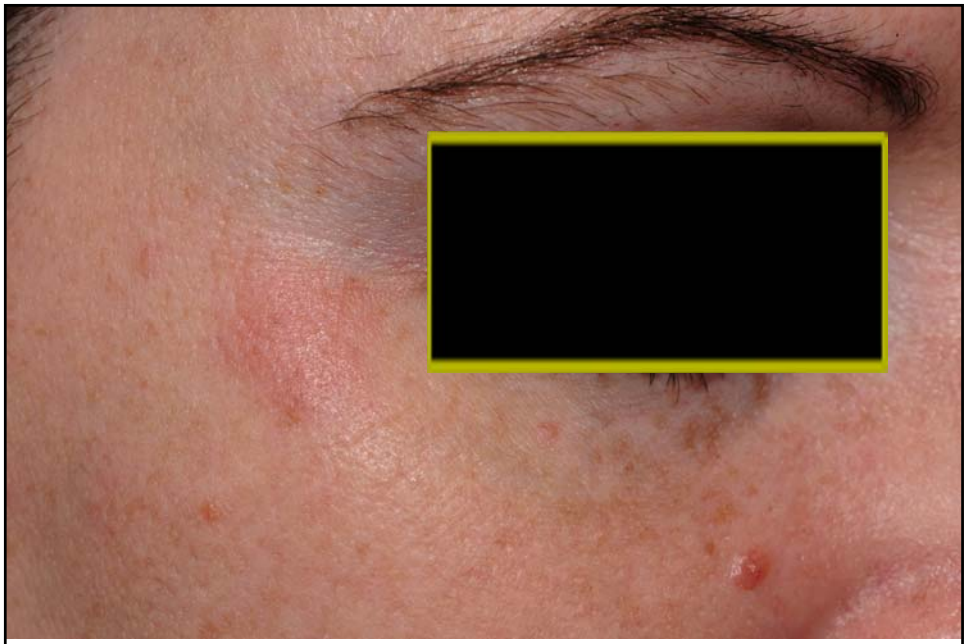
- No scaling
- No scarring but persistent
- Photodistributed on face and torso

- Inflammation restricted to dermis
  - Associated with mucin deposition

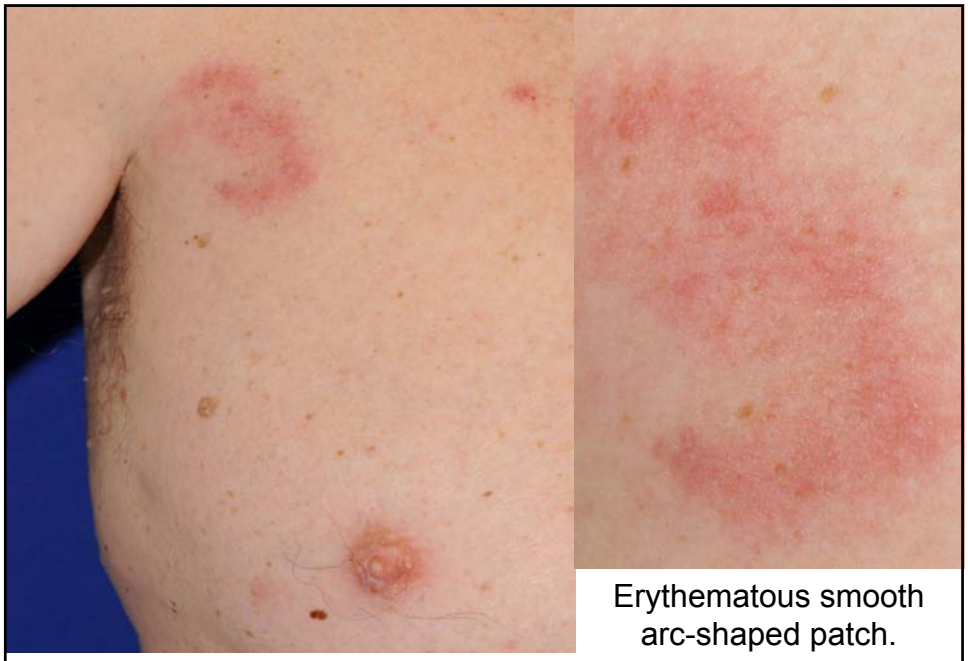
- Smooth erythematous papules and plaques
  - Sometimes annular or arc shaped



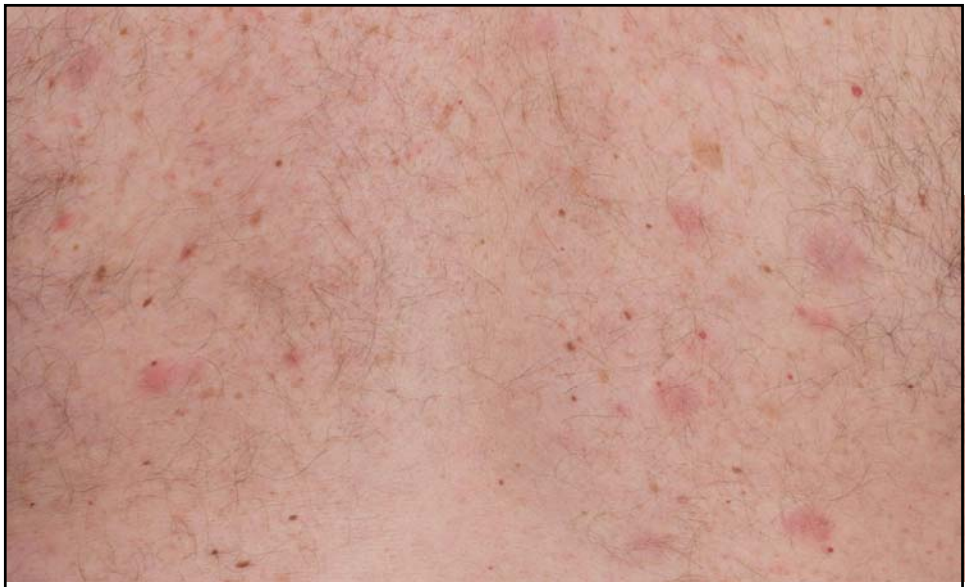
Smooth minimally erythematous periocular smooth plaques



Smooth minimally erythematous periocular smooth plaque.
No scarring



Erythematous smooth arc-shaped patch. No scarring.

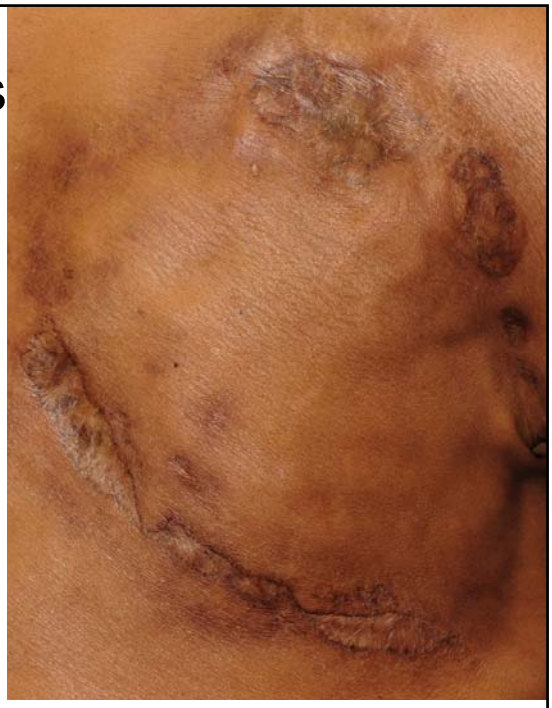


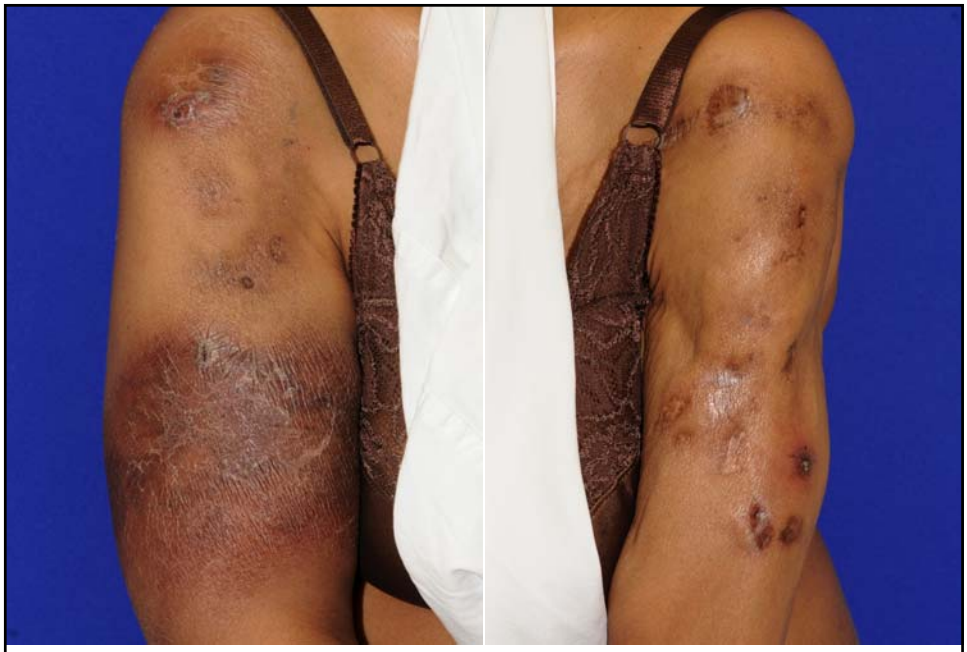
Smooth erythematous non-follicular papules. No scarring.

Subtle skin eruptions can have highly diagnostic skin biopsies

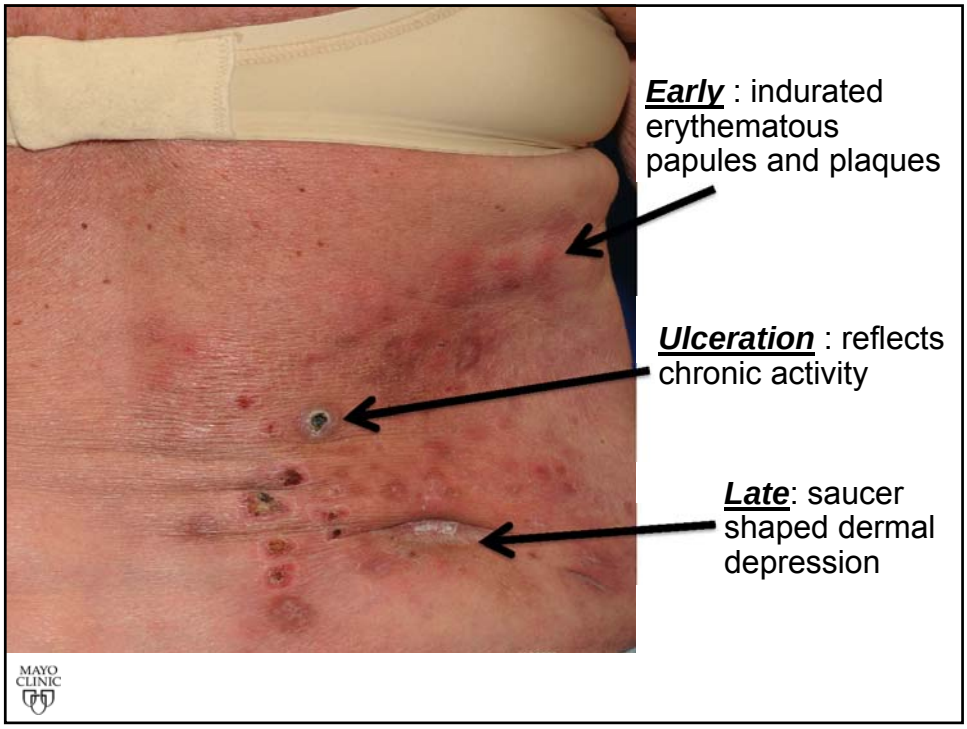
Lupus

- Inflammation in the subcutaneous fat
- Torso preferentially
- Forms dermally atrophic plaques : "*Saucer shaped depressions*"
  - Can ulcerate
  - Can sometimes show overlying discoid lupus





Marked subcutaneous atrophy. Overlying discoid lupus changes.

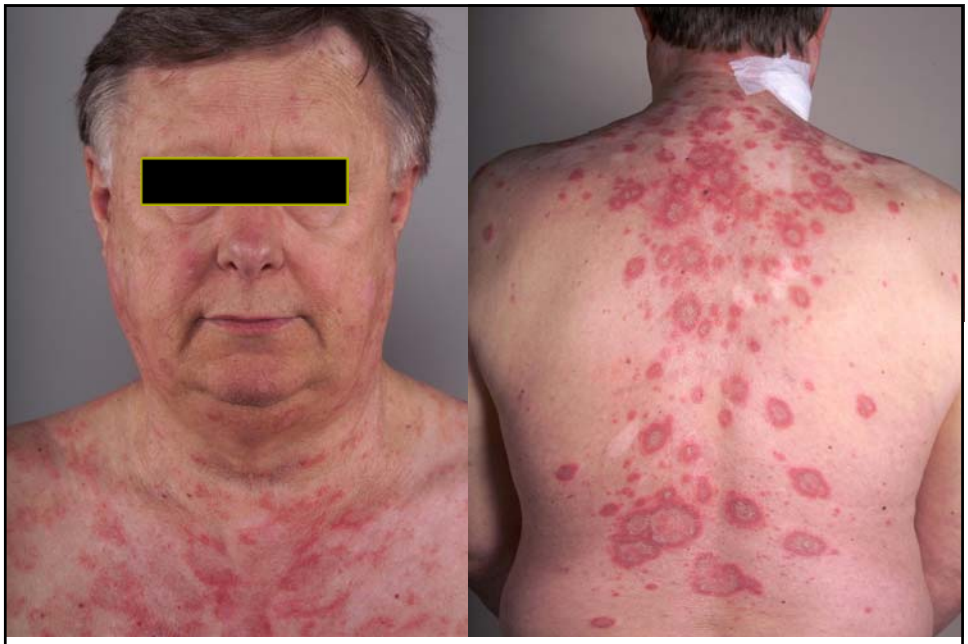


MAYO CLINIC

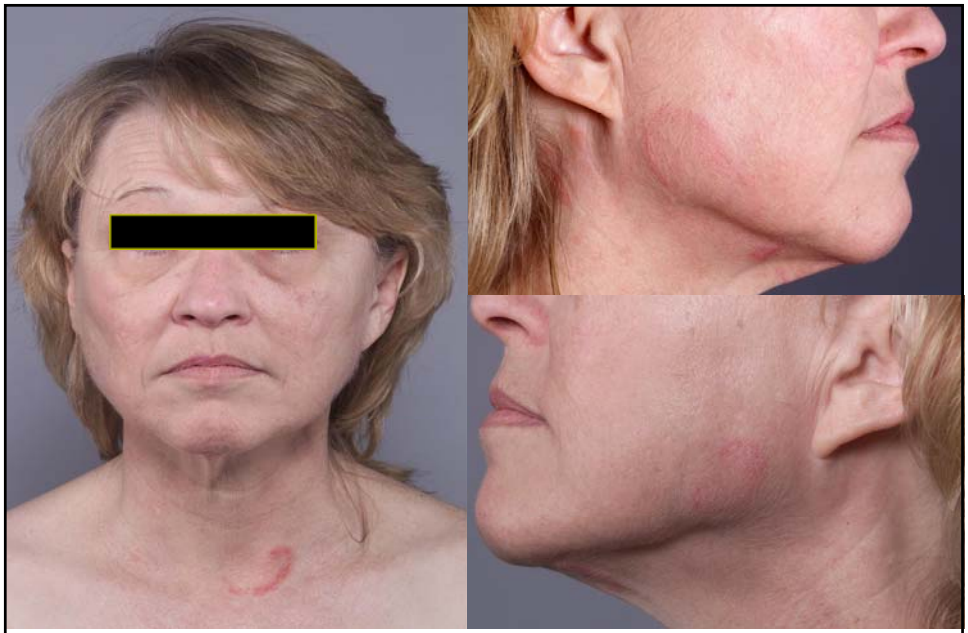
Subacute Lupus

- Distinct constellation of signs and symptoms
  - Photosensitive
  - Skin Eruption
    - Annular
    - Psoriasis-like
  - Limited systemic symptoms – arthritis, fatigue
  - ANA positive, Ro and/or La positive
- May meet ACR criteria for SLE but never progress and extra-cutaneous manifestations are otherwise mild.

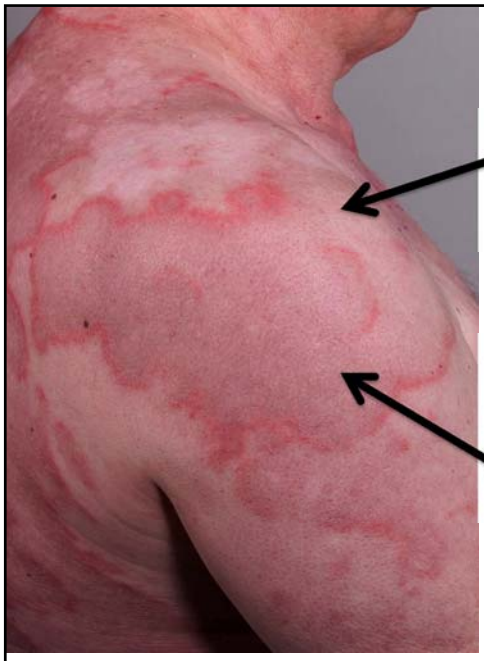
MAYO CLINIC



Photodistributed (face, chest, back)
annular erythematous scaling plaques



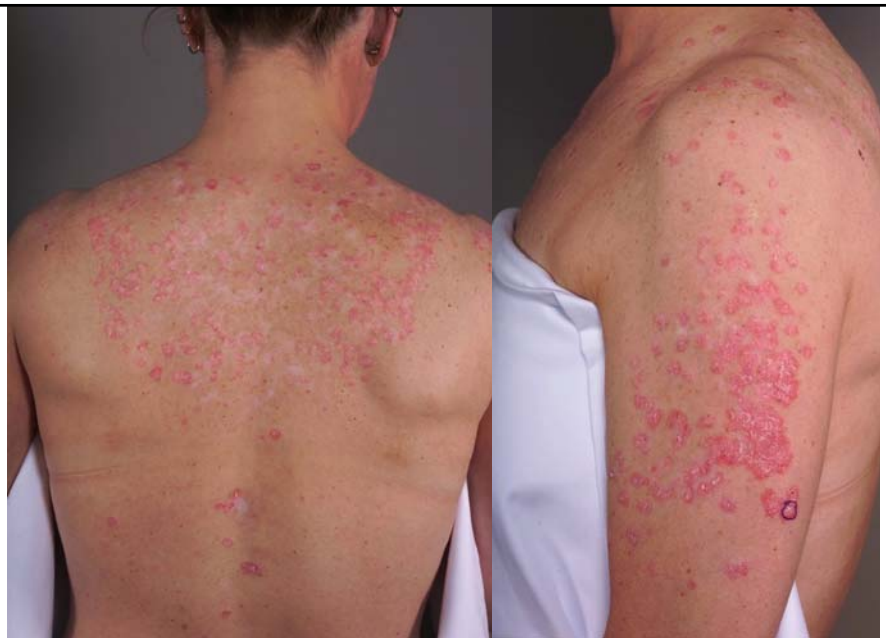
Photodistributed but preferential
lateral face involvement.



Discrete & confluent **annular** plaques

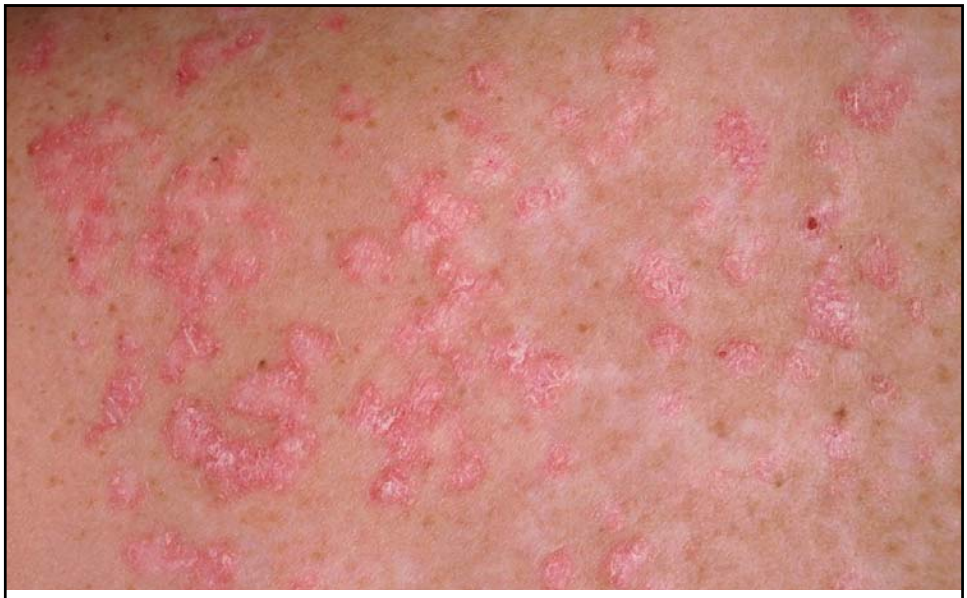
Post-inflammatory Dyspigmentation
<u>No scarring</u>

MAYO CLINIC

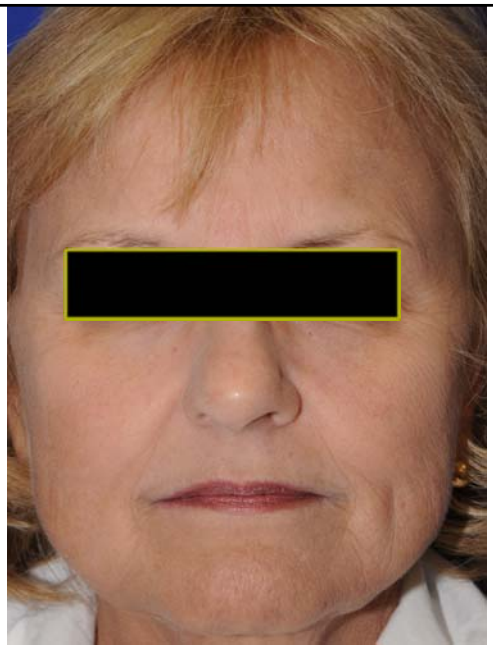


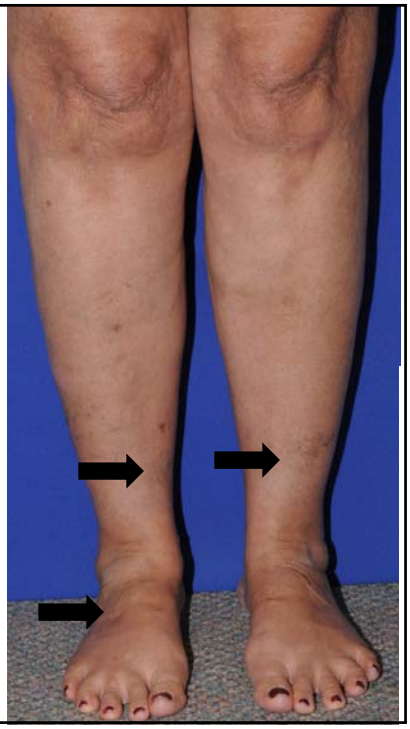
More commonly lesions resemble psoriasis.
Same photodistribution.

MAYO CLINIC

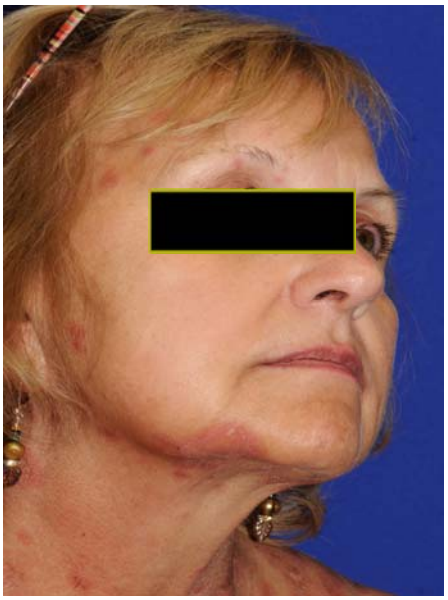


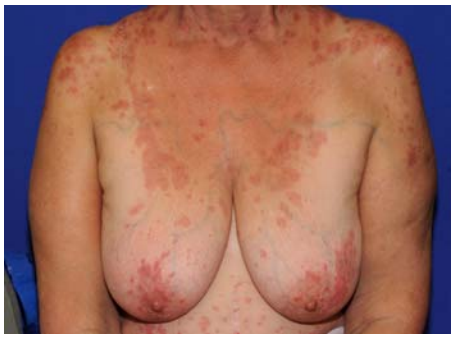
Psoriasis-like papules and plaques. Resolve <u>without</u> scarring but can temporarily leave areas of hypopigmentation

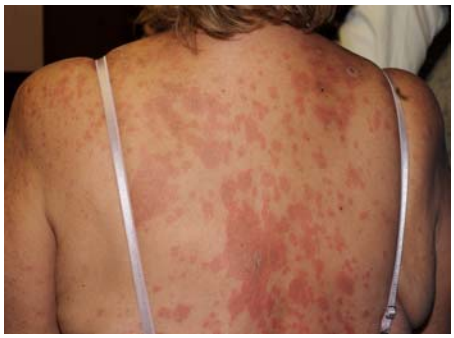




Arrows highlight Plaquenil induced hyperpigmentation







2 WEEKS LATER

Most presentations of subacute lupus are rapid and acute.

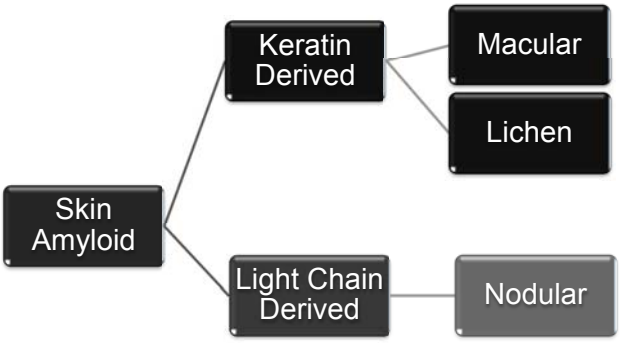
Sjögren's Syndrome

- Rarely has skin involvement:
  - Subacute lupus-like eruption
    - Less extensive often annular
  - Nodular amyloidosis
    - With chronic disease: 10-15 years after dx
    - Part of the lymphoproliferative process that underlies Sjogren's

Arthritis Rheum. 2008 Jul;58(7):1992-9.

Sjögren's syndrome and localized nodular cutaneous amyloidosis: coincidence or a distinct clinical entity?

Meijer JM, Schonland SO, Palladini G, Merlini G, Hegenbart U, Ciocca O, Perfetti V, Leijsma MK, Bootsma H, Hazenberg BP.
University of Groningen, Groningen, The Netherlands.



[1] Localized cutaneous (clonal) plasma cell proliferation
[2] Monoclonal Gammopathy
-- r/o Systemic Amyloidosis
-- r/o Multiple Myeloma

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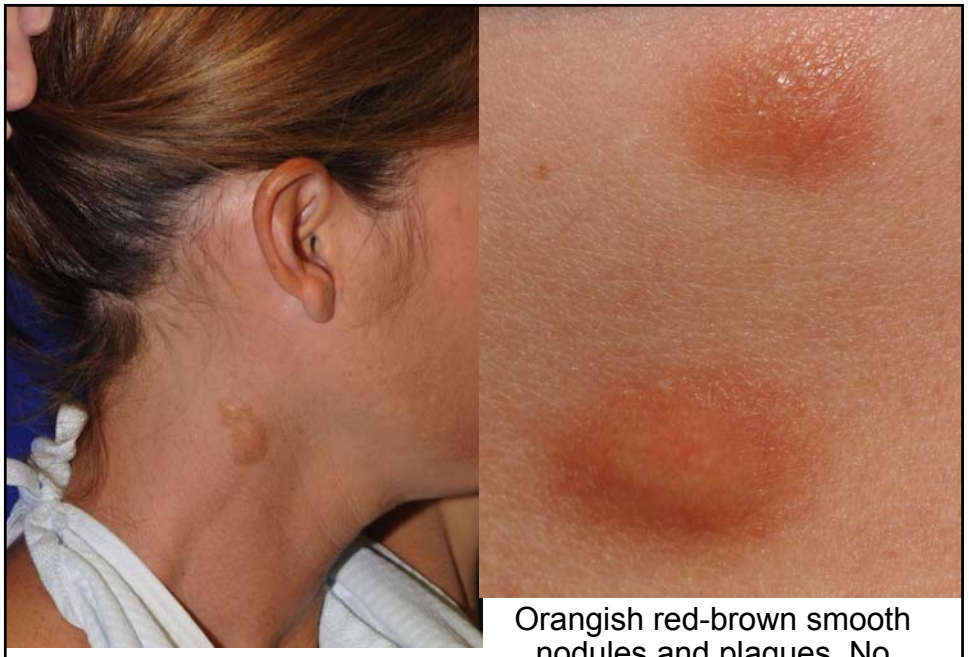

Orangish red-brown smooth nodules and plaques. No specific distribution.

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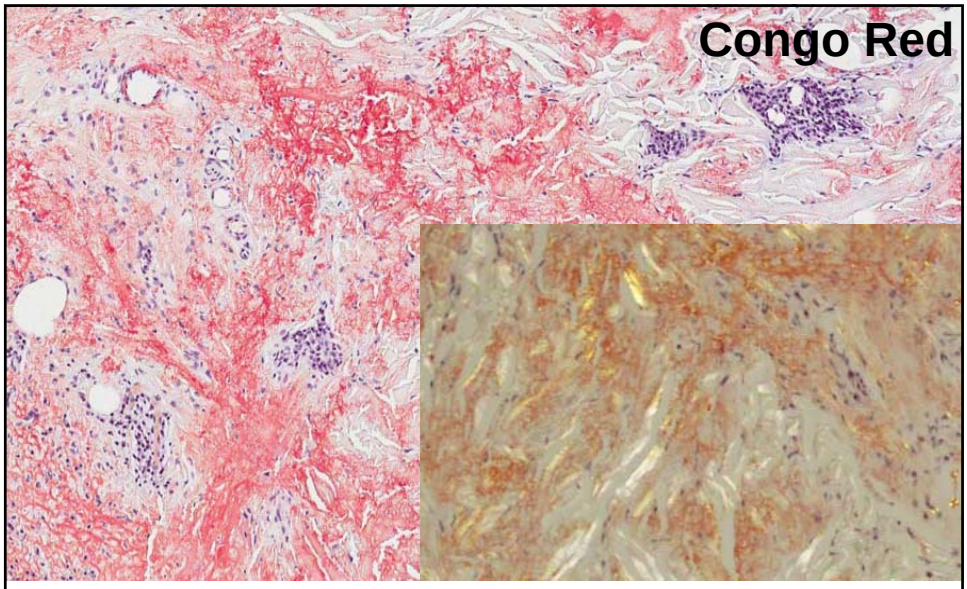

Diffuse dermal deposition of amyloid
Apple green birefringence with polarization

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Dermatomyositis

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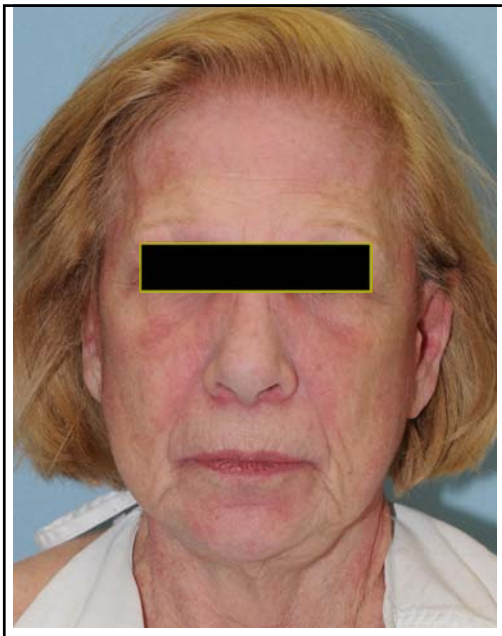

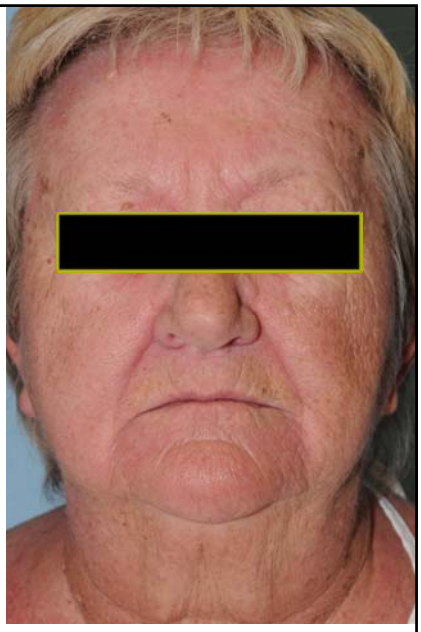

Heliotrope : violaceous patch, with variable edema, symmetrically involving the periorbital face and often forehead

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Notable Notes

The Heliotrope Sign of Dermatomyositis: The Correct Meaning of the Term *Heliotrope*

A common misconception is that the word *heliotrope* refers to the localization of the cutaneous lesions on sun-exposed areas. The terms *heliotrope* and *heliotropic* mean "turning towards the sun" and derive from Greek *helios* (ηλιος), meaning "sun," and *trepein* (τρέπειν), meaning "to turn." Over the years, the term *heliotrope* has been used to indicate things that either reflect or turn to the sun, including an instrument for land survey, a mineral, and, above all, a flower.

The heliotrope sign (HS) indicates a violaceous to dusky erythematous skin eruption, with or without edema, symmetrically involving the periorbital regions and often the forehead (**Figure**, A). Sometimes, a milder form appears as a slight discoloration of the eyelid border. Although it is rare in lupus erythematosus and scleroderma, the HS is a typical feature of acute dermatomyositis. The HS refers to the flower *Heliotropium*, a genus of flowering plants belonging to the family of Boraginaceae. The genus *Heliotropium* includes hundreds of different species, among which *Heliotropium peruvianum* is the most representative and shows small, fragrant, purplish petals (Figure, B). The color heliotrope has been defined in relationship to this flower and has received specific color coordinates that are registered in *A Dictionary of Color*.[1] The similarity between the hue of the periorbital rash of dermatomyositis and that of the petals of the flower justifies the use of the term *heliotrope*.

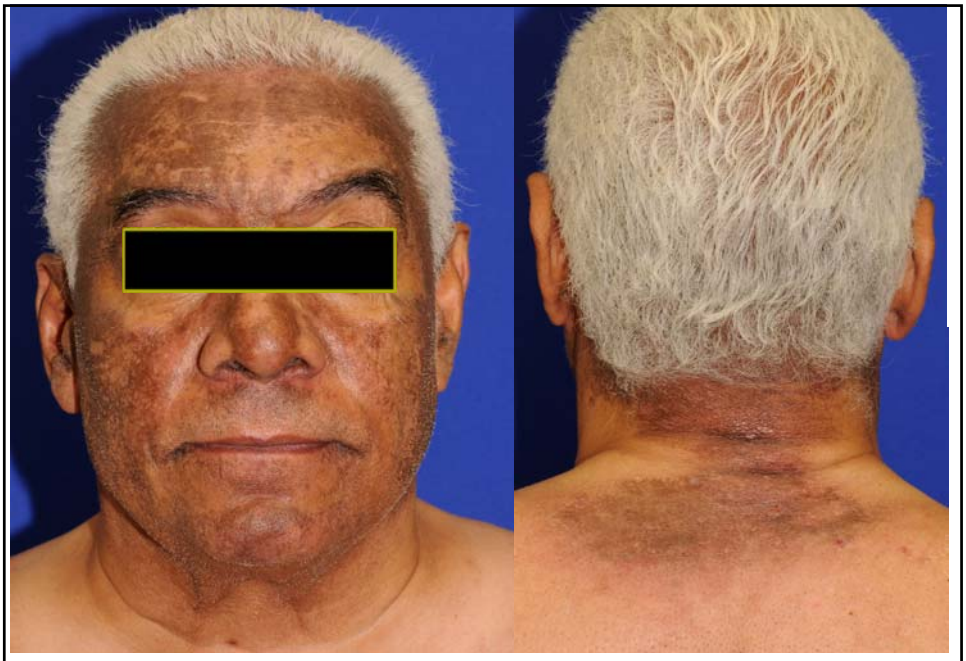
The flower that turns to the sun in the European countries is the sunflower (*Helianthus annuus*), which Van Gogh immortalized with a vivid yellow color (Figure, C). Therefore, in the absence of knowledge about *H peruvianum*, the HS associated with dermatomyositis would not make sense to European dermatologists, who have their own heliotropic flower, but with a different color. The correct etymology of the term *heliotrope* may be found in the Rheumatology Image Bank website, which mentions the "association rash-flower."[2] Consideration of the etymology of medical terms may be useful to better understand their significance.

Teresa Russo, MD
Vincenzo Piccolo, MD
Eleonora Ruocco, MD, PhD
Adone Baroni, MD, PhD

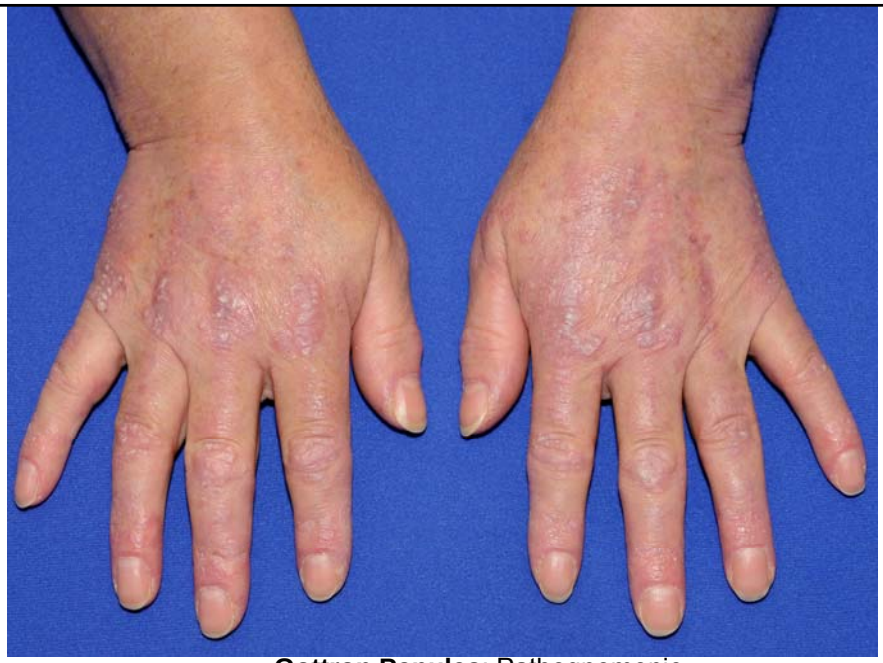
Figure. A, Heliotrope sign of dermatomyositis; B, *Heliotropium peruvianum*; and C, *Helianthus annuus*.

Author Affiliations: Department of Dermatology and Venereology, Second University of Naples, Naples, Italy.
Contact Dr Russo at c/o II Policlinico, Edificio 3, Quarto Piano, Via Pansini 5, 80131 Napoli, Italy (russo.teresa87@gmail.com).

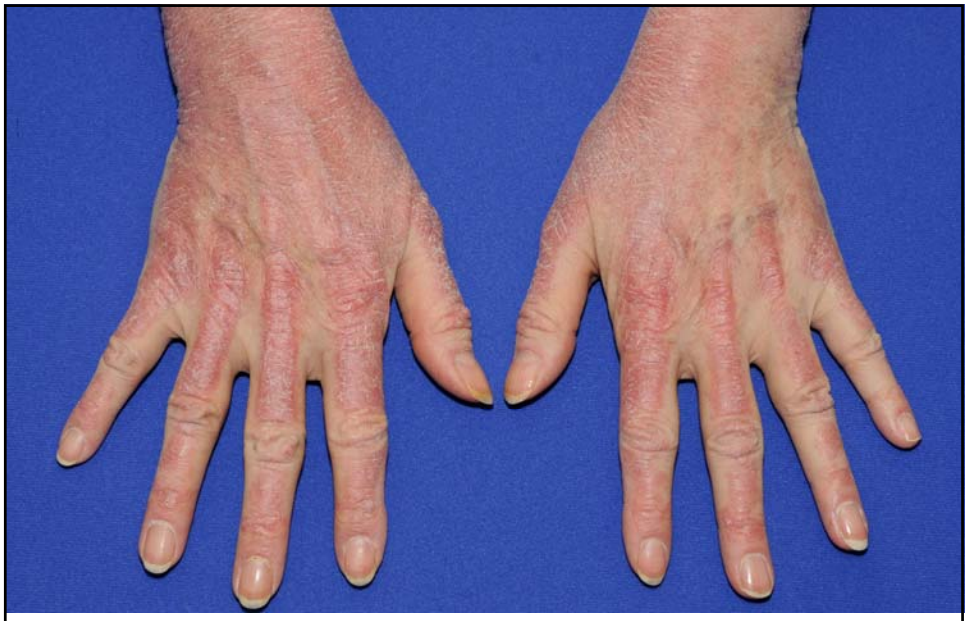
MAYO CLINIC



Highly photosensitive but often not symptomatic

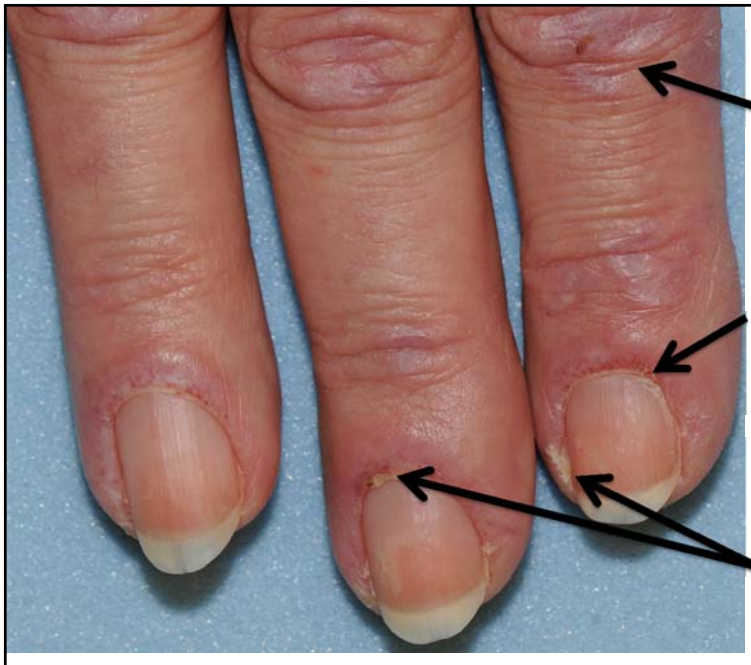


Gottron Papules: Pathognomonic
Violaceous papules overlying bony prominences usually over knuckles



Gottron Papules: May be become confluent and associated with variable erythema and scaling of the dorsal hands

MAYO CLINIC



Gottron Papule

Cuticular Erythema: telangiectasia commonly

Cuticular Scaling:

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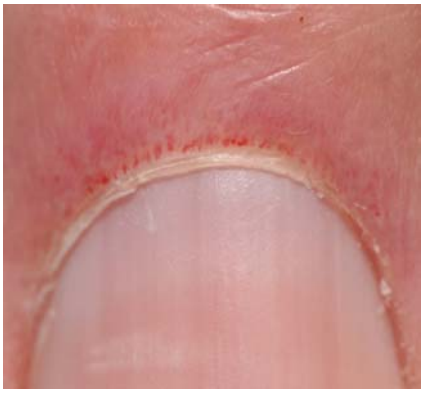
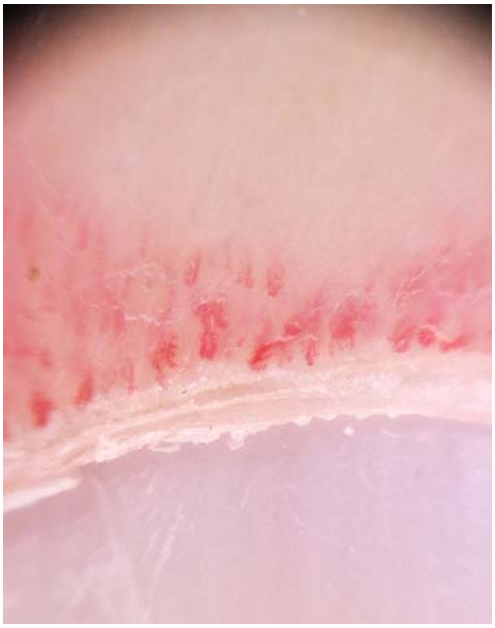
Cuticular Erythema:

Nail-fold telangiectasias consisting of loop dilation and arborization





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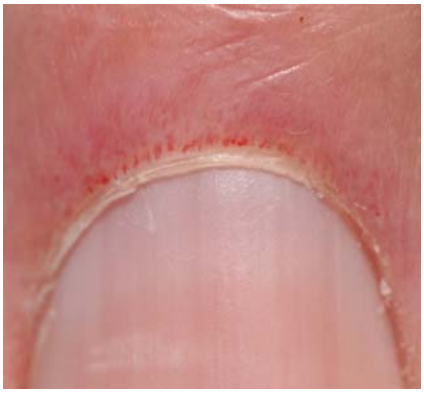
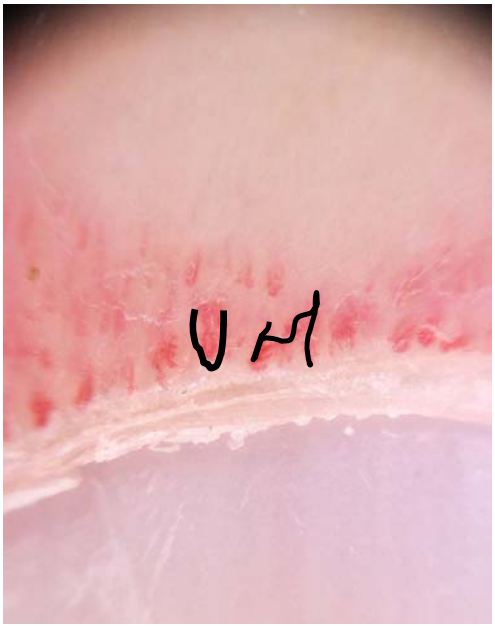
Cuticular Erythema:

Nail-fold telangiectasias consisting of loop dilation and arborization





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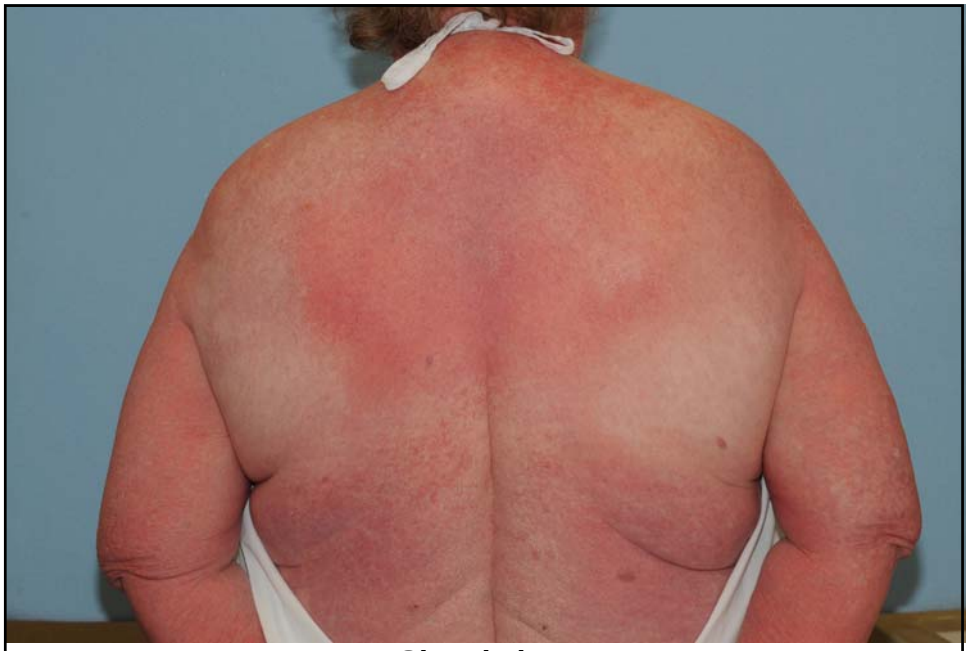
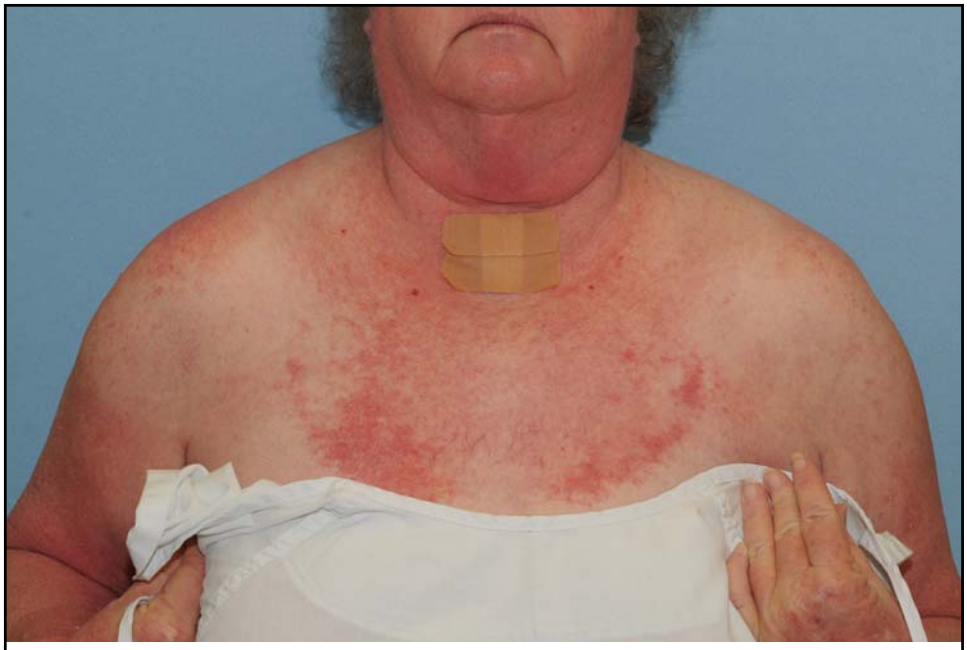
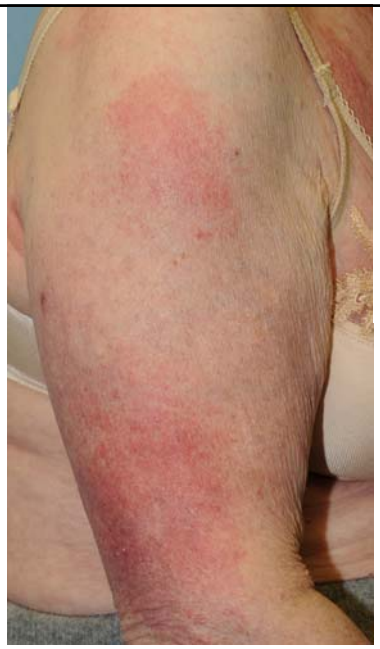
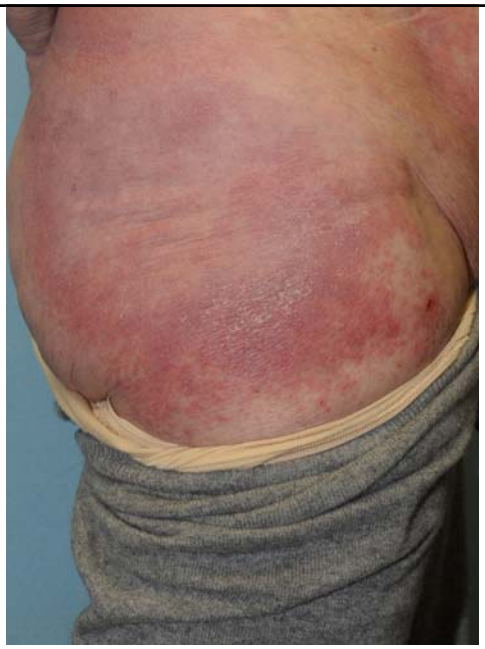


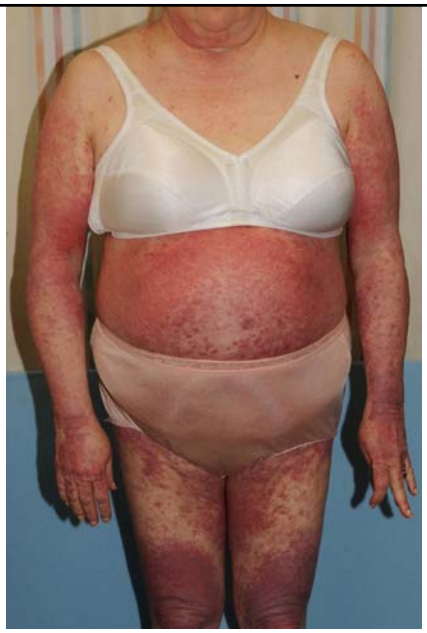
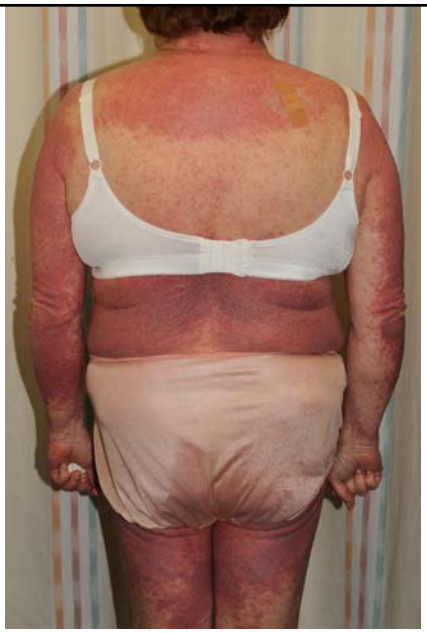
Shawl sign:
Smooth patches over neck, upper back, and shoulders



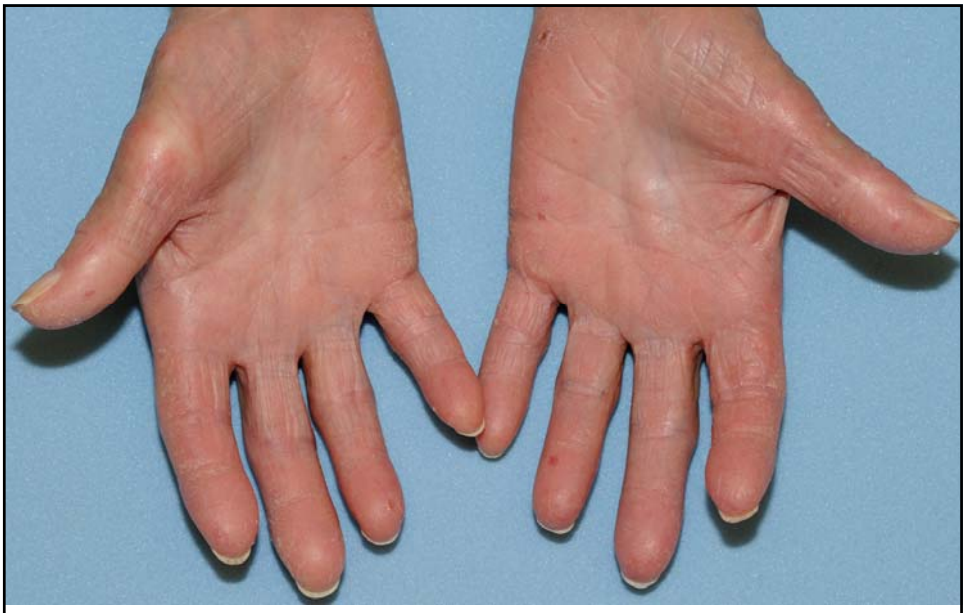
V-sign:
Smooth patches over neck and upper chest

Extensor violaceous erythema common
Hollister Sign: involvement of the lateral hips

Livid intense erythema with dusky areas and/or frank necrosis is associated with malignancy



Mechanic's Hands
Hyperkeratotic scaling and fissuring of the hands
Associated with underlying interstitial lung disease

Anti-tRNA Synthetase Syndrome

Myositis specific antibodies against the enzyme that links amino acids to transfer RNA

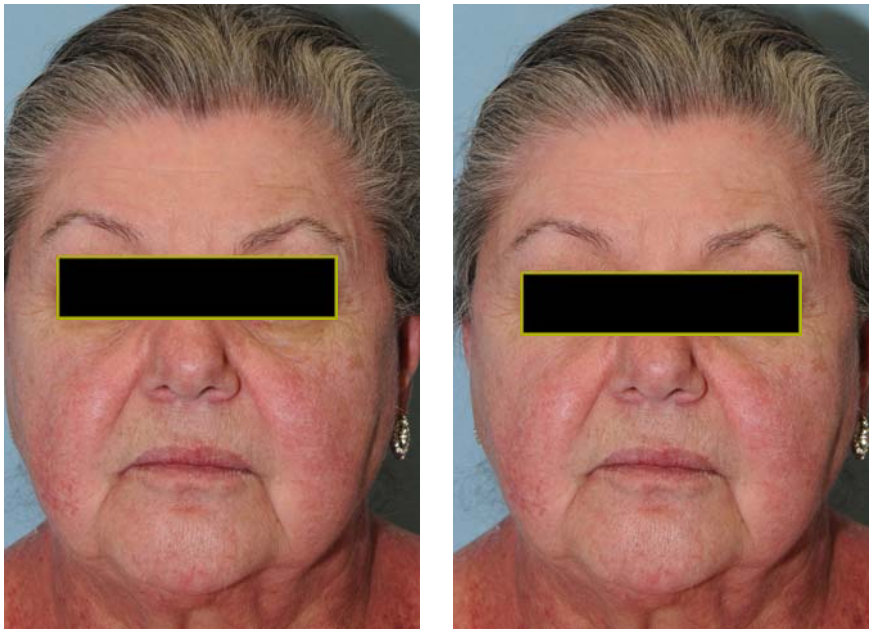
Jo-1: Histidine, PL-7: Threonine, PL-12: Alanine, etc..

Feature	%
Anti-tRNA Synthetase Ab	100%
Myositis	> 95%
Interstitial Lung Disease	> 60%
Arthritis	> 50%
Raynaud's Phenomena	> 40%
Mechanic's Hands	**30%**
Fever	20%

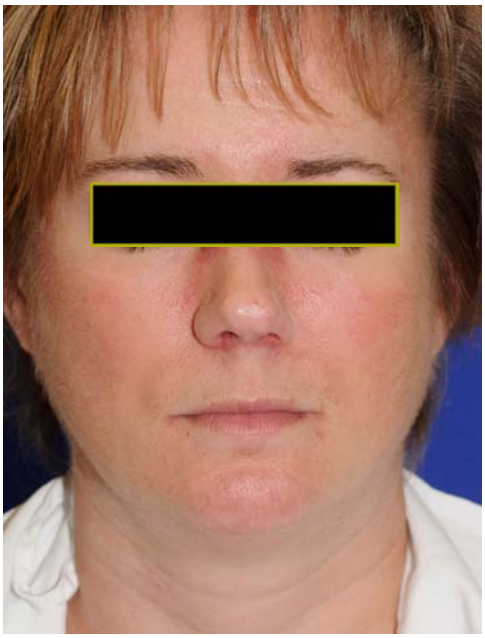
Mechanic's Hands
Not specific to Dermatomyositis.
Can be seen as isolated sign in other conditions

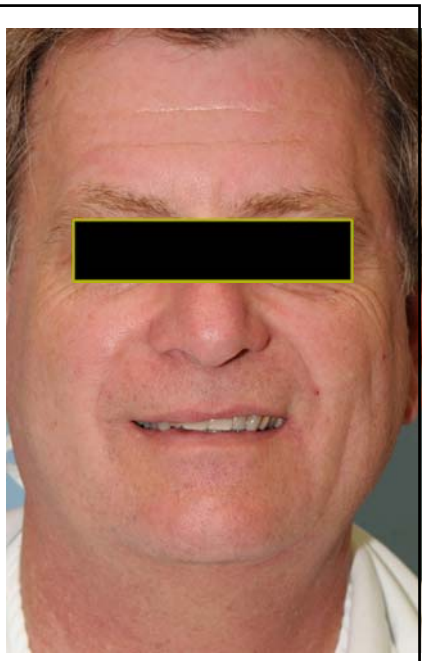
Dermatomyositis

- Skin findings are heterogeneous
  - Incomplete/absence of any sign
    - Slow insidious presentations
  - Overlap with other conditions
    - Biopsy cannot separate from lupus
- Other confounders:
  - Absence of muscle weakness
  - Negative serologies
    - ANA negative in up to 20% of cases
- Skin signs are
    - Heterogeneous: many, and incomplete



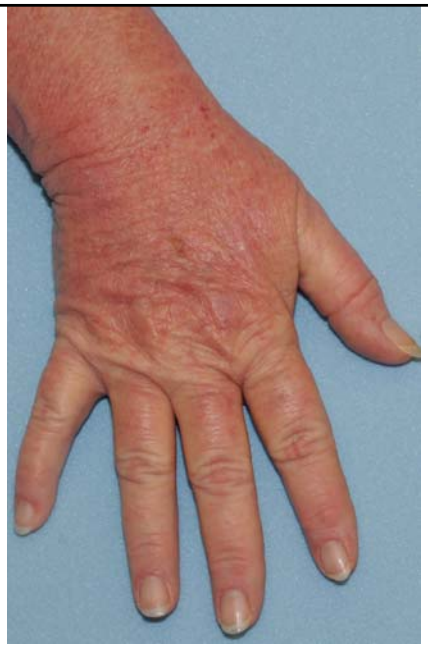
Heliotrope often not prominent

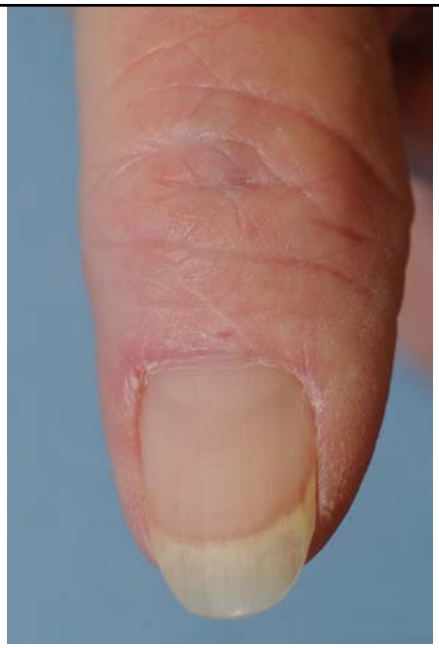




Seborrhea-like Heliotrope

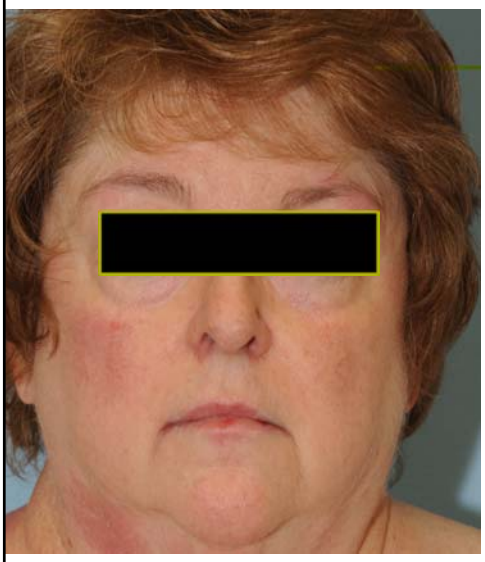
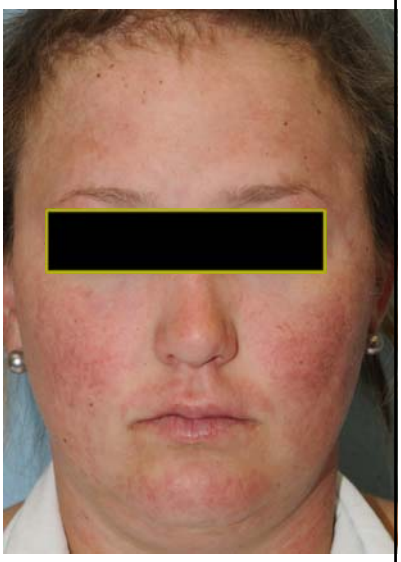
No Heliotrope



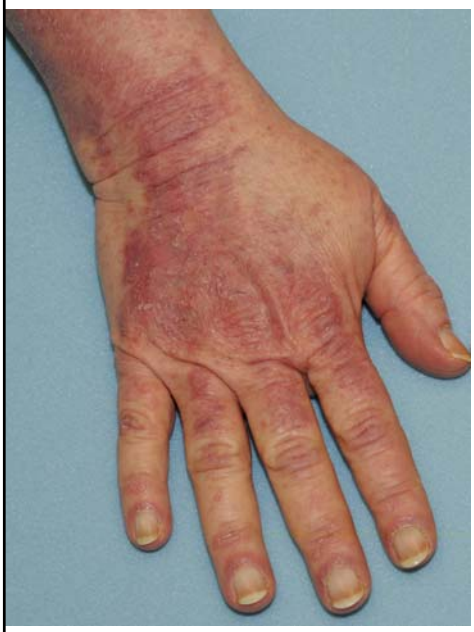
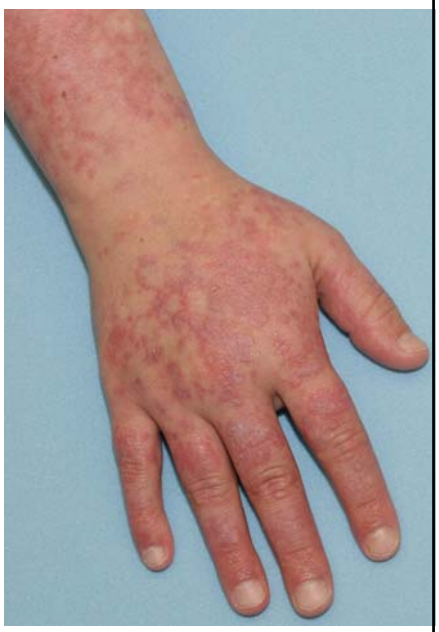


Minimal Gottron Change

Subtle Cuticular Change

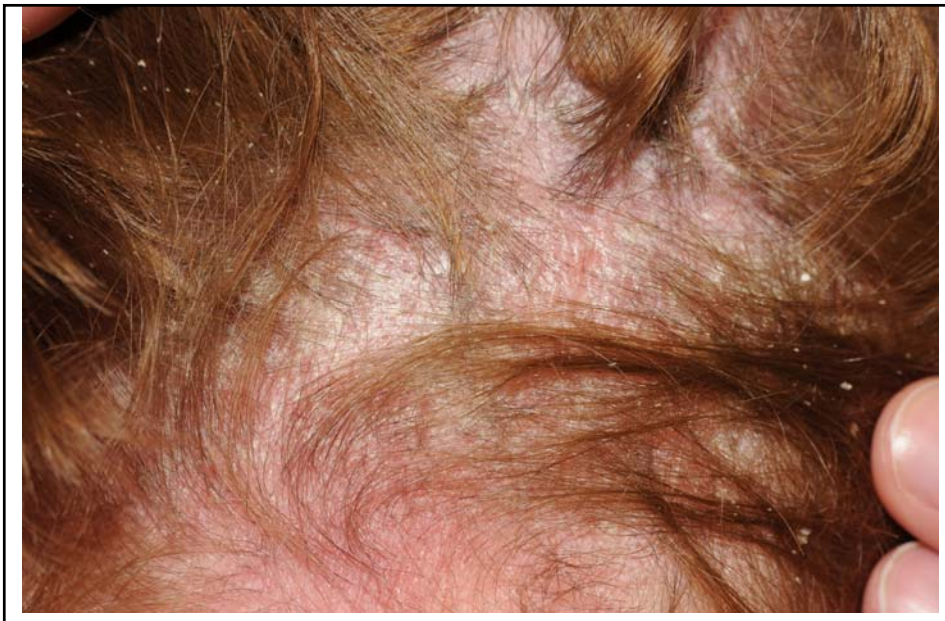
SLE or DM?

SLE or DM?

Dermatomyositis : Other Clues

- Pruritus
  - DM – often intense; unique among all connective tissue disorders
  - SLE – not pruritic
- Scalp Dermatitis
  - Resembles seborrheic dermatitis or psoriasis
    - No scarring
    - No significant alopecia



Dermatomyositis Scalp Dermatitis
Often pruritic. Resembles seborrheic dermatitis or psoriasis.
No scarring or extensive alopecia.

Multicentric Reticulohistocytosis vs DM

Dermatology. 2011;222(2):102-8. Epub 2011 Jan 20.

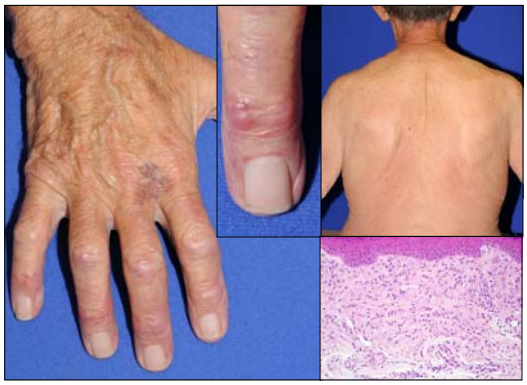
Multicentric reticulohistiocytosis with dermatomyositis-like features: a more common disease presentation than previously thought.

Fett N, Liu RH.
Philadelphia VA Medical Center, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. nicole.fett@uphs.upenn.edu

Systemic histiocytic disorder
- Skin Lesions
- Inflammatory arthritis

Mimics some features of DM:
- Muscle weakness
- V & Shawl sign
- ¼ malignancy association

Gottron-like lesions on the hands very common



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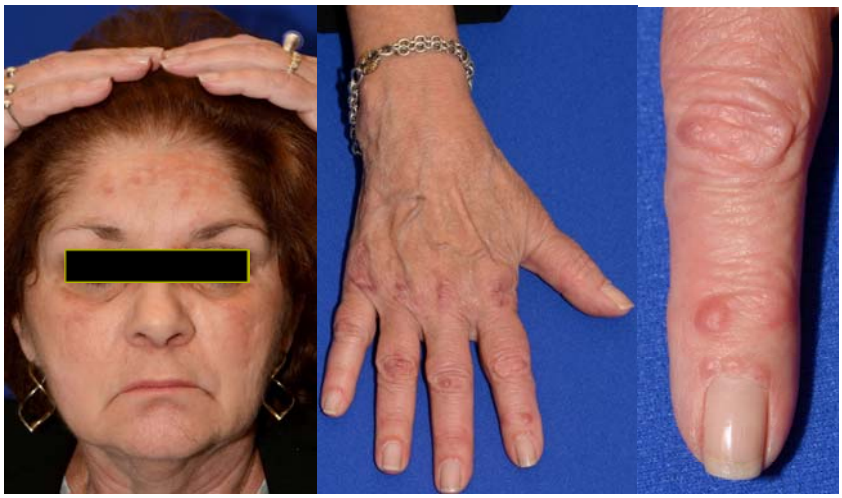
Multicentric Reticulohistocytosis

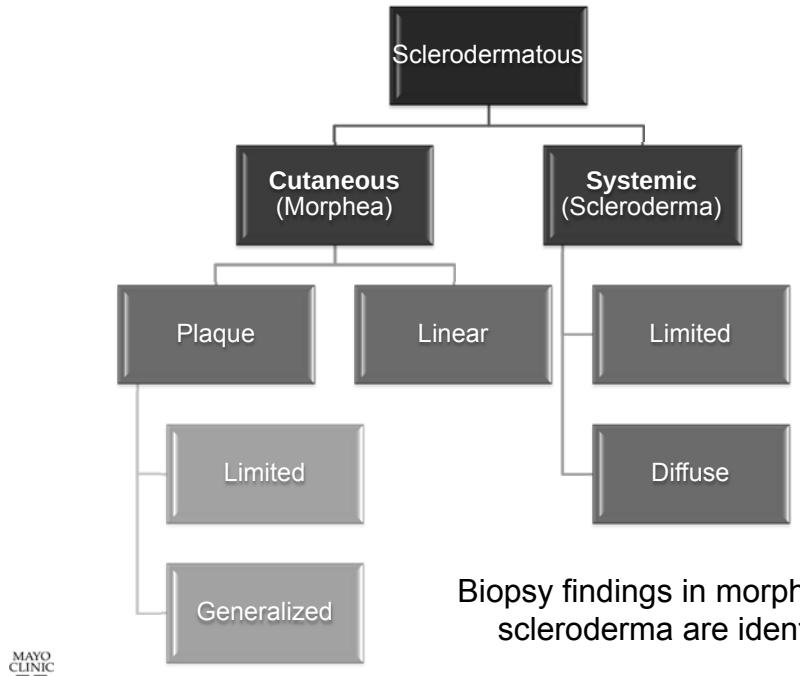


Discrete and confluent skin-colored to reddish-brown papules involving face and dorsal hands

"String of Pearls"
"Coral Beads"

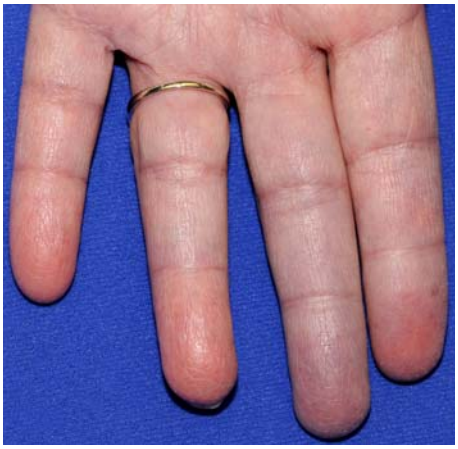
MAYO CLINIC

Scleroderma



Biopsy findings in morphea and scleroderma are identical.

Scleroderma



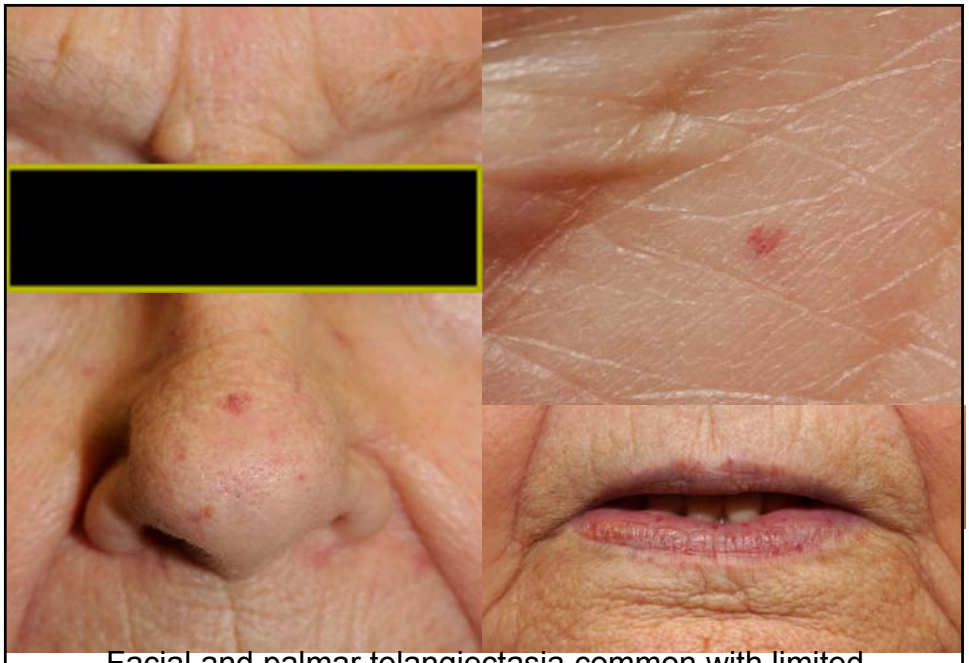
Always Raynaud's

Limited

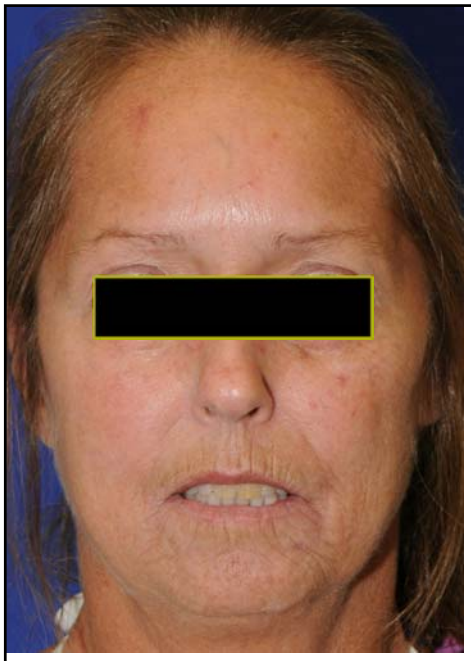
- Face
- Acral
- "CREST" phenotype
  - Anti-centromere+

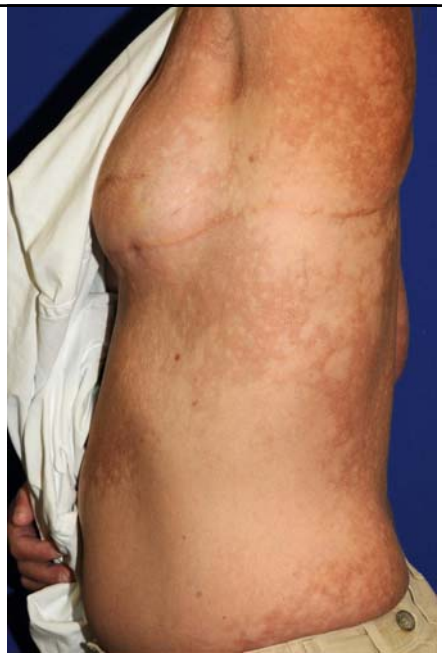
Generalized

- Face
- Acral
- Truncal
- Scl-70+ other end-organ



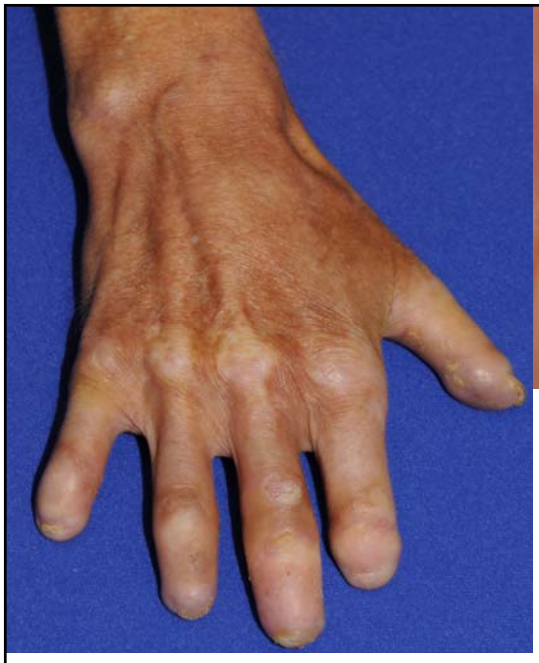
Facial and palmar telangiectasia common with limited scleroderma





Perioral Furrowing

Mottled tan-brown patches



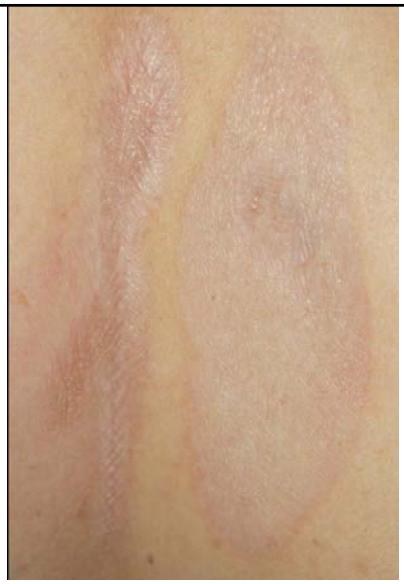
Cuticular Change:

Nail-fold capillary hyperplasia consisting of loop dilation and knock-out

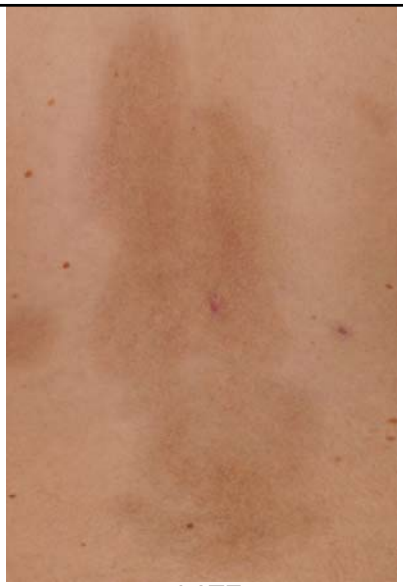
Sclerodactyly:

Progressive distal sclerosis along with vasospasm can result in nail loss and distal ulcers

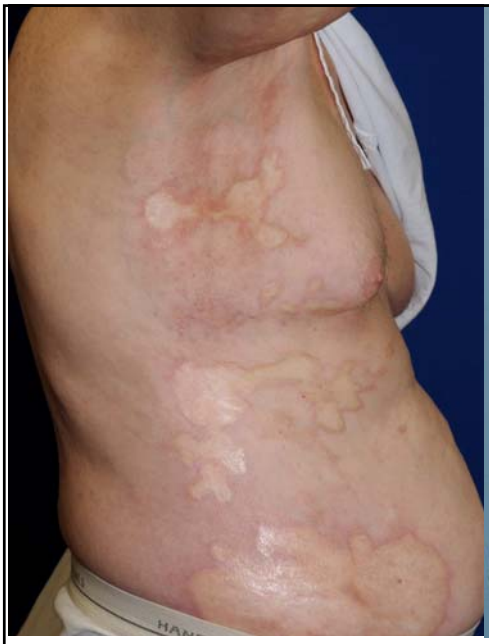
Localized Scleroderma (Morphea)

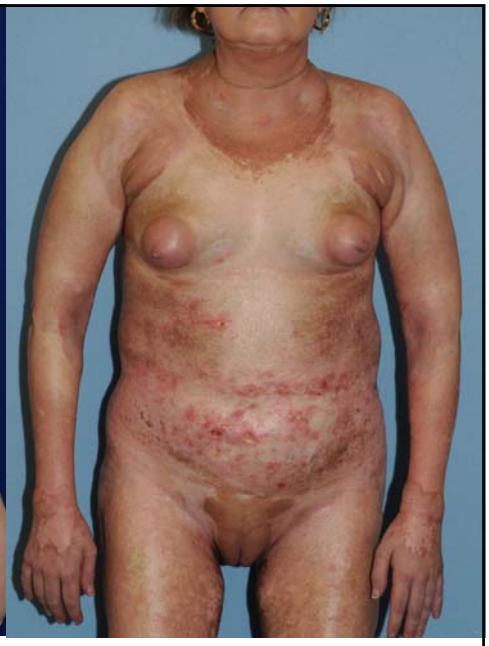


EARLY
Hypopigmented indurated plaque with a dusky erythematous to violaceous rim



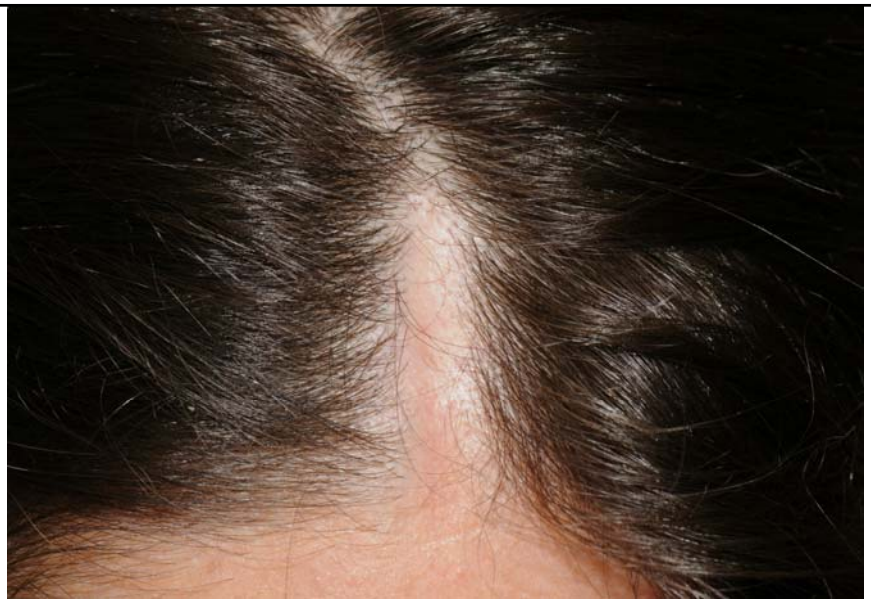
LATE
Smooth tan-brown ill-defined patches



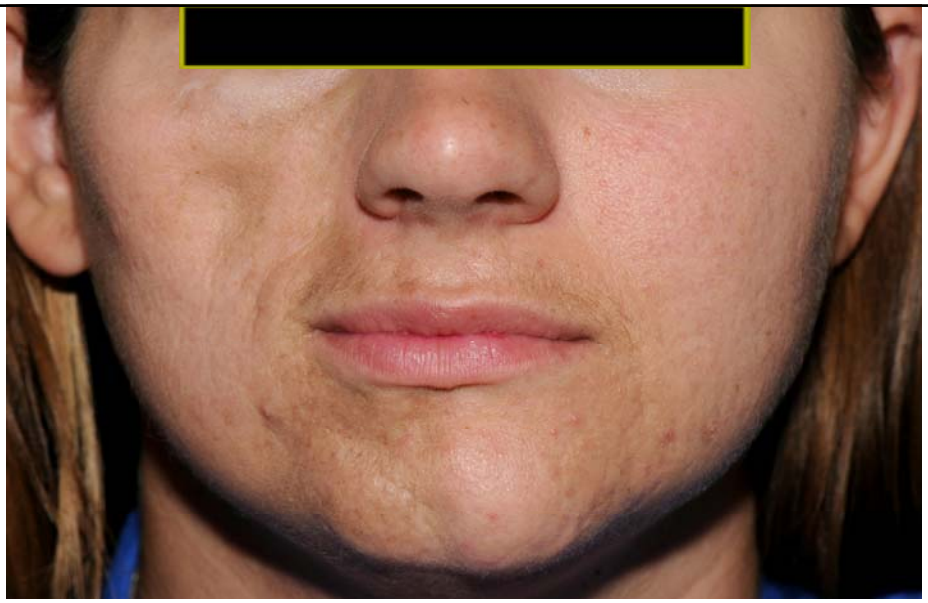


Extensive generalized cutaneous involvement

Rare pan-sclerotic presentation



Coup de Sabre : Frontal linear scleroderma
Linear band of scleroderma involving frontal-parietal scalp
Produces alopecia



Parry-Romberg Syndrome : Idiopathic hemifacial atrophy
Possible variant of linear morphea
Distinctive feature is pronounced soft tissue loss

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Rheumatoid Arthritis

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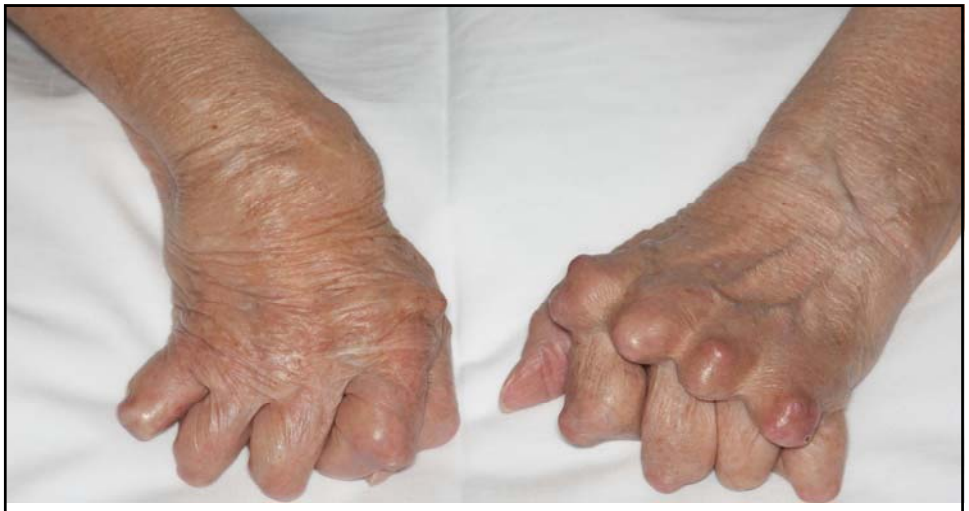

Rheumatoid Nodules: Subcutaneous nodules over bony prominences, extensor surfaces or in juxta-articular areas

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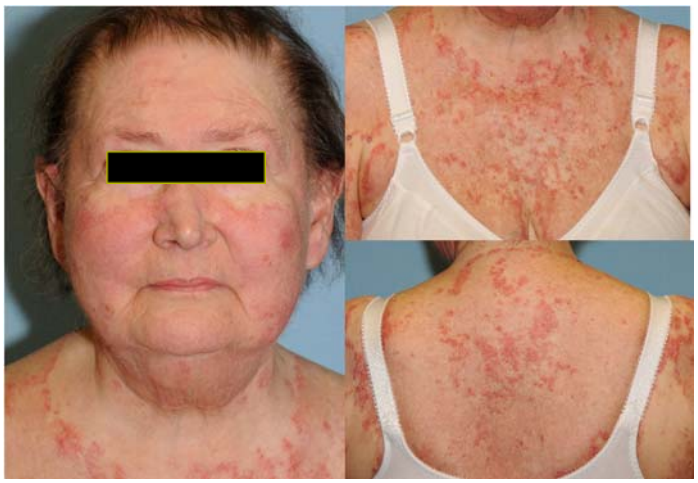
TAILS - TNF-α antagonist-induced lupus-like syndrome



Usually seen in the setting of Rheumatoid Arthritis
Reported with etanercept and infliximab
Can switch to another TNF-α inhibitor

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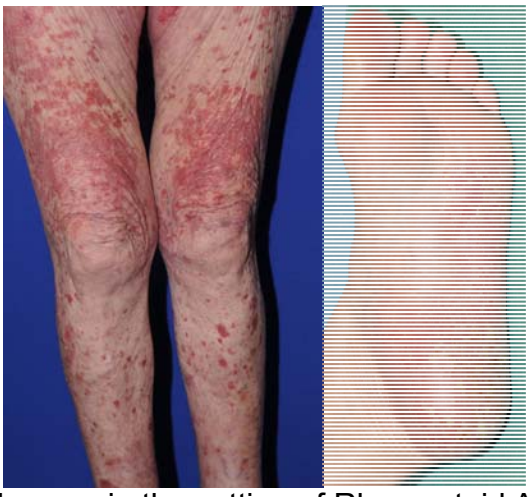
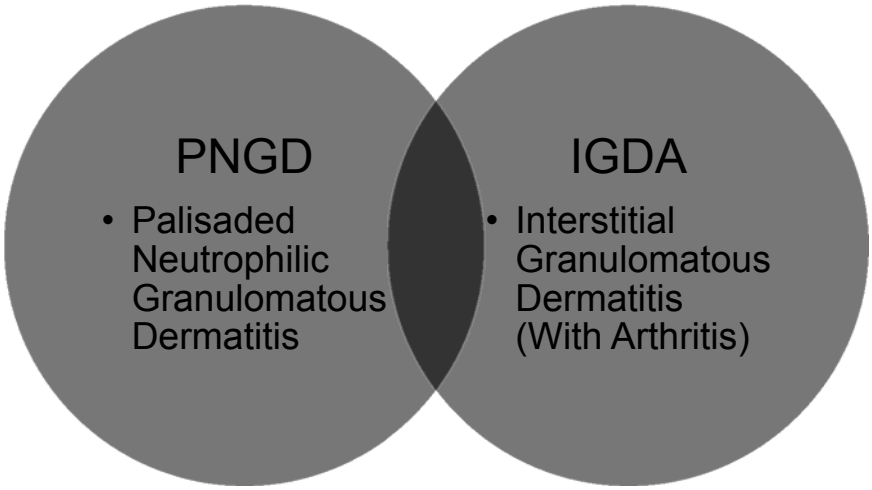
Psoriasiform reactions to TNF-α inhibitors



Usually seen in the setting of Rheumatoid Arthritis
Reported with adalimumab, etanercept, and infliximab
Is a class effect. Attempt topical management.

Other Eruptions

Granulomatous Dermatitis



RA, SLE, ANCA vasculitis, overlap CTD
May precede diagnosis. Also seen with flares.

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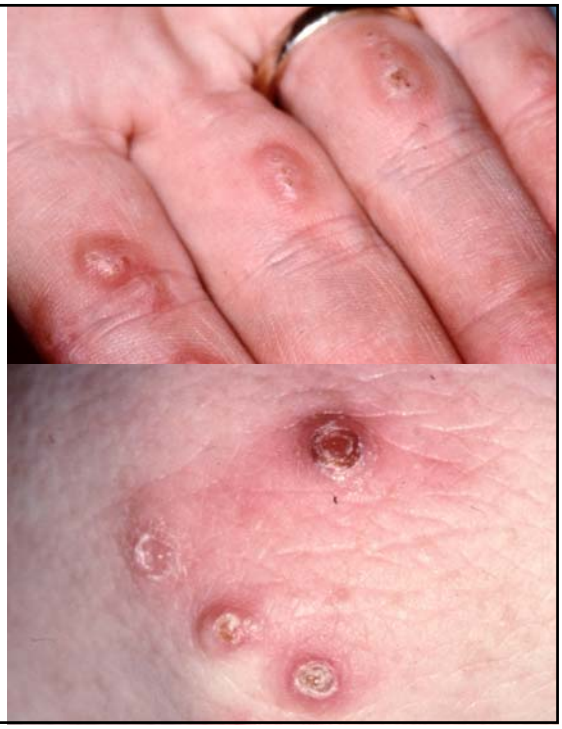
PNGD

- Grouped eruption of erythematous papules with frequent ulceration
- Favors hands and elbows
- Often painful



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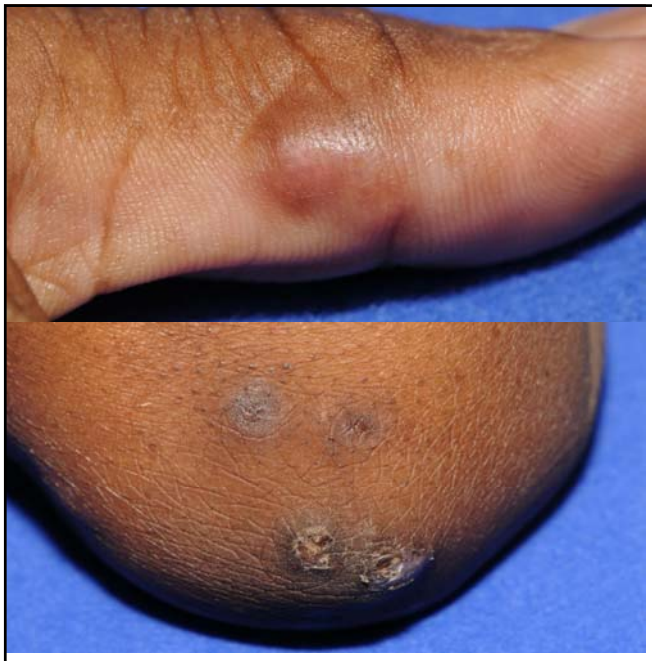

Early PNGD: red smooth papules often with a pseudo-vesiculated quality

Late PNGD: crusted eroded scaling papules

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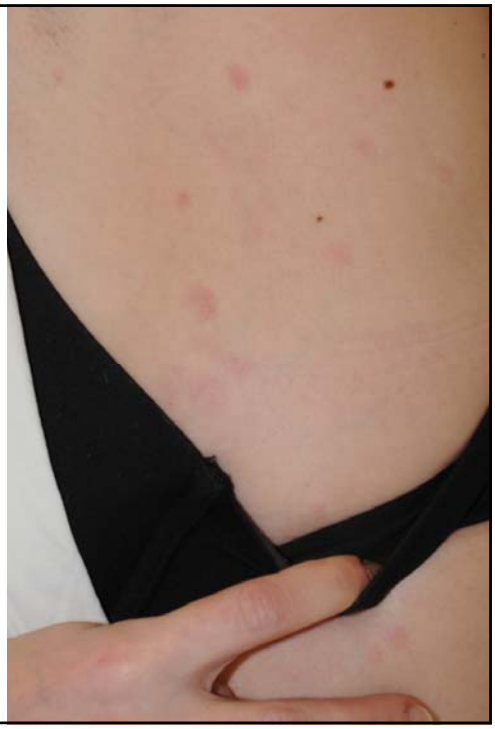
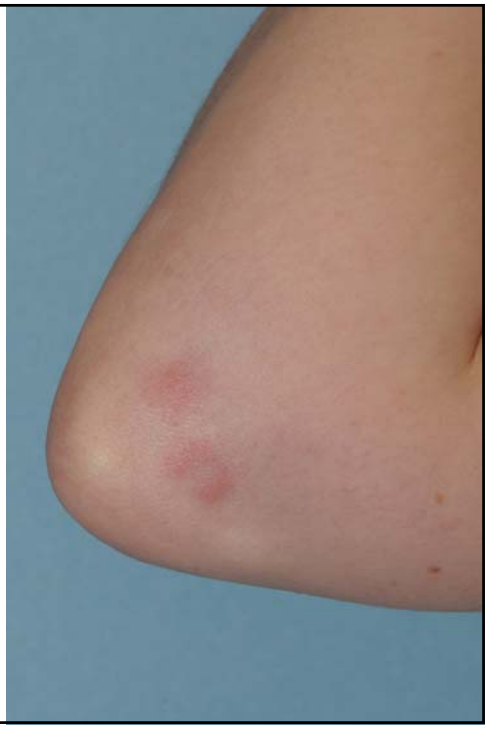
IGDA

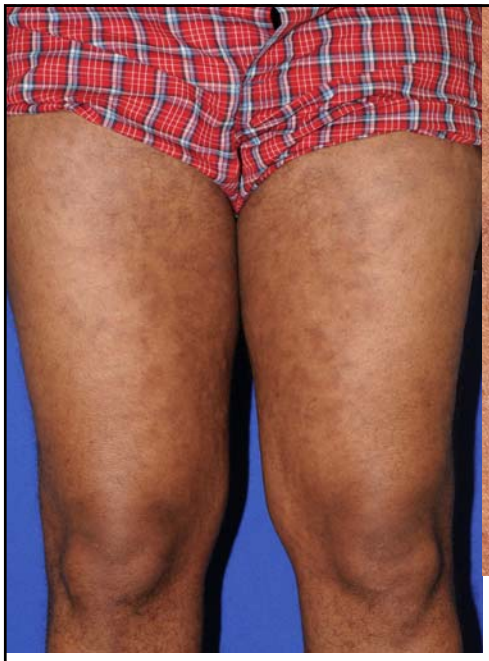
- Slightly erythematous smooth papules and plaques on the trunk and proximal limbs
- Lesions Asymptomatic
- Arthritis often



IGDA

- Slightly erythematous smooth papules and plaques on the trunk and proximal limbs
- Urticarial quality





Clinically subtle changes can have a high diagnostic yield

IGDA: no ulceration, fixed lesions, urticarial quality

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Return to Program Schedule

Psoriatic Arthritis

Gurjit S. Kaeley, MBBS, MRCP, FACR
Division Chief,
Associate Professor of Medicine,
Director of Musculoskeletal Ultrasound,
University of Florida College of Medicine, Jacksonville.

Objectives

- **Describe the clinical features of Psoriatic Arthritis**
- **Explain how to differentiate it from Rheumatoid Arthritis and other Spondyloarthropathies**
- **List common co-morbidities of Psoriatic Arthritis**
- **Summarize the treatment approach to Psoriatic Arthritis**

Return to Program Schedule

Disclosures

- None

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Concept of Spondyloarthritis (SpA)

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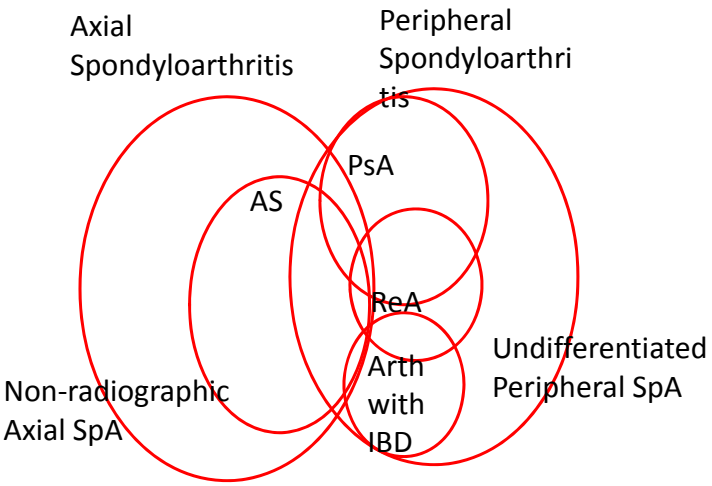
ASAS

Spectrum of Spondyloarthritis: Current Concept



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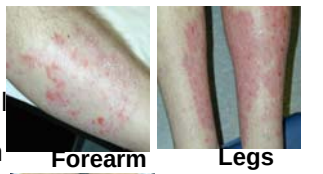
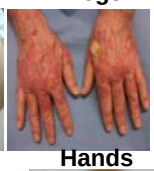
Psoriasis

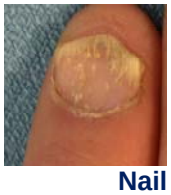
- An inflammatory skin disease
  - affects nails as well
- 1-3% of the population
- Varies from mild to erythroderma
- Leads to reduced QOL
- Increased mortality
- Co-morbidities

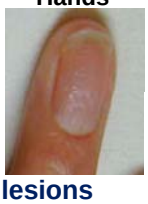

Forearm

Legs


Elbows


Hands




Nail lesions

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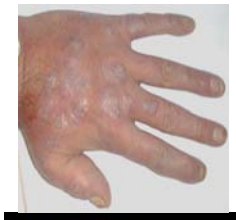
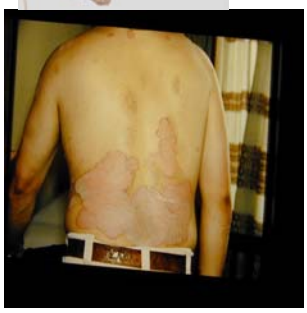
Psoriatic Arthritis

- Inflammatory musculoskeletal disease
- Associated with psoriasis
- Usually seronegative (RF)
- Associated features
  - Spondylitis
  - Enthesitis
  - Dactylitis
  - Iritis
  - Mucous membrane ulcers
  - Urethritis
  - Other extra-articular features of SpA





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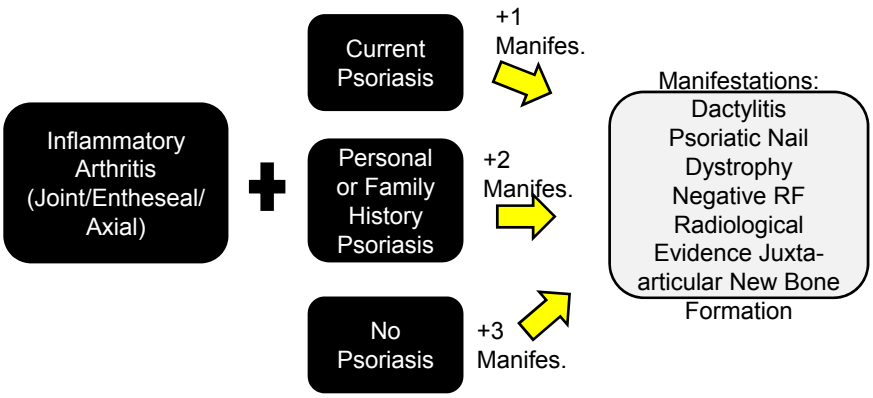
Caspar Criteria for Psoriatic Arthritis



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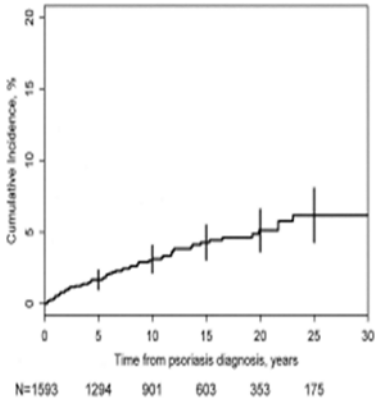
Taylor et al, Arthritis Rheum 2006; 54: 2665-2673

Clinical Predictors of PsA



Cumulative Incidence at 20 Years: 5.1%
Predictors of PsA
- Scalp Lesions (HR3.9)
- Nail Lesions (HR 2.9)
- Inter-gluteal lesions (HR 2.4)

(Upto 10% of patients may present with arthritis prior to psoriasis)

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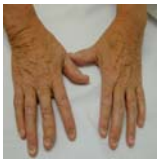
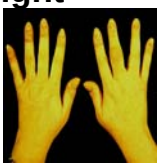
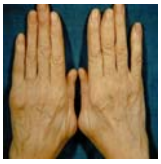
Wilson FC et al Arthritis Rheum. 2009 Feb 15;61(2):233-9.

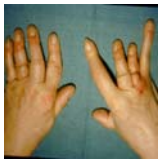
Psoriatic Arthritis

- **5 patterns initially described by Moll and Wright**


Distal


Oligoarthritis


Polyarthritis


Arthritis mutilans


Axial

- **Patterns may change over time**

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Moll JMH, Wright V. Semin *Arth Rheum* 1973; 3:55
Khan M, *et al*. *J Rheumatol* 2003; 30:1022-6

PsA is not Similar to Rheumatoid Arthritis

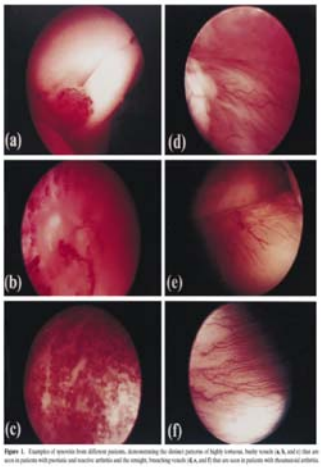
Synovitis
- PsA – Tortuous Busy Vessel
- RA – Straight Branching Vessels

Osteoproliferation
- Feature of PsA
- No osteoproliferation in RA and erosion healing is poor

Erosions
- Hetrogeneous morphology in PsA

Periarticular Inflammation
- Seen more commonly in PsA

Genetics
- RA – DR4/Shared Epitope
- Ps/PsA – HLA Class 1 mild association



Reece RJ et al Arthritis Rheum. 1999 Jul;42(7):1481-4

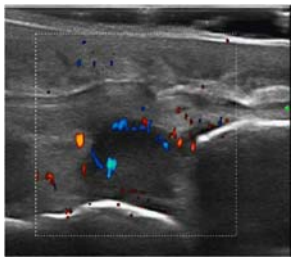
Differential Diagnosis of PsA

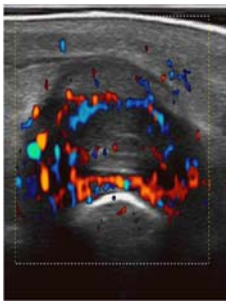
Clinical Feature	PsA	Osteoarthritis	Rheumatoid Arthritis	Gout	Ankylosing Spondylitis
Psoriasis	+	-	-	-	-
Nail Dystrophy	+	-	-	-	-
Enthesitis	+	-	- (rare)	-	+
Peripheral Joints	+	+	+	+	- (Prox Oligoarthritis)
DIP Involvement	+	+	-	+	-
Axial Involvement	+ (Jug like syndesmophytes)	+ (Spondylosis)	+ (C1/2 Level)	+ (rare deposition)	++ (Fine Syndesmophytes)
RF Positive	-	-	+	-	-

Mease PJ, et al Drugs. 2014 Mar;74(4):423-41

Polyarthritis

- Symmetric and asymmetric patterns
- Symmetric disease
  - Rheumatoid pattern: PIP,MCP,MTP, wrists, ankles, elbows, knees
  - Symmetric disease is usually more severe with poorer prognosis
- Interphalangeal and wrist joint fusion may occur





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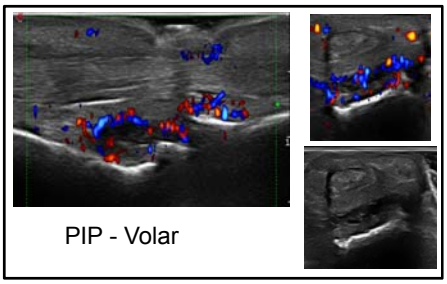
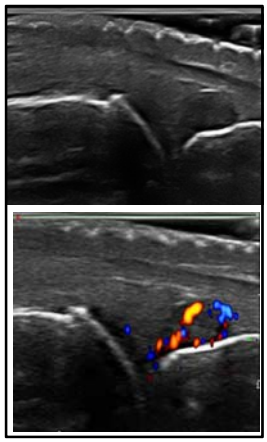
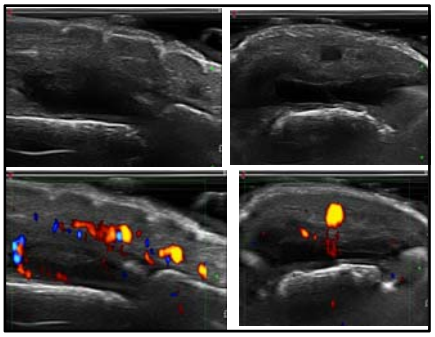
Synovitis



PIP - Volar



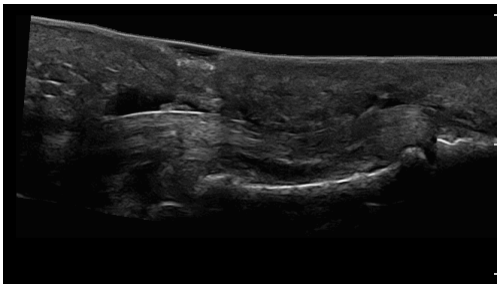
2nd MCP - Dorsal

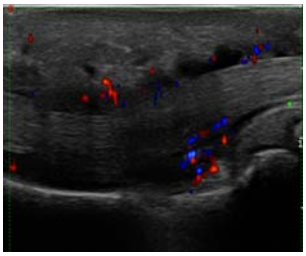


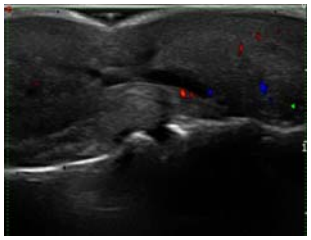
PIP - Dorsal

MAYO CLINIC

Tenosynovitis



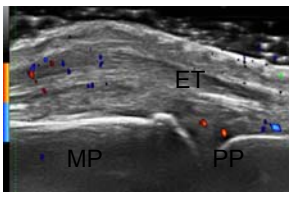


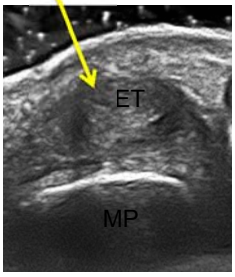


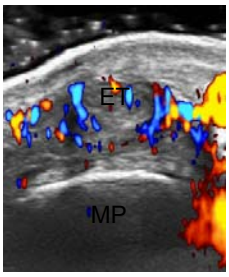
Husic et al Ann Rheum Dis. 2013
Kaeley GS et al. J Rheumatol. 2012;39(2):404-7.

PsA Joint Disease: EXTENSOR TENONITIS

Hypoanechoic material



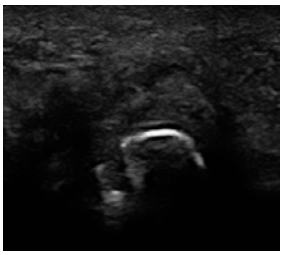




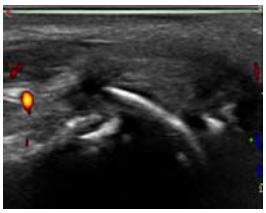
ET – Extensor tendon,
MP – Metacarpophalangeal bone
PP – Prox phalanx

Specific for PsA?? Ramrattan et al ACR 2013, Guiterrez et al ARD. 2011;70(6):1111-4.

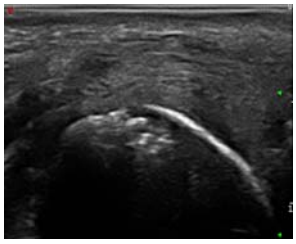
Erosions



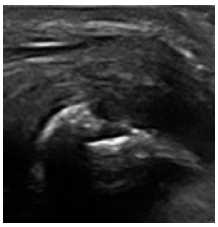
MTP 4 – “RA like erosion”



MCP 1 LONG



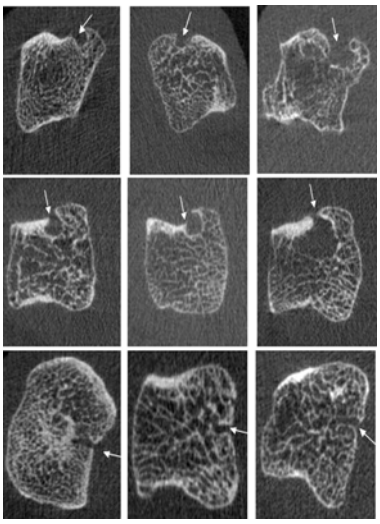
MCP 2 LAT LONG



MCP 1 Short

Husic et al Ann Rheum Dis. 2013
Finzel et al Ann Rheum Dis. 2011;70(1):122-7

Patterns of Bone Erosions Psoriatic Arthritis (PsA)



U-Shaped Erosions – RA and PsA

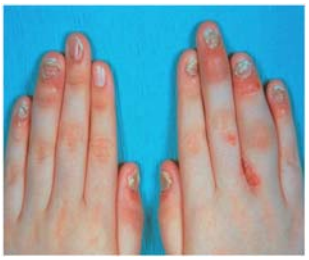
Ω-shaped Erosions – PsA

T (tubule)-shaped bone erosions
- Channels reaching the bone marrow
- Palmar joint compartment of patients with PsA

Finzel S et al. Ann Rheum Dis 2011;70:122-127

Asymmetric Oligoarthritis

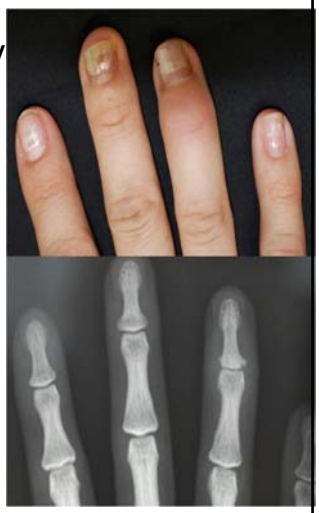
- Oligoarticular or monoarticular distribution
- Affected joints: DIP, PIP, MCP, MTP, Knees, Ankles, Hips
- Dactylitis as well as nail pitting may be seen.

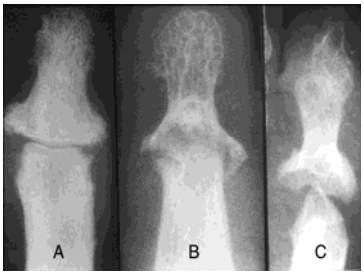


MAYO CLINIC

Distal Interphalangeal Joint Arthritis

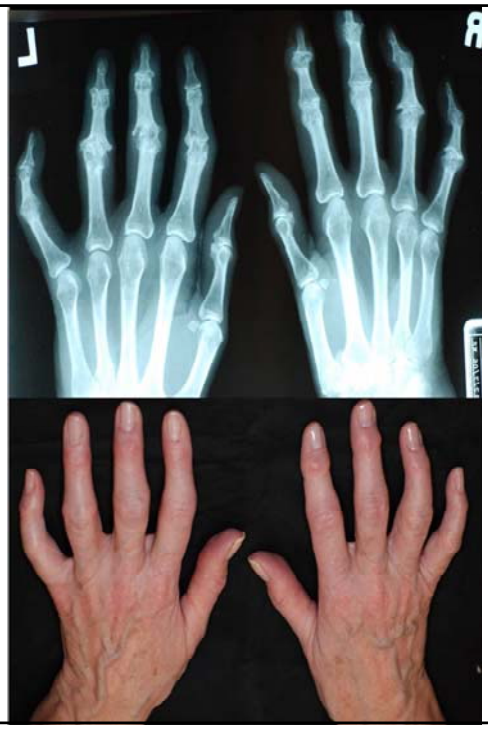
- Nail and finger changes frequently associated with DIP arthritis
- May be symmetric or asymmetric
- Associated with distal erosions
- Can be difficult to distinguish from OA in early stages





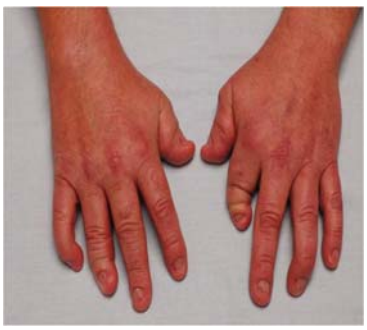
MAYO CLINIC

Is This PsA?



Arthritis Mutilans

- DIP and PIP joints of hands frequently involved
- Osteolysis and bone loss results in “telescoping” of digits



Clinical Damage in PsA

Predictors for progression

- ≥ 5 swollen joints and a high medication level at presentation
  - Gladman DD, *et al*. *Arth Rheum* 1995; 22:675-9
- Actively inflamed joints at each visit
  - Gladman DD, Farewell VT. *J Rheumatol* 1999; 26:2409
- Number of actively inflamed and damaged joints are independent predictors of damage
- Initial ESR is predictive of future damage
  - Bond S, *et al*. *Ann Rheum Dis* 2007; 66:370-6

MAYO CLINIC

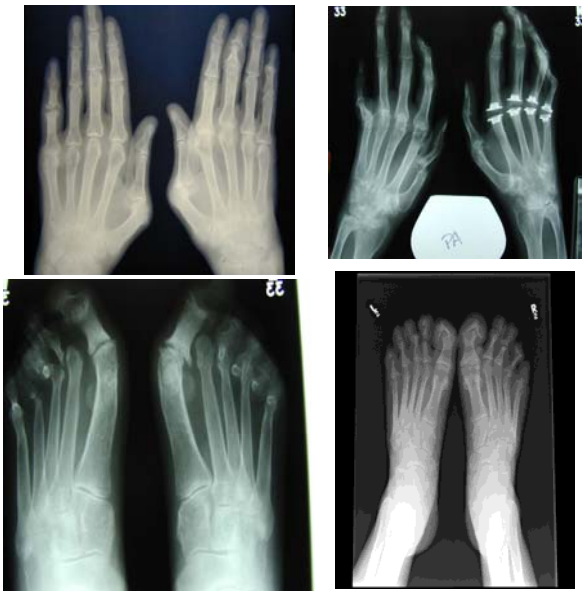
Radiological Damage in PsA

Predictors of Damage & Progression

- Polyarticular presentation predicts future deformities and erosions
  - Queiro-Silva R, et al. Ann Rheum Dis 2003;62:68
- Digits with dactylitis are more likely to have erosive disease than digits without dactylitis
  - Brockbank J, et al. Ann Rheum Dis 2005;64:188-90
- Number of actively inflamed and damaged joints are independent predictors of damage
- Initial ESR is predictive of future damage
  - Bond S, et al. ARD 2007;66:370-6

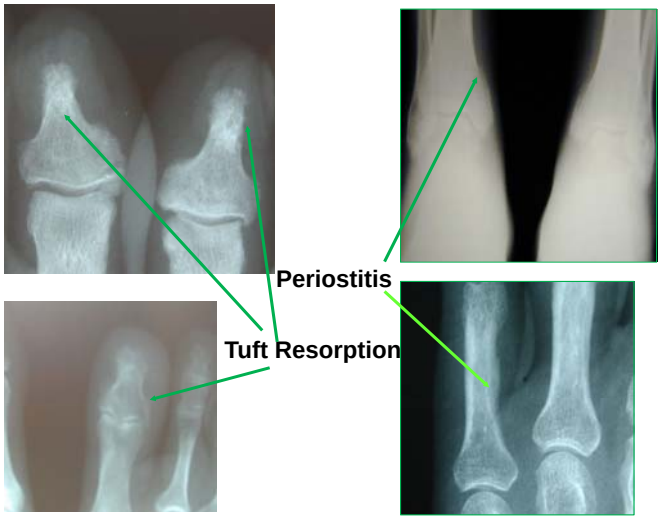
MAYO CLINIC

Radiological Damage in PsA



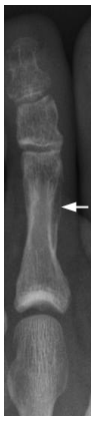
MAYO CLINIC

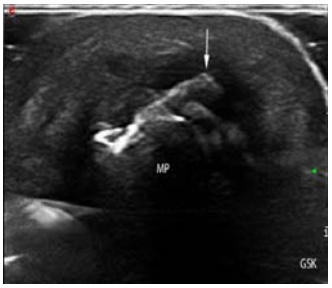
Other Radiological Features of PsA



MAYO CLINIC

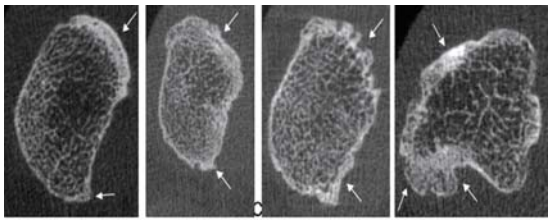
Osteoproliferation





MAYO CLINIC

Osteophytes and Cortical Surface Lesions in Psoriatic Arthritis (PsA)



Corona-shaped pattern with widespread involvement of the cortical bone

Finzel S et al. Ann Rheum Dis 2011;70:122-127

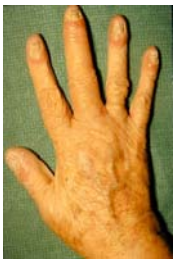
MAYO CLINIC

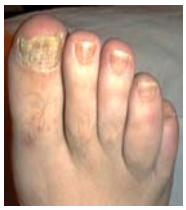
ARD

Dactylitis in PsA

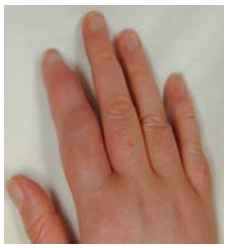
- "Sausage Digit"
- Swelling of whole finger
  - Acute
  - Chronic
- Associated with increased inicidence of erosions.

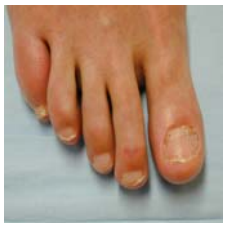
Chronic



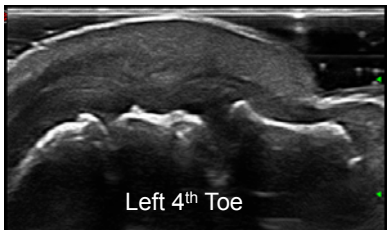


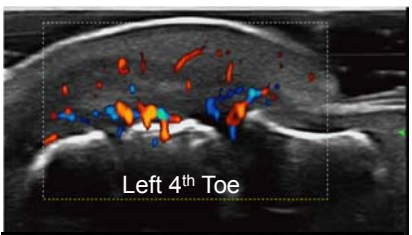
Acute

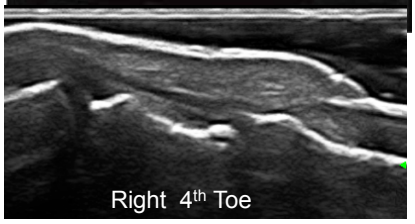


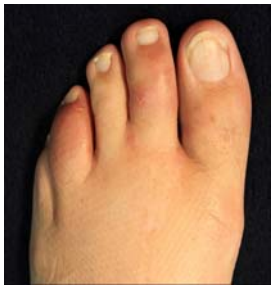


MAYO CLINIC

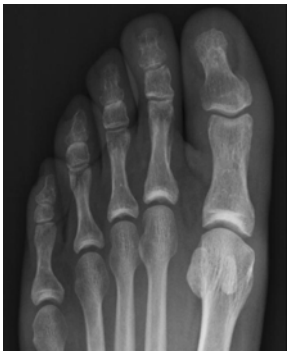








Left Foot

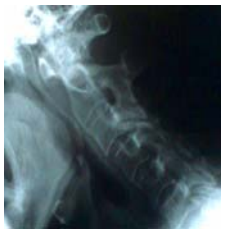


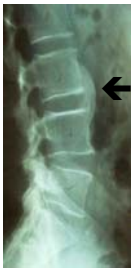
Kaeley G, Curr Rheumatol Rep (2011) 13:338–345

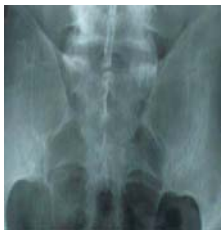
MAYO CLINIC

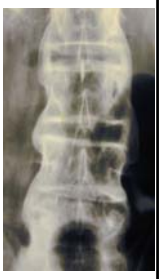
Axial Psoriatic Arthritis

- 15% of PsA patients will develop axial disease by 10 years
- 5% have only axial involvement
- May be asymptomatic
- HLA-B27 Association
- Nail dystrophy, number of radiographically damaged joints, periostitis and elevated ESR increased the risk of developing AxPsA, whereas swollen joints decreased risk
- Radiographic Signs
  - Asymmetric sacroilietis and spondylitis
  - "Jug like" handle syndesmophytes
  - Spondylitis can occur without sacroilietis









Chandran V, et al. *J Rheumatol* 2010; 37:809-5

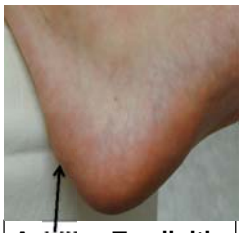
Extra-articular Manifestations: Enthesitis

- Classical Sites
  - Achilles Tendon
  - Plantar Fascia
  - Pelvic, thoracic and spine insertions

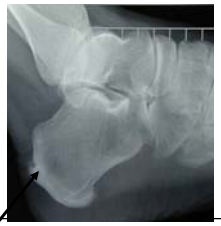
Extra-articular Manifestations: Nails

- 80% of patients with PsA will have nail lesions (>20 pits)
- However, only 40-45% of patients with Psoriasis and not PsA will have nail changes
- Changes include: pitting, transverse ridging, onycholysis, hyperkeratosis, and nail yellowing

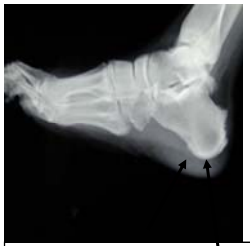
Enthesitis in PsA



Achilles Tendinitis

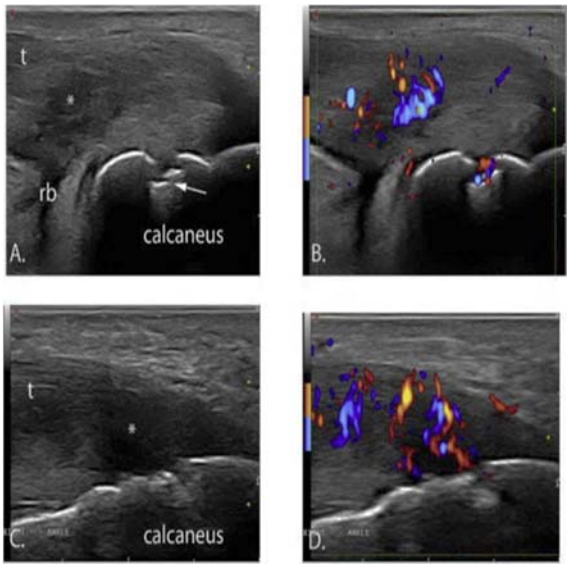


Achilles Tendon Spur



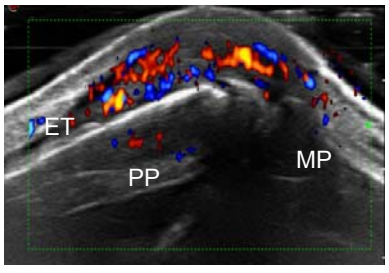
Achilles Tendon Insertion Erosion
Plantar Spur

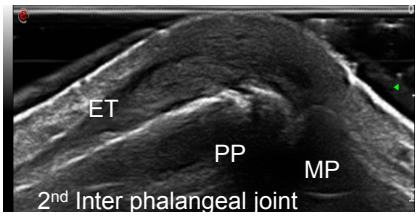
Sonographic Features of Achilles Enthesitis



Lennart Jans , Jacob L. Jaremko , Gurjit S. Kaeley
Novel imaging modalities in spondyloarthritis
Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 729 - 745

PsA Joint Disease: Periarticular Inflammation





ET – Extensor tendon,
MP – Mid Phalange, PP – Prox phalanx
ET – Extensor tendon

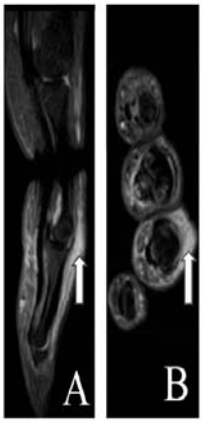
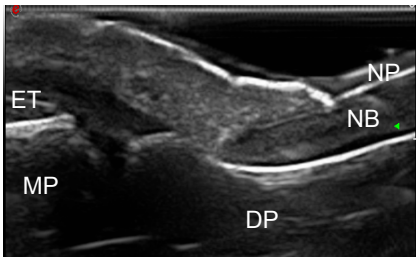


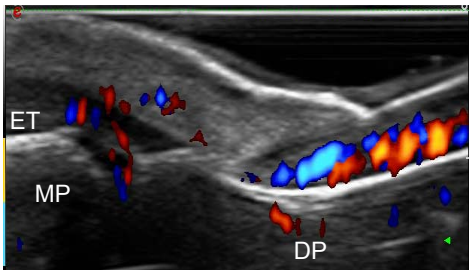
Figure 3. Sagittal (A) and axial (B) short tau inversion recovery (STIR) magnetic resonance images of the 4th finger. Arrows mark periarticular inflammation.

Poggenborg RP, et al. Ther Adv Musculoskelet Dis. 2011;3(1):43-53.

PsA Joint Disease: Extensor Tendon Enthesitis



ET – Extensor tendon,
MP – Mid Phalanx
DP – Distal phalanx
NB – Nail bed
NP – Nail plate



EXTENSOR TENDON ENTHESITIS

NAIL BED THICKENING AND HYPERVASCULARITY

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Uveitis in PsA and SpA

	PsA (n=16)	SpA (n=89)
Insidious onset	19%	3%
Bilateral	37.5	7.0%
Continuous inflammation	31%	6%
Posterior	44%	17%

Pattern of uveitis in PsA similar to that observed in IBD

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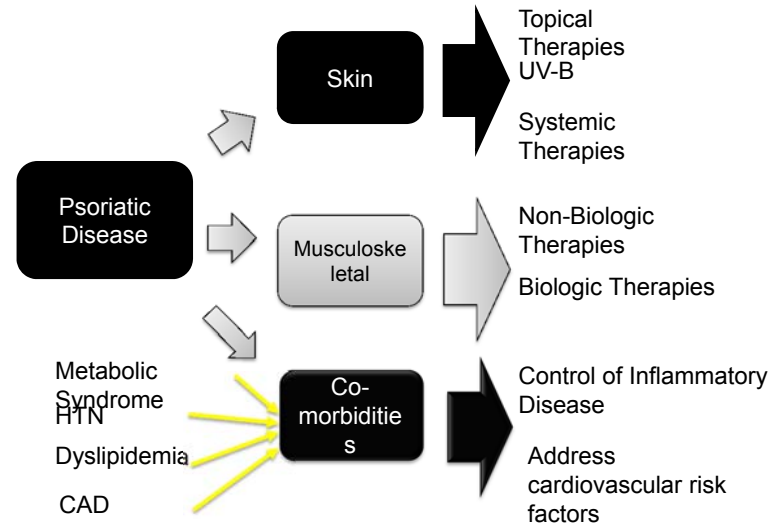
Paiva ES *et al*. *Ann Rheum Dis* 2000; 59:670

Treatment of Psoriatic Disease



Musculoskeletal: Joints / Entheses / Dactylitis/ Axial Disease

Approved Therapies for PsA

Drug	Class	Region(s) where approved for PsA	Dose
Treatments approved for PsA			
Methotrexate[105,106]	Nonbiologic DMARD	Canada, Europe	Up to 25 mg per week (oral)
Leflunomide[159]	Nonbiologic DMARD	Europe	20 mg per day (oral)
Adalimumab[101,106]	TNF inhibitor	U.S.A., Europe, Japan	40 mg SC every other week
Etanercept[106,122]	TNF inhibitor	U.S.A., Canada	50 mg SC every week
		Europe	25 mg SC twice per week
Golimumab[106,123]	TNF inhibitor	U.S.A., Europe, Canada	50 mg SC every month
Infliximab[106,124]	TNF inhibitor	U.S.A., Europe, Canada	5 mg kg^{-1} body weight IV at weeks 0, 2 and 6, and every 8 weeks thereafter
Certolizumab pegol[159,167]	TNF inhibitor	U.S.A.	400 mg SC at weeks 0, 2 and 4, followed by 200 mg every other week; for maintenance dosing, can consider 400 mg every 4 weeks
Ustekinumab[155,159]	IL-12/−23 inhibitor	U.S.A., Europe	45 mg SC initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients > 100 kg with coexistent moderate-to-severe plaque psoriasis: 90 mg SC initially and 4 weeks later, followed by 90 mg every 12 weeks

Boehncke WH et al Br J Dermatol. 2014 Apr;170(4):772-86.

Non-approved Therapies for PsA

Treatments not approved for PsA			
Sulfasalazine[116,159]	Nonbiologic DMARD	Not applicable	2–3 g per day (oral) in two divided doses[a]
Ciclosporin A[121,159]	Nonbiologic DMARD	Not applicable	2·5 mg kg^{-1} per day in two divided doses[a,b]
Abatacept[159,168]	T-cell costimulatory inhibitor	Not applicable	10 mg kg^{-1} 2 and 4 weeks after first infusion, then once per month IV or a single infusion loading dose (10 mg kg^{-1}), followed by 125 mg SC within 1 day, and 125 mg every week thereafter[c]
Tocilizumab[159,169]	IL-6R inhibitor	Not applicable	4–8 mg kg^{-1} IV every 4 weeks[c]
Secukinumab[159–161]	IL-17 inhibitor	Not applicable	Up to 300 mg per month (SC)[d]
Brodalumab[159]	IL-17R inhibitor	Not applicable	70–210 mg (SC) every 2 weeks or 280 mg (SC) monthly[e]
Apremilast[164]	PDE-4 inhibitor	Not applicable	20 mg twice daily or 40 mg once daily (oral)
Tofacitinib[159,165,170]	Selective JAK inhibitor	Not applicable	5 mg twice daily (oral)[f]

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Boehncke WH et al Br J Dermatol. 2014 Apr;170(4):772-86.

Therapies for Psoriatic Arthritis

Drug	Signs/ Symptoms	Radiographic Progression	Enthesitis	Dactylitis	Axial Involvement
Methotrexate	+/-	Inconclusive	Unknown	Unknown	-
Sulfasalazine	+	-	-	-	-
Leflunomide	+	Unknown	Unknown	Unkown	-
Cyclosporin	+	Unknown	Unknown	Unknown	-
Apremilast	+	Unknown	Unknown	Unknown	Unknown
Anti-TNF Ab	+	+	+	+	Unknown
Anti IL 12/23 (Ustekinemab)	+	+	+	+	Unknown

Anti-TNF: Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumab,

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Mease PJ et al Drugs. 2014 Mar;74(4):423-41.

Psoriatic Disease and Systemic Corticosteroids

- Psoriasis
  - Use discouraged due to flareup of Pustular Psoriasis on withdrawal
  - Use of systemic steroids common amongst primary care providers
  - Limited evidence for use of systemic steroids in Psoriasis
- PsA
  - Limited data for use of oral corticosteroids
  - Intra-articular injections – one trial has shown fair response

Semble AL et al, Dermatol Online J. 2014 Mar;20(3)
Acosta Felquer et al J Rheumatol. 2014 Nov;41(11):2277-85
Mrowietz U et al J Eur Acad Dermatol Venereol. 2013 Aug;27(8):1022-5.

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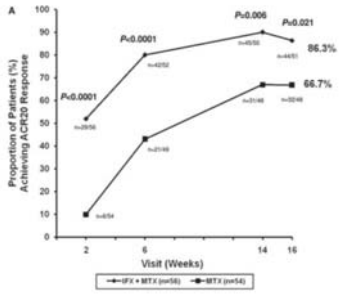
PsA and the Methotrexate Conundrum

- MIPA Study - RCT
  - 221 Subjects
  - MTX (upto 15mg oaw) vs Placebo
  - Approx 2/3 patients recruited
  - No clinical differences noted between groups
- Baranauskaite et al – open label study
  - Mild PsA disease
  - MTX vs MTX + Infliximab
  - Good response to MTX in this group

MIPA: Methotrexate in Psoriatic Arthritis



Hepatotoxicity Concern
AAD:Liver Bx
- Low Risk Patients: 3.5 – 4.0g cum dose
- High Risk Patients: 1.0-1.5g cum dose

ACR: No recommendations

Acosta Felquer ML et al J Rheumatol. 2014 Nov;41(11):2277-85
Baranauskaite A et al Ann Rheum Dis. 2012 Apr;71(4):541-8.

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Anti-TNF Therapies in PsA

- No Head to Head Studies
- Generally robust ACR 20/50/70 responses
- Methotrexate can reduce anti drug antibodies and raise levels fo adalimumab and infliximab
- Methotrexate may contribute to decreasing cardiovascular risk

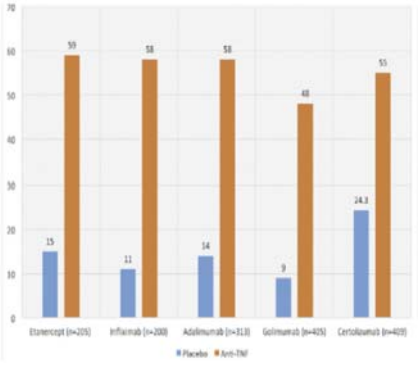
- Factors affecting choice of Anti-TNF therapies

  Antibody construct may be preferred for
  - Presence of concurrent Uveitis
  - Concurrent IBD
- Caution
  - Contra-indicated if melanoma present
  - Caution if previous squamous cell skin cancer

Boehncke WH et al 2014 Apr;170(4):772-86.

Anti-TNF Efficacy in PsA

- FDA Approved Dosing:
  - Adalimumab 40mg SC every other week
  - Etanercept 50mg SC every week
  - Golimumab 50 mg every month
  - Infliximab 5mg/kg 0,2,6 wks then q 8 wks
  - Certolizomab Pegol 400mg SC 0,2,4 wks then 200mg every 2 weeks or 400mg every 4 weeks



ACR 20 response rates. Trial results cannot be compared directly given differences in study populations and trial design.

Huynh D et al Rheumatology (Oxford). 2015 Jan;54(1):20-8
Paccou J et al, Joint Bone Spine. 2015 Mar;82(2):80-5.
Boehncke WH, et al Br J Dermatol. 2014 pr;170(4):772-86.

Anti-TNF Efficacy in PsA

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(Table does not show head to head trials)

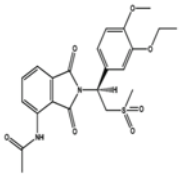
Huynh D et al Rheumatology (Oxford). 2015 Jan;54(1):20-8
Boehncke WH, et al Br J Dermatol. 2014 pr;170(4):772-86.

TABLE 1 Summary of results of clinical trials of TNFis in PsA

Agent/trial	Study size	Patients meeting reponse criteria, % ACR20	PASI75
Etanercept [38, 39]			
Week 12	205	59	38
Week 24		55	40
Week 48	169	64	40
Infliximab/IMPACT [40, 47, 48]			
Week 14	200	58	64
Week 24		54	60
Week 54	173	59	50
Week 98	104	62	64
ADA/ADEPT [41, 42]			
Week 12	315	58	49
Week 24		57	59
Week 48	245	59	59
Week 104		57	58
Golimumab/GO-REVEAL [43–45]			
50 mg			
Week 14	405	51	40
Week 24		52	56
Week 52	360	67	62
Week 104	335	67	86
100 mg			
Week 14		45	58
Week 24		61	66
Week 52	360	71	68
Week 104	335	70	86
Certolizumab/ rapid-PsA [46]	409		
200 mg			
Week 12		58	47
Week 24	138	64	62
400 mg			
Week 12		51	47
Week 24	135	56	61

TNFis: tumour necrosis factor inhibitors; ADA: adalimumab; ACR20: 20% response to ACR criteria; PASI75: Psoriasis Area and Severity Index 75.

Apremilast and PsA



- cAMP – key secondary messanger in many biological processes
- Regulated by degradation by phosphodiesterases(PDE)
- PDE4 expressed in hemapoetic, non-hemapoetic cells and sensory/memory neurons
- 4 PDE4 genes -> upto 19 geneproducts
- Apremilast binds to catalytic site of PDE4 (Less selective than cilomast, and no CNS SE like rolipram)
- Inhibition of T-Cell cytokine production
- Loading 6 day regime then 30mg bid
- Renal impairment – 30 mg qd

- Note
  - Main SE Nausea and Diarrhea
  - No structural data

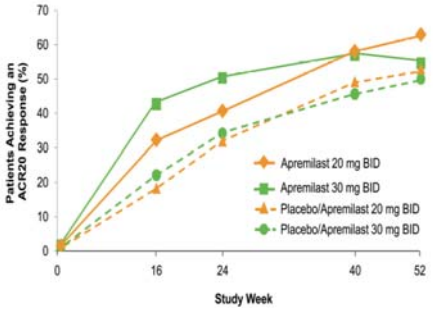
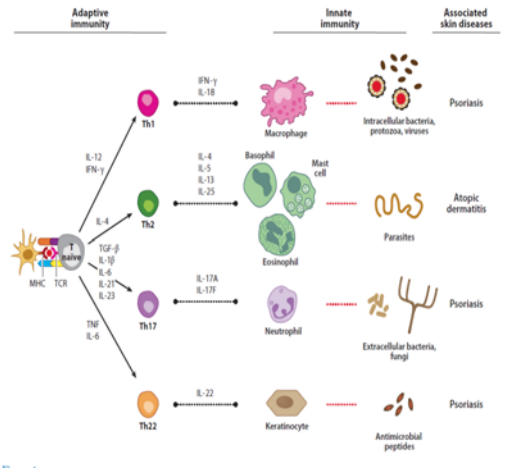


Figure: 52 Week Results Phase III Study

Schett G et al Ther Adv Musculoskelet Dis. 2010 Oct;2(5):271-8 Kavanaugh A et al J Rheumatol. 2015 Mar;42(3):479-88.

IL23/TH17 Axis – New Targets

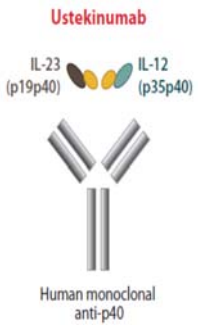
- IL23 secreted by monocytes, macrophages, skin dendritic cells
  - IL23p19 discovered in 2000
  - Needed to bind with IL12p40 to form hetrodimeric cytokine IL23
- IL23 assosciated with autoimmune disease – gene defects in exon 9 of IL23 R associated with protection against
  - Psoriasis
  - Crohns dis, UC, AS, GVH-D
  - Additional variants associated with RA, Psoriasis, Graves disease
- IL23 aids in proliferation of Th17 cells (Th17 is a potent pro-inflammatory cytokine)



Di Cesare A et al, J Invest Dermatol. 2009 Jun;129(6):1339-50.
Perera GK et al, Annu Rev Pathol. 2012;7:385-422.
Mease PJ, Curr Opin Rheumatol. 2015 Mar;27(2):127-33.

Ustekinumab for PsA

- Dose: Weight based for both Ps and PsA
  - Wt <100kg 45mg
  - Wt >100kg 90mg
  - Subcutaneous, baseline, 4 weeks, then 12 weekly thereafter
- Major Side Effects
  - Nasopharyngitis
  - Headaches
- Addition of MTX did not have synergistic effect (see next slide)



Mease PJ et al Drugs. 2014 Mar;74(4):423-41.

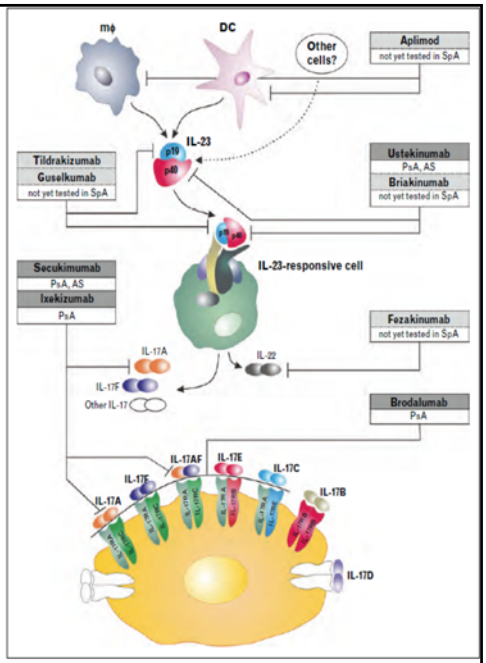
Ustekinumab for PsA

Outcome measure	Study	Concurrent therapy	Treatment groups				P-values
			Placebo		Ustekinumab 63 or 90 mg		
ACR 20 response	Gottlieb et al[25]	All patients	32/76 (42%)		10/70 (14%)		0.0002
			Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg	Combined ustekinumab	
	McInnes et al[26]	All patients	47/206 (22.8%)	87/205 (42.4%)	101/204 (49.5%)	188/409 (46.0%)	<0.0001 for all comparisons versus placebo
		With MTX treatment	25/96 (26.0%)	43/99 (43.4%)	46/101 (45.5%)	89/200 (44.5%)	
		Without MTX treatment	22/110 (20.0%)	44/106 (41.5%)	55/103 (53.4%)	99/209 (47.4%)	
	Ritchlin et al[27]	All patients	21/104 (20.2%)	45/103 (43.7%)	46/105 (43.8%)	91/208 (43.8%)	<0.001 for all comparisons versus placebo
		With MTX treatment	14/49 (28.6%)	27/54 (50.0%)	21/52 (40.4%)	48/106 (45.3%)	
		Without MTX treatment	7/55 (12.7%)	18/49 (36.7%)	25/53 (47.2%)	43/102 (42.2%)	

Davari P et al Clin Cosmet Investig Dermatol. 2014;7:243-9.

Future Targets IL23/IL17 Axis

- 3 IL17 A inhibitors in development -PsA
  - Secukinumab
    - IL17A monoclonal Ab
    - Phase III trials reported at ACR for PsA
  - Ixekizumab
    - In Phase III
    - Did not show efficacy in Phase II RA trials
  - Brodaliumab
    - Human anti IL17A receptor
    - Phase II – two events of neutropenia
    - Not efficacious in RA
    - Not being persued in IBD

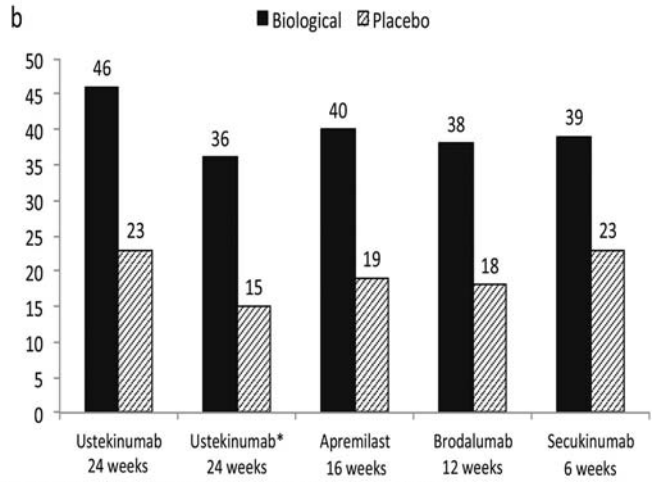


Yeremenko N, et al Curr Opin Rheumatol. 2014 Jul;26(4):361-70.
Mease PJ et al Drugs. 2014 Mar;74(4):423-41.

Different Biological Agents in PsA

ACR 20 Responses

DATA IS NOT HEAD TO HEAD



*Subgroup of PsA patients treated with ustekinumab that were TNFi inadequate responders (PSUMMIT-2 trial).
Results shown for apremilast are with the currently licenced dose of 30 mg BID.
Results shown for secukinumab were not statistically significant.

Filip Van den Bosch , Atul Deodhar. **Treatment of spondyloarthritis beyond TNF-alpha blockade**
Best Practice Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 819 - 827

Conclusion

- Psoriatic disease is a multidimensional disease
- Multiple areas need to be evaluated including co-morbodities
- Several FDA therapies are available for treatment
- Newer targeted therapies are evolving

Acknowledgements

- Spartan- Grappa Network
- ACR Image Bank

Anti IL17A – Receptor: Secukinumab

Week 24 Data	Secukinumab 300 mg s.c.	Secukinumab 150 mg s.c.	Secukinumab 75 mg s.c.	PBO
[a]ACR20 (% responders)	54.0*	51.0*	29.3‡	15.3
TNF-IR (% responders)	45.5‡	29.7	14.7	14.3
TNF-naïve (% responders)	58.2‡	63.5‡	36.9‡	15.9
[a]ACR50 (% responders)	35.0‡	35.0	18.2	7.1
ACR70 (% responders)	20.0‡	21.0‡	6.1	1.0
[a]PASI 75/90 (% responders)	63.4*/48.8†	48.3‡/32.8‡	28.0/12.0	16.3/9.3
[b]Dactylitis (resolution of, %)	56.5‡	50.0‡	30.3	14.8
[b]Enthesitis (resolution of, %)	48.2‡	42.2‡	32.4	22.5

*$P<0.0001$; †$P<0.001$; ‡$P<0.01$; §$P<0.05$

[a]*P*-values adjusted for multiplicity

[b]Data from patients with dactylitis (n = 138) and enthesitis (n = 253) at baseline.

ACR, American College of Rheumatology response criteria; PASI, Psoriasis Area and Severity Index; PBO, placebo; s.c., subcutaneous; TNF-IR, inadequate response to/intolerant of tumor necrosis factor inhibitor therapy

Subcutaneous Dosing

ACR 2014, Abstract L1

http://acrabstracts.org/abstracts/secukinumab-a-human-anti-interleukin-17a-monoclonal-antibody-improves-active-psoriatic-arthritis-24-week-efficacy-and-safety-data-from-a-phase-3-randomized-multicenter-double-blind-placebo-contr/

Secukinumab: Structural Damage

Table. Radiographic progression at Week 24 by treatment group

Week 24 (Mean change from baseline)	Secukinumab 10 mg/kg IV → 75 mg SC n = 202	Secukinumab 10 mg/kg IV → 150 mg SC n = 202	PBO n = 202
mTSS	0.02†	0.13†	0.57
Erosion score	0.08†	0.04‡	0.35
JSN score	−0.06†	0.10	0.23
TNF-naïve/IR	n = 142/n = 60	n = 143/n = 59	n = 143/n = 59
mTSS	−0.06†/0.21	0.15/0.10†	0.57/0.58
Erosion score	0/0.25	0.02/0.08‡	0.29/0.50
JSN score	−0.06†/−0.05	0.13/0.02	0.28/0.09
Concomitant MTX use, yes/no	n = 122/n = 80	n = 121/n = 81	n = 125/n = 77
mTSS	−0.07†/0.14	0.14/0.12	0.57/0.58
Erosion score	0.01†/0.17	0.04†/0.02	0.34/0.37
JSN score	−0.08/−0.03	0.10/0.10	0.24/0.21

†$P < 0.05$ vs. placebo; ‡$P < 0.01$ vs. placebo
JSN, joint space narrowing; mTSS, modified total Sharp score; MTX, methotrexate; TNF-naïve/IR, tumor necrosis factor inhibitor naïve/inadequate responder
/Values based on a non-parametric ANCOVA model.

2-year, multicenter, randomized, double-blind, placebo (PBO)-controlled, phase 3 trial (FUTURE 1; NCT01392326).

randomized to PBO or one of two secukinumab treatment arms:
secukinumab 10 mg/kg i.v. followed by 75 mg s.c. (10 IV→75 SC) or
150 mg s.c. (10 IV→150 SC).

ACR 2014, Abstract 954
http://acrabstracts.org/abstracts/secukinumab-a-monoclonal-antibody-to-interleukin-17a-provides-significant-and-sustained-inhibition-of-joint-structural-damage-in-active-psoriatic-arthritis-regardless-of-prior-tnf-inhibitors-or-conc/

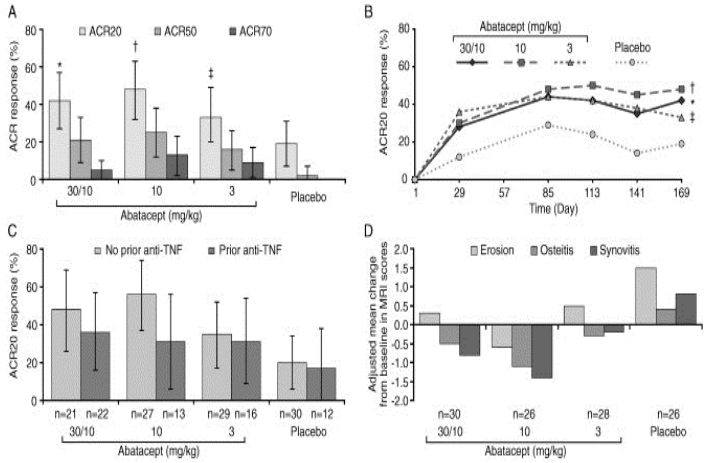
MAYO CLINIC

Abatacept and PsA

- RA Dose :

MAYO CLINIC

Abatacept and PsA



Abatacept in the treatment of patients with psoriatic arthritis: Results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial

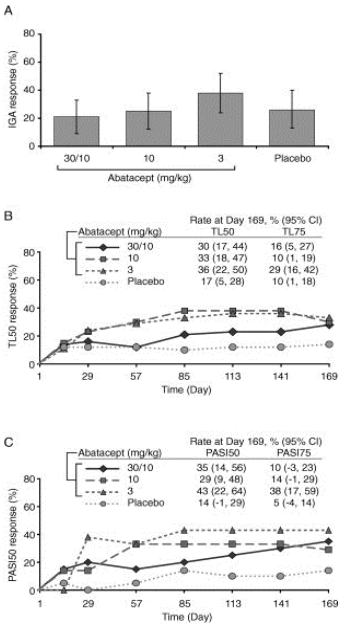
Arthritis & Rheumatism
Volume 63, Issue 4, pages 939-948, 30 MAR 2011 DOI: 10.1002/art.30176
http://onlinelibrary.wiley.com/doi/10.1002/art.30176/full#fig1

Abatacept – Psoriasis Responses

A. Percentages of patients achieving an investigator's global assessment (IGA) response (lesions judged to be "clear or almost clear") on day 169, by treatment group.

B. Percentages of patients achieving an improvement in the target lesion score of ≥50% versus baseline (TL50 response) over time, by treatment group.

C. Percentages of patients achieving an improvement in the Psoriasis Area and Severity Index of ≥50% versus baseline (PASI50 response) over time, by treatment group.



Arthritis & Rheumatism
Volume 63, Issue 4, pages 939-948, 30 MAR 2011 DOI: 10.1002/art.30176
http://onlinelibrary.wiley.com/doi/10.1002/art.30176/full#fig2

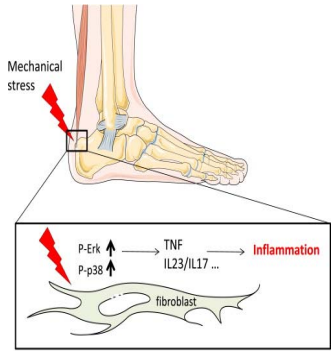


Fig. 1 Experimental models including TNF overexpression and IL-23 overexpression are associated with the development of SpA phenotypes that start at the Achilles enthesis. The TNF model is associated with stromal production of TNF as an early disease initi...

Peggy Jacques , Dennis McGonagle

The role of mechanical stress in the pathogenesis of spondyloarthritis and how to combat it

Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 703 - 710

http://dx.doi.org/10.1016/j.berh.2014.10.009

MAYO CLINIC

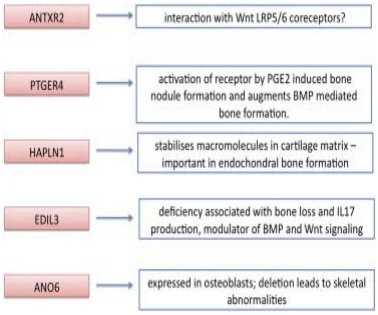


Fig. 1 Ankylosing spondylitis susceptibility genes with links to new bone formation.

Rik J. Lories , Nigil Haroon

Bone formation in axial spondyloarthritis

Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 765 - 777

http://dx.doi.org/10.1016/j.berh.2014.10.008

MAYO CLINIC

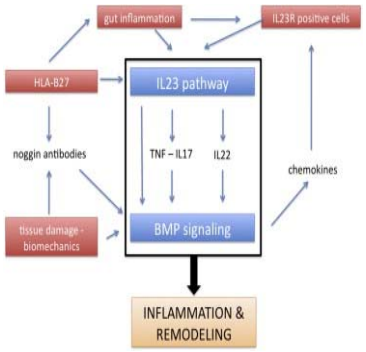


Fig. 2 Conceptual framework of inflammation and new bone formation in axial spondyloarthritis.

Rik J. Lories , Nigil Haroon

Bone formation in axial spondyloarthritis

Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 765 - 777

http://dx.doi.org/10.1016/j.berh.2014.10.008

MAYO CLINIC

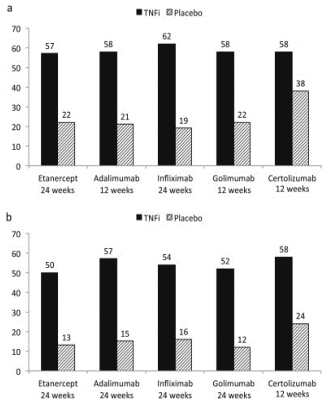


Fig. 1 a: ASAS20 responses in five separate trials in AS patients (*not* head to head) (results at 12–24 weeks). b: ACR20 responses in five separate trials in PsA patients (*not* head to head) (results at 12–24...

Filip Van den Bosch , Atul Deodhar

Treatment of spondyloarthritis beyond TNF-alpha blockade

Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 819 - 827

http://dx.doi.org/10.1016/j.berh.2014.10.019

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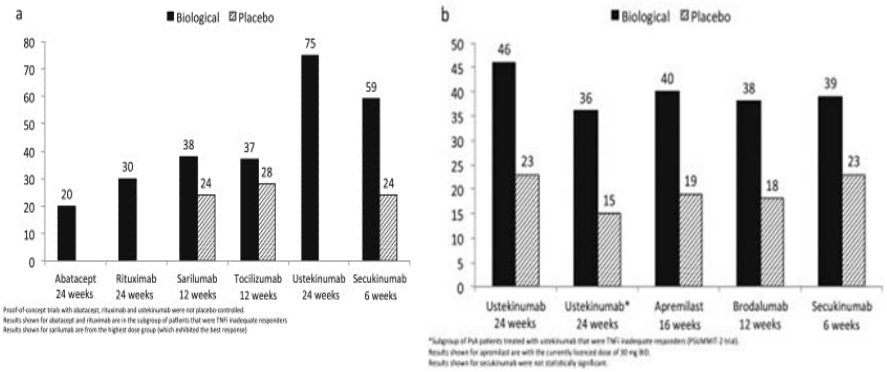

Fig. 2 a: ASAS20 responses with different biological agents in separate trials in AS patients (*not* head to head) (results at 6–24 weeks). b: ACR20 responses with different biological agents in separate trials in PsA patients (<ce:i...

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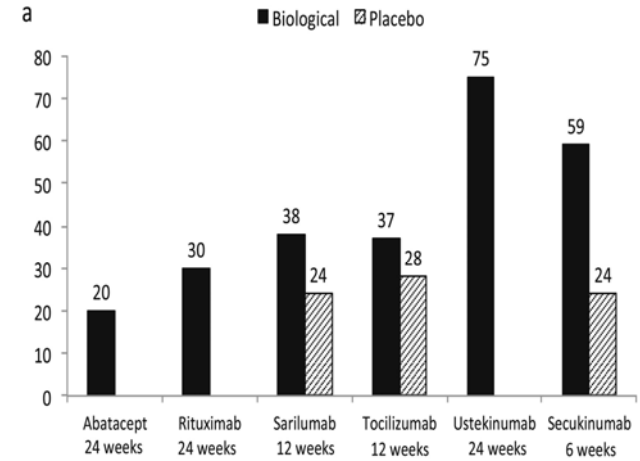

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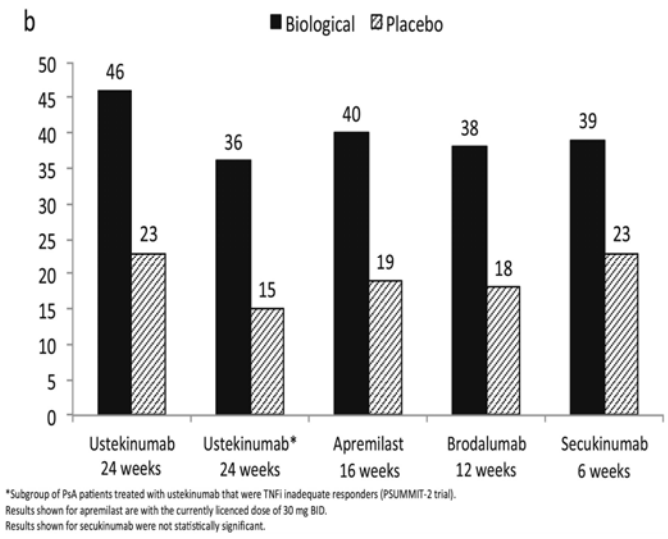

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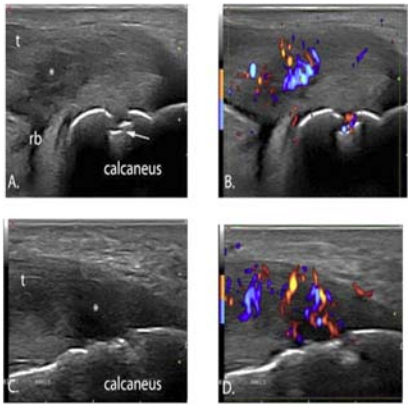

Fig. 7 Sonographic features of enthesitis at the Achilles tendon. Marked Achilles tendinosis (A&B), with loss of fibrillar echotexture (*), retrocalcaneal bursitis (rb), and corresponding vascularity within the tendon as well as abutting the erosion. (...

Lennart Jans , Jacob L. Jaremko , Gurjit S. Kaeley

Novel imaging modalities in spondyloarthritis

Best Practice & Research Clinical Rheumatology, Volume 28, Issue 5, 2014, 729 - 745

http://dx.doi.org/10.1016/j.berh.2014.10.006

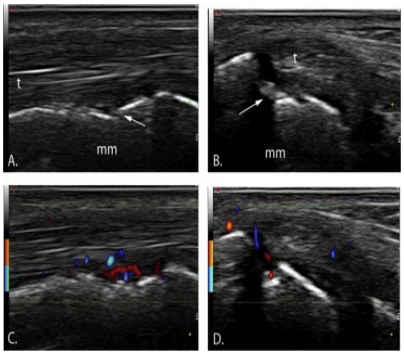

Fig. 8 Longitudinal and transverse images (A&B) of the posterior tibial tendon at the level of the medial malleolus and corresponding Power Doppler images (C&D). Images depict tenosynovitis of the posterior tibial tendon (t), with adjacent cortical...

Lennart Jans , Jacob L. Jaremko , Gurjit S. Kaeley

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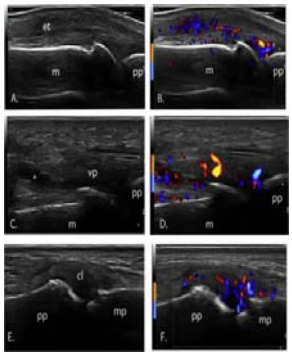

Fig. 1 Sacroiliitis in a 17-year-old female patient. (a) Radiograph of the SI joints is normal. (b–c) Paracoronal STIR MR images show subchondral/periarticular bone marrow edema (arrows) of both SI joints in keeping with sacroiliitis.

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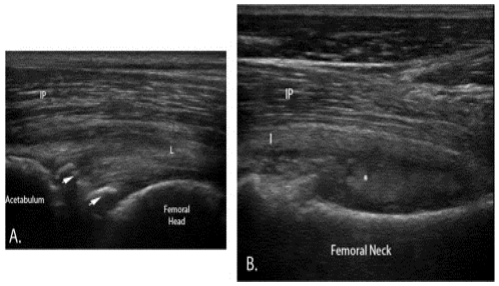

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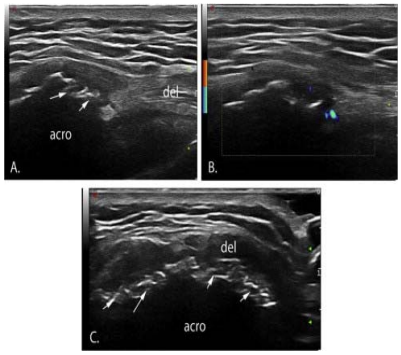

Fig. 9 B-Mode and Doppler images of the lateral deltoid origin (A &B), as well as transverse image of the lateral acromion. (C). Marked irregularity (arrows) of the acromial entheseal origin (acro) as well as vascularity of the deltoid origin (B) is de...

Lennart Jans , Jacob L. Jaremko , Gurjit S. Kaeley

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http://dx.doi.org/10.1016/j.berh.2014.10.006

Return to Program Schedule

Spondyloarthritis

Clement Michet MD
Mayo Rochester

Disclosures

None

Return to Program Schedule

Objectives

- Describe the evolution of the concept of the spondyloarthritis disorders
- Describe inflammatory back pain and other early manifestations
- Review new imaging techniques for the diagnosis of spondyloarthritis
- Review new treatment strategies

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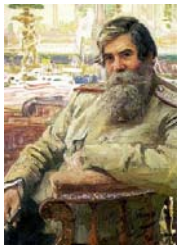
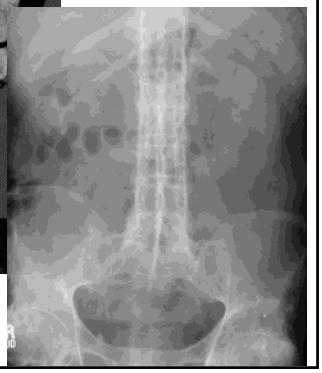
Ankylosing Spondylitis
Early 20th Century Concept





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Rheumatoid "Variants" "Rheumatoid Spondylitis"

Classical Variants

- Ankylosing spondylitis
- Psoriatic Arthritis
- Reactive Arthritis
- Arthritis of Inflammatory Bowel Disease

Unique Musculoskeletal Features

- Spine involvement
- Sacroiliitis
- Oligoarticular peripheral arthritis
- "Sausage digits"

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Which One of These Conditions is the Most Common Spondyloarthritis You Encounter in Your Practice?

1. Ankylosing spondylitis
2. Psoriatic Arthritis
3. Reactive Arthritis
4. Arthritis of Inflammatory Bowel Disease
5. None of these

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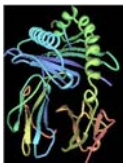
Discovery of HLA-B27
1973



- Demonstrated the strong genetic heritability of AS
  - > 90% positive
  - Prevalence of the disease is determined by the variation of HLA-B27 in different racial and ethnic groups
  - Associated with axial disease and uveitis
- HLA-B27 (-) patients tended to have more peripheral arthritis, psoriasis and IBD

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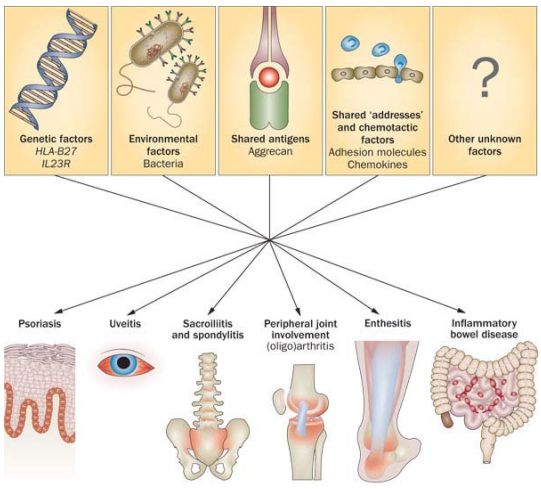
More than HLA-B27



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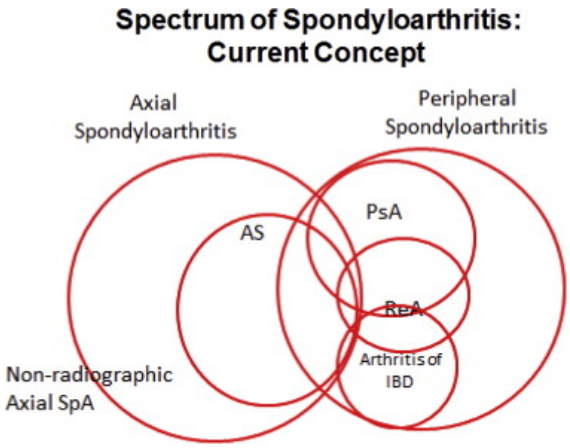
Nature Rheumatology 2012

More than the Classical Four "Variants"



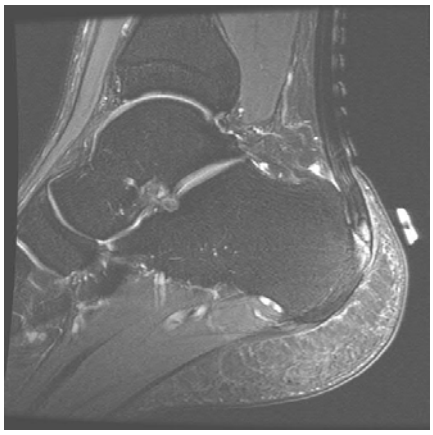
This spectrum is as common as rheumatoid arthritis!

Best Practices & Research Clinical Rheumatology 2014

How we think about early spondyloarthritis

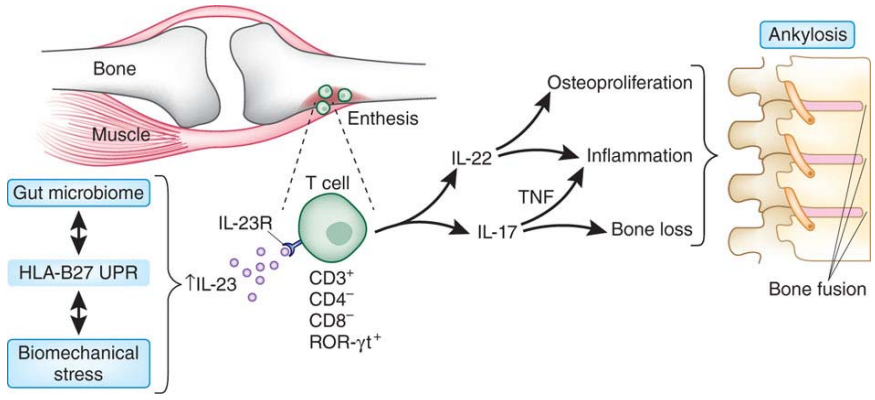
Persistent Achilles Enthesitis in a Young Athlete

- Refractory to usual treatments by trainer
- MRI reveals boney edema
- Mild wrist extensor tenosynovitis
- HLA-B27 positive
- Positive family history for IA in young cousin



Enthesitis

The Primary Target of Inflammation in Spondyloarthritis



Nature Med 2012

Clinical Differences SpA versus RA

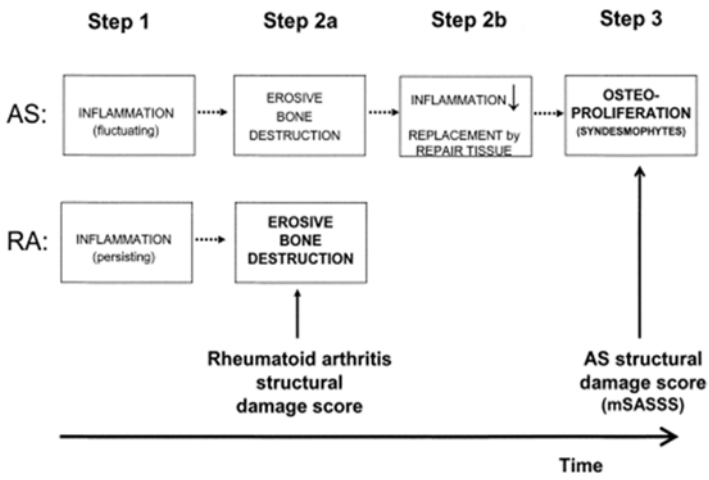
Spondyloarthritis

- Enthesitis, bone inflammation and bone formation
- Asymmetric oligoarticular peripheral arthritis LE>UE
- Rays of joints (dactylitis)
- Calcaneus, plantar fascia
- Axial involvement
  - **"Inflammatory LBP"**
  - Chest wall

Rheumatoid Arthritis

- Synovial disease, bone and cartilage loss
- Symmetric small joints
- Rows of joints – MCPs, MTPs
- "First step" morning metatarsalgia
- Atlantoaxial disease C1-2

New Bone Formation in the Spondyloarthritis Disorders



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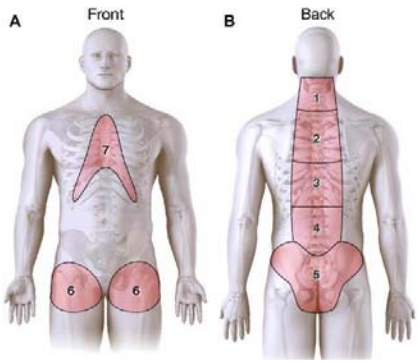
Inflammatory Back Pain

Characteristics

- Age of onset < 40 years
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night, improved by getting up
- 4/5 best for Dx



Not just low back pain

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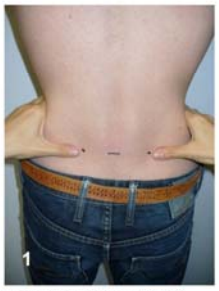
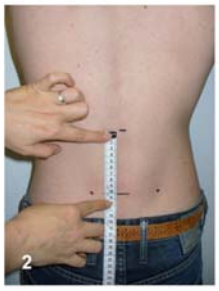
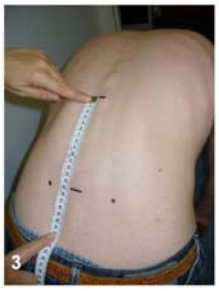
Spinal Mobility – Modified Schober







- Patient standing erect
- Mark an imaginary line connecting both posterior superior iliac spines (close to the dimples of Venus) (1)
- A next mark is placed 10 cm above (2)
- The patient bends forward maximally, measure the difference between the two marks (3)
- Report the increase (in cm to the nearest 0.1 cm)
- The best of two tries is recorded.

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

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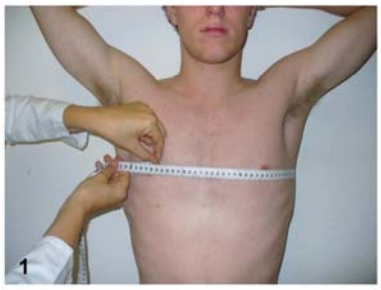
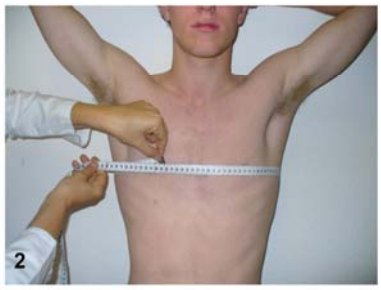
Spinal Mobility – Chest Expansion





- Hands resting on - or behind the head
- Measure at 4th intercostal level anteriorly
- Difference between maximal inspiration (1) and exspiration (2) in cm (eg. 4.3 cm) is recorded
- Report the best of two tries

ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

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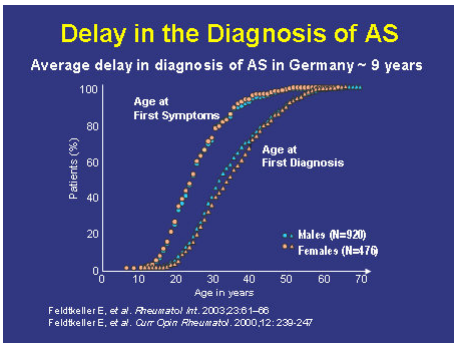
Symptoms frequently precede radiographic changes for years – the history is paramount!



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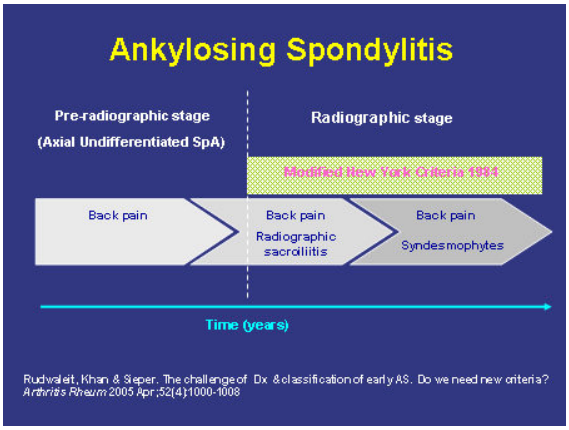
Diagnosis of AS is delayed
Alternative ways of considering AS diagnosis?



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Background Clues in Patients with IBP
An example of the importance of a good history

- Peripheral arthritis 24%
- Enthesopathy 28%
- Dactylitis 7%
- Anterior chest wall pain 19%
- Uveitis 4%
- Psoriasis 15%
- IBD 3%
- Family history of IA, Ps, IBD

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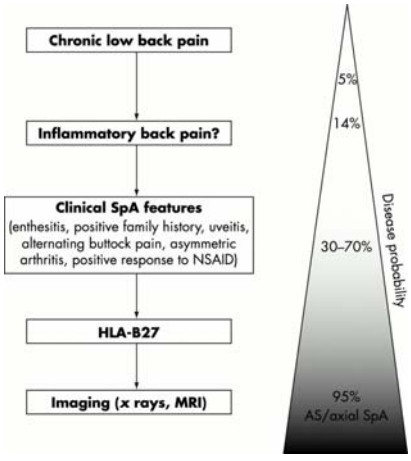
Think About Non-Radiographic, Non-Axial Features to Make an Early Diagnosis

Non-Axial Manifestations

- Enthesitis
- Peripheral arthritis
- Anterior chest wall pain
- Psoriasis
- Dactylitis
- Uveitis
- IBD



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Spondyloarthritis Contemporary Diagnosis

- Less Emphasis on Radiographic Findings
- More Emphasis on Clinical Features
  - Non axial manifestations
  - Non-radiographic axial disease
- New Imaging Techniques
  - MRI for non-radiographic axial disease
  - US for enthesitis

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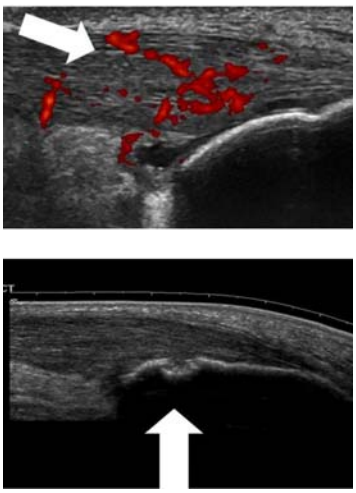
Calcaneal Enthesitis On Ultrasound Exam



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ASAS Criteria for Spondyloarthritis

ASAS Classification Criteria for Peripheral Spondyloarthritis (SpA)

Peripheral Arthritis and/or Enthesitis and/or Dactylitis
PLUS

≥ 1 SpA feature	OR	≥ 2 other SpA features
• Uveitis • Psoriasis • Crohn's / colitis • Preceding infection • HLA-B27 • Sacroiliitis on imaging		• Arthritis • Enthesitis • Dactylitis • Inflammatory Back Pain (ever) • Family history of SpA

Sensitivity 77.8% Specificity 82.2%

Rudwaleit M et al. Ann Rheum Dis 2011;70:25-31

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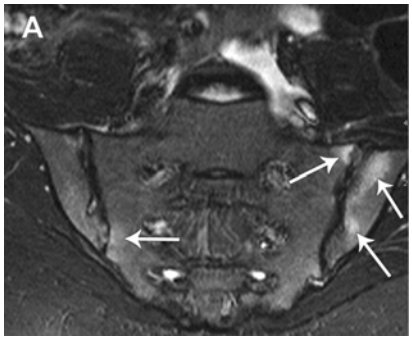
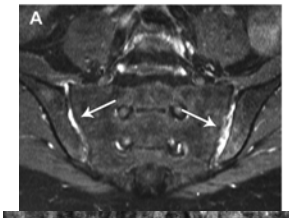
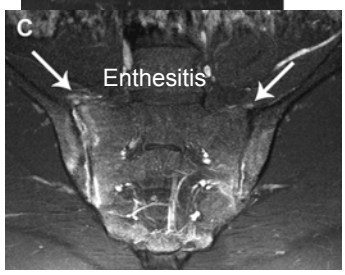
MRI Findings in Non-Radiographic Sacroiliitis



BONE EDEMA



Synovitis



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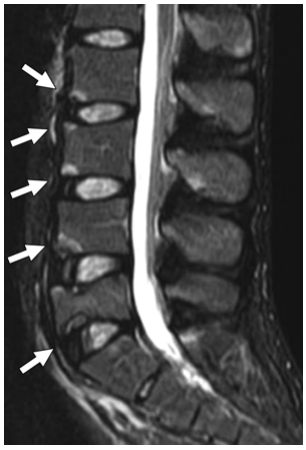
MRI Findings in Active Spondylitis



STIR weighted image

MRI Inflammation

- "Romanus" lesions
  - Inflammation at the edges of vertebral bodies
  - Enthesitis
    - Anterior longitudinal ligament
    - Posterior longitudinal ligament
  - Anterior corner inflammatory lesions (CILs) are the subject of most studies
- No need for gadolinium

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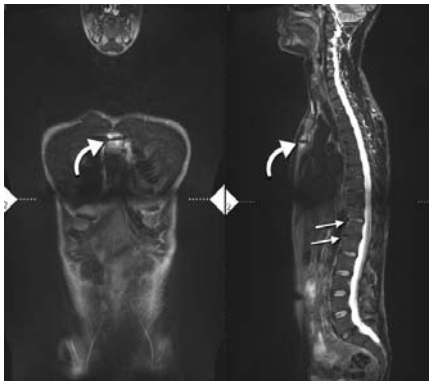
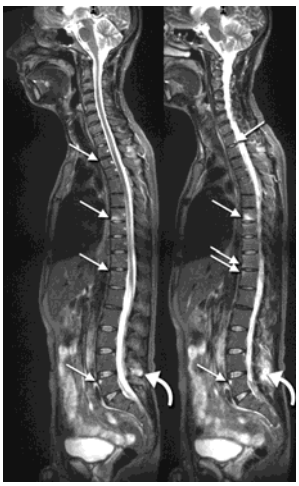
Spotty Involvement in Early AS Documented by Whole Body MRI



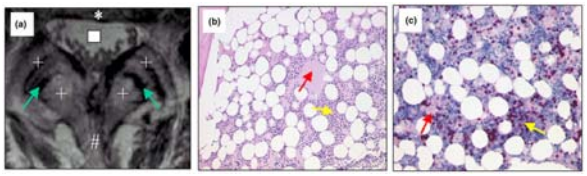
Chest Wall



MAYO CLINIC

False Negative MRI Study

Facet Imaging and Biopsy
No test is 100% sensitive



No inflammation CD3+ T cells with minimal edema

MAYO CLINIC

Arthritis Research & Therapy 2006

Radiological Diagnosis of Inflammatory Back Pain

- Conventional AP pelvis radiographs are more sensitive than MRI for detecting structural changes in the SI joint
  - Obliques views not routine
- MRI imaging with T2FS/STIR is more sensitive for detecting inflammation (bone edema)
  - Multiple lesions one slice or one lesion in more than one consecutive slices considered a positive scan
  - Gadolinium is rarely necessary
- Start with a pelvis x-ray and proceed only to MRI in persons with a negative film

MAYO CLINIC

Pelvis Film Negative, MRI Positive Patients

- The natural history of this subset of patients remains to be clarified
- Not all progress to structural changes, especially persons with unilateral inflammatory edema on MRI
- Severe bone edema and positive HLA-B27 may indicate greatest progression risk to AS (LR 8.0)

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Case

- Your patient, a 45 year old woman with severe AS related to Crohn's Disease asks you to see her son for evaluation. He is 20 years old and is in a VoTech program for carpentry. He previously was very athletic but is now having a lot of pain in his back, neck and anterior chest. Pain is present every AM, responds partially to NSAIDS, improves during the day but disrupts his sleep.
- His exam is normal. He is HLA-B27 positive. Plain x-rays are all normal.
- Given his planned occupation what would you recommend?
  1. Send to PT and continue NSAIDS
  2. Consider other career options
  3. Discuss MRI scan of the SI joints and then see back for review

MAYO CLINIC

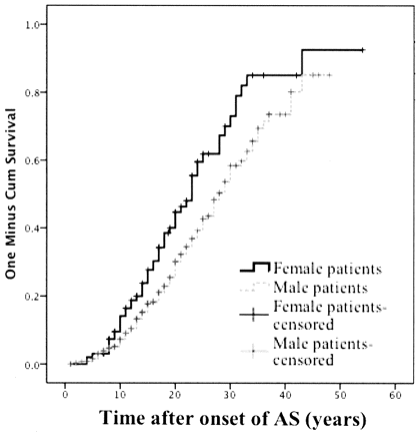
When would I put a patient through MRI evaluation?

Would it make a difference in your recommendations?

Counseling

Treatment

Spondyloarthritis Work Disability



Early polyarthritis and heart disease are significant risk factors for early disability

Non-manual work and the ability to self pace a work reduce the risk of work disability

J Rheum 2011

Advantages to Imaging in Non-Radiographic Disease

- Confirm the diagnosis
- Avoid mislabeling and misdiagnosis
  - HLA- B27 positive mechanical back pain
  - HLA-B27 positive fibromyalgia
- Understand the limitations of imaging
  - False positive scans with bone edema
    - DJD
  - False negative scans

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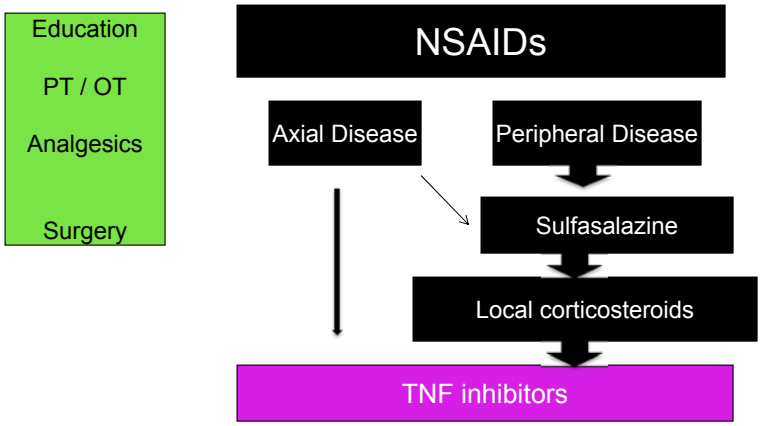
ASAS/EULAR Recommendations for Management of AS 2006



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What can you expect from NSAID therapy?

- Over 70% of patients will derive some benefit
- But only 40% experience more than a 40% reduction in ASAS response
- Long term (2 years or more) continuous use may slow radiological progression in the subset of patients with syndesmophytes and elevated CRP
- At this point symptoms management is the primary indication for NSAID use in SpA
  - Consider GI and CV risks

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NSAID Therapy in Spondylitis

Choosing NSAID Drugs

- There is no preferred agent based on efficacy
  - Symptom relief should be rapid but MRI reduction of inflammation is minimal (<20% demonstrate reduction)
  - Dose at maximum recommended for at least 4 weeks
- **Avoid** NSAIDs in patients with inflammatory bowel disease related spondylitis
  - Start with a low dose and only increase in a month if bowel symptoms don't flare (Celecoxib?)

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TNF Inhibition in Spondylitis

- Who do we consider?
  - BASDAI > 4 and failure of 2 NSAIDs after 4 week trials
  - ASDAS ≥ 2.1 – less stringent
  - Refractory peripheral arthritis after trial of sulfasalazine or methotrexate
  - Hip joint synovitis
  - Refractory uveitis
- What to expect
  - Symptoms respond within a few weeks and plateau at 3 months
  - A minority (20%) of patients enter remission
  - Stop if no response in 8 weeks

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TNF Inhibition in Spondylitis

- Does the choice of product matter?
  - Monoclonal antibody for arthritis related to IBD
  - Monoclonal antibody for etanercept refractory uveitis
- What we don't know
  - Would early intervention with a TNFi slow boney proliferation?
  - Would treatment of non-radiographic AS prevent progression of the disease?

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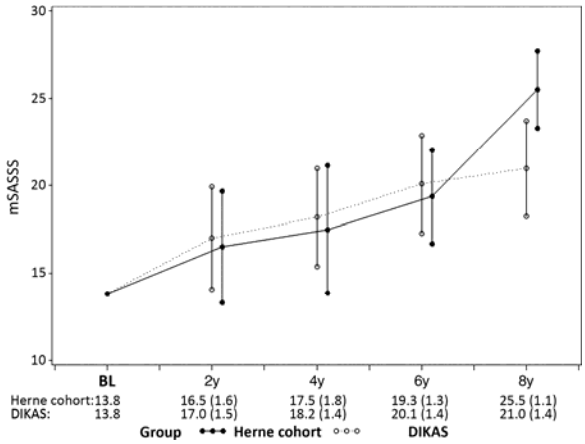
TNF Inhibitors are Not Curative

No Impact on Long term Structural Progression



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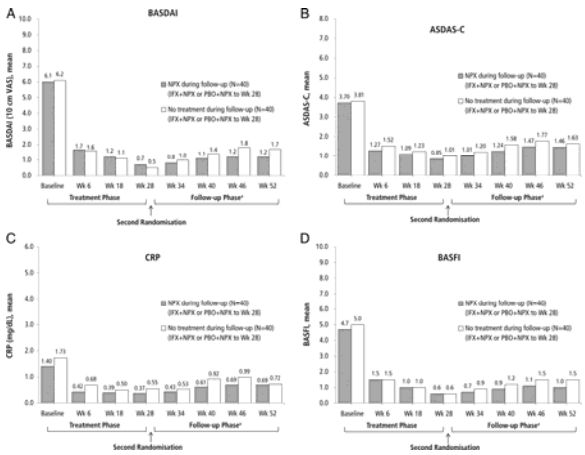
Annals Rheumatic Dis 2013

Can TNF Inhibitors be Used Short Term?

INFAST Study of Infliximab and Naproxen



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Ann Rheum Dis 2014

Summary

- The spondyloarthritis disorders are more common than previously thought
- Inflammatory back pain is a key component for early identification of axial disease
- Consider a spondyloarthritis when seeing patients with iritis, plantar fasciitis, Achilles tendonitis or chest wall pain
- MRI has enabled early detection of axial disease
- The long term role of biologic therapy is still under investigation

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Return to Program Schedule

Hip Pain

Thomas D. Rizzo, Jr., M. D.
Department of Physical Medicine and Rehabilitation
Mayo Clinic
Jacksonville, Florida

Mayo Clinic Rheumatology Update
April 18, 2015

Disclosures

- I will not speak about any off-label use of medications
- I do not receive payments from Big Pharma or Device Manufacturers
- I am still not beholden to The Man.

Return to Program Schedule

Objectives

- Discuss the evaluation of the patient's complaint of Hip Pain
- Present different scenarios that can be confused with hip joint pain
- Appreciate therapeutic interventions and the time frame for their efficacy

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"LISTEN TO THE PATIENT. THEY ARE TRYING TO TELL YOU THE DIAGNOSIS."

Sir William Osler

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“THE PATIENT DID NOT (NECESSARILY) GO TO MEDICAL SCHOOL. IT IS YOUR JOB TO MAKE THE DIAGNOSIS. SOMETIMES YOU HAVE TO LOOK AT THE PATIENT.”

Dr. Rizzo’s corollary

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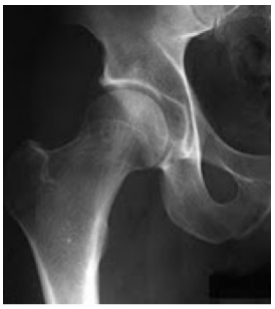
Case #1

50 something with “hip pain

Had seen multiple specialists

Negative hip x-rays

Frustrated by her condition



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Case #1

Physical exam
Normal neuro-vascular exam
Normal hip, knee and Lumbar spine exam
Patient demonstrated location of her pain:

A test was performed

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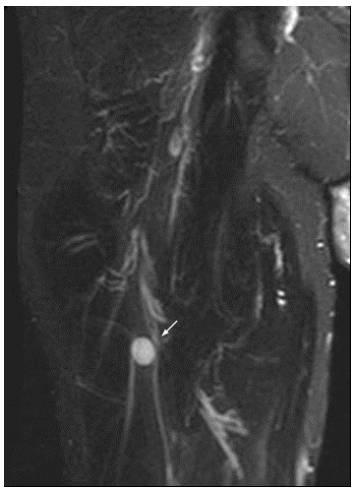
Case # 1



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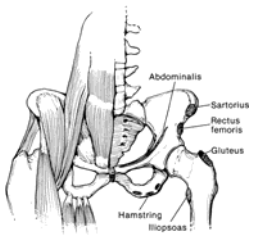
Normal ROM
Hip



Chapter 25 – Hip and Pelvis Stephen L. Nuccion, MD David M. Hunter, MD Gerald A.M. Finerman, MD in DeLee and Drez's Orthopaedic Sports Medicine, 2nd ed., Copyright © 2003 Saunders

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Normal AROM
Hip

- Flexion 0-125 degrees
- Extension 0-15 (0-30)
- Abduction 0-45
- Adduction 45-0 (0-25)
- External Rotation 0-45 (0-60)
- Internal Rotation 0-45 (0-45)

http://www.merck.com/mmpe/sec22/ch336/ch336b.html#CIHEFGGH
http://www.vba.va.gov/bln/21/Benefits/exams/disexm34.htm

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Flexion ABduction External Rotation

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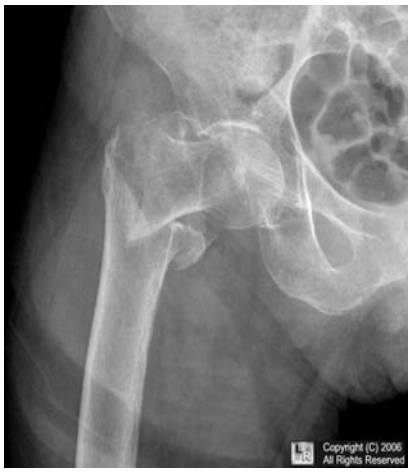
Joint Evaluation
Hip



- Groin pain
- Short leg
- Externally rotated
- Pain with passive motion

www.learningradiology.com/.../cow213lg.jpg

Hip Area Injuries

- Hip joint pathology
  - History
  - Location
  - Exam
  - Pathology
    - Degenerative Joint Disease
    - Avascular Necrosis
    - Joint capsule pathology

Joint Evaluation Methods

Observation

- Let the patient demonstrate
- Compare side to side
- Take your time
- Mentally assess unaffected area to decrease exam time

http://www.youtube.com/watch?v=tcfGb6b2KWQ&NR=1

Joint Evaluation Methods

Manual Muscle Testing

- Reinforces what you see
- Make the patient comfortable
- Don't inflict pain yourself…at first
  - Patient demonstrate
  - Unaffected joint
  - Isometric testing
  - Hone in on the pathology
- Gain the advantage

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Joint Evaluation Principles

Compare When Possible

- The patient has paired joints so you have a reference.
  - Requires you to know which one is normal
    - Fortunately, the patient can often tell you which is abnormal
- Symmetric disease poses a problem
  - Can compare to yourself…assuming you lack pathology

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Joint Contractures

- A joint contracture is a limitation in the passive range of motion of a joint
  - Determine AFTER eliminating pain or spasticity
- Naming convention: Joint involved + Opposite the lack of range
  - Knee flexion contracture lacks full extension

From "Joint Contractures" by Campbell M, Dudek N, Trudel,G in Essentials of Physical Medicine and Rehabilitation, 3rd Ed, 2013 Elsevier, Frontera, Silver, Rizzo eds.

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Joint Contractures

- Joint contractures
- Reasons for joint limitation:
  - Heterotopic ossification
    - Brain injury
    - SCI
  - Myositis ossificans
  - Fracture

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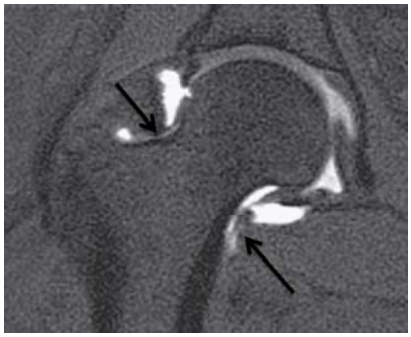
Adhesive Capsulitis of the Hip

- Gradual onset of stiffness
  - Limitation in crossing legs
  - Difficulty with activities requiring hip flexion
- Pain with extremes of External Rotation or Abduction

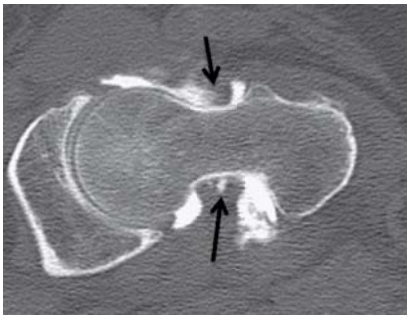
Frozen Hip

from PMcIntosh Adhesive Capsulitis of the Hip in Essentials of PM&R 3rd ed.

MRI arthrogram

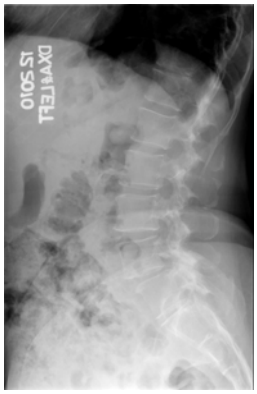


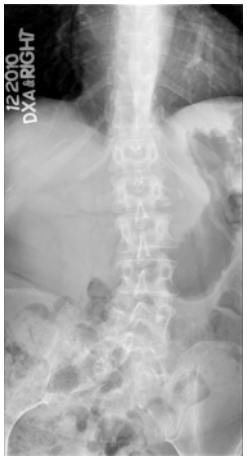
CT arthrogram



Case #2

- 50 something referred for LBP
- History of smoking and Graves disease
- Family history of Ehlers-Danlos Syndrome (daughter)
- Exam positive for increased lumbar lordosis and painless decrease in hip motion





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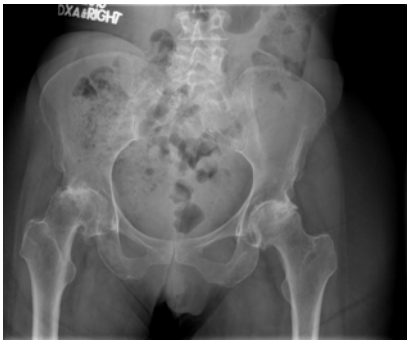
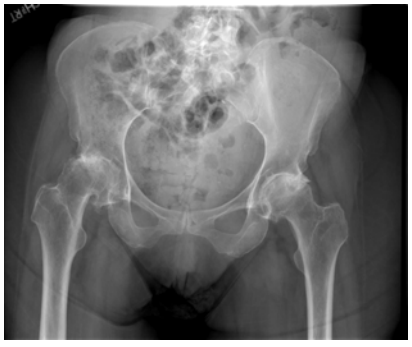
Case #2

December 10, 2010



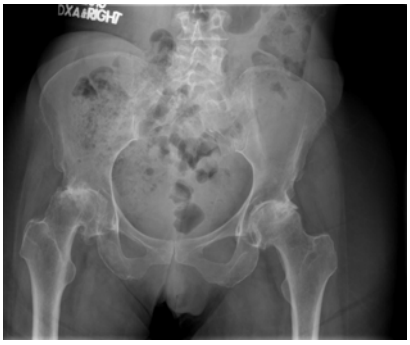
September 2, 2011



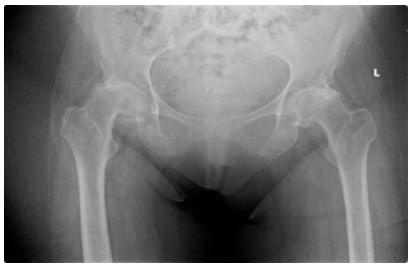
MAYO CLINIC

Case #2

December 10, 2010



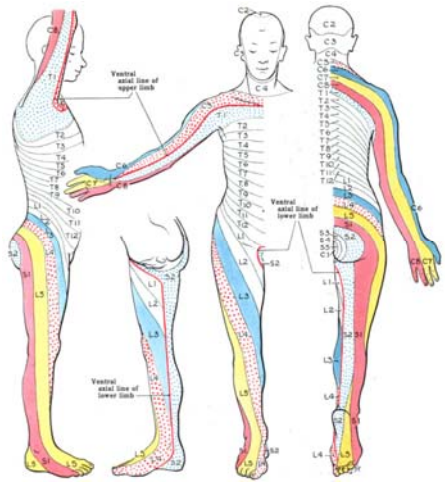
March 8, 2013



Testing for “hip pain”

- Imaging
  - x-rays
  - MRI +/- contrast
  - CT scan +/- contrast
  - Ultrasound evaluation
- EMG
  - r/o L2/femoral neuropathy

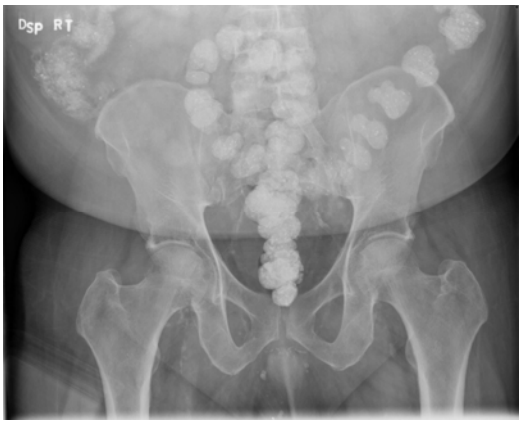
Dermatome map



MAYO CLINIC

Case #3

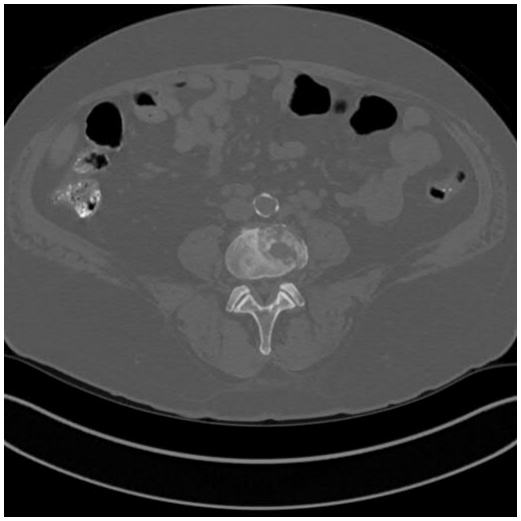
- 59 yo with 2 month history of Left groin/thigh pain
- History of Hepatocellular Carcinoma
- No trauma



MAYO CLINIC

Case #3

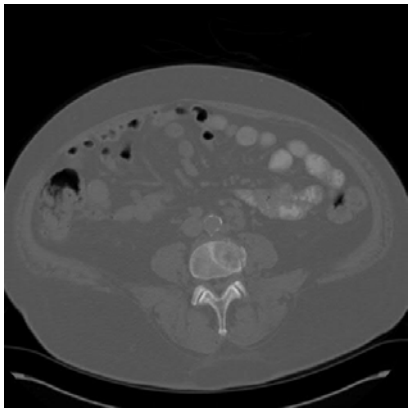
- Physical Exam
- Pain with Manual Muscle testing of Proximal Lower limb muscles
- No Pain with Passive ROM



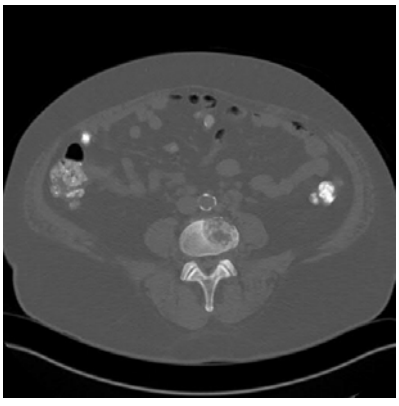
MAYO CLINIC

Case #3

CT June 3 2014



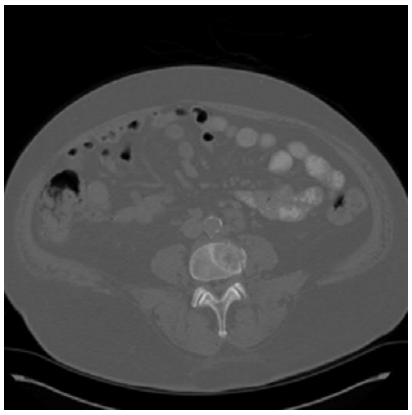
CT August 21, 2014



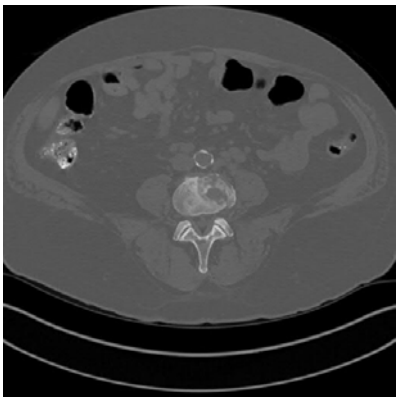
MAYO CLINIC

Case #3

CT June 3 2014

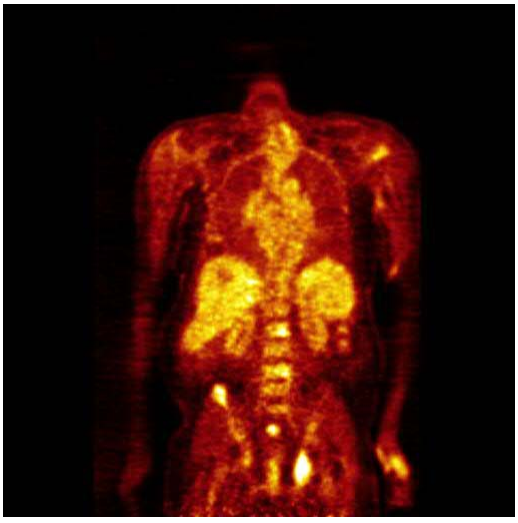


CT September 18, 2014



Case # 3

- Further testing included a PET scan done October 7, 2014
- L4 and L2 involvement
- Left Acetabular involvement



Case # 3

- Patient underwent Vertebroplasty at L2 and L4 October 21, 2014
- Radiation Therapy to Lumbar spine and Left hip

- By December 3, 2014
  - Pain down from 8/10 to a 3/10
  - Improved activities

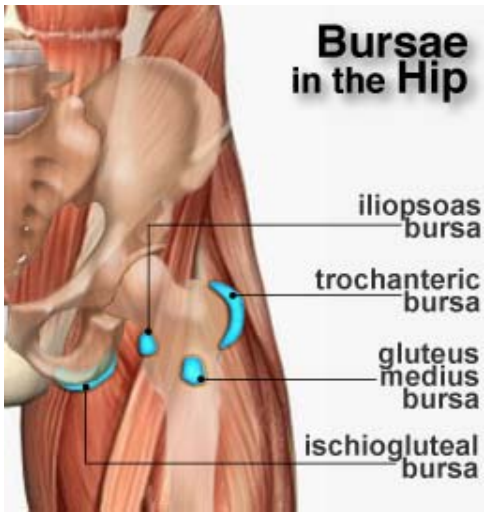
Hip Area Injuries

- Anatomy
  - Joint
  - Muscles
  - Pelvis
  - Buttock

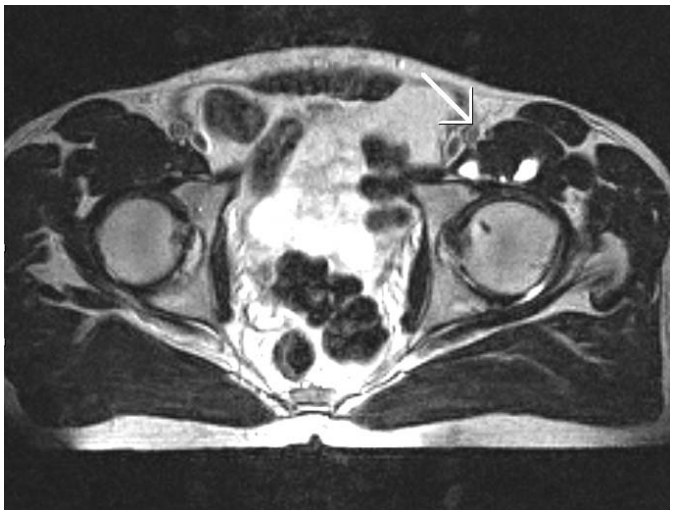
Hip Area Injuries

- Muscles and muscle attachments
  - Hip flexors
  - Lesser trochanter
  - Greater trochanter--Trochanteric bursitis
  - Ilio-tibial band (ITB)
  - Gluteus medius

Hip area bursae



MRI of Ilio-psoas bursa

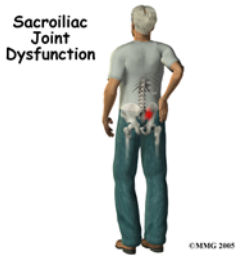


http://sumerdoc.blogspot.com/2011/01/iliopsoas-bursitis-tenditis-mri.html

Sacro-iliac Pain

- Symptoms
  - Complaint of pain in SI area
  - Reports feeling twisted
  - May be asymptomatic standing or sitting but symptomatic sitting or standing
- Exam
  - Normal neuro-vascular exam
  - Normal hip joint exam
  - Restricted SI joint motion
  - Tight hip flexors
  - Tight hip external rotators

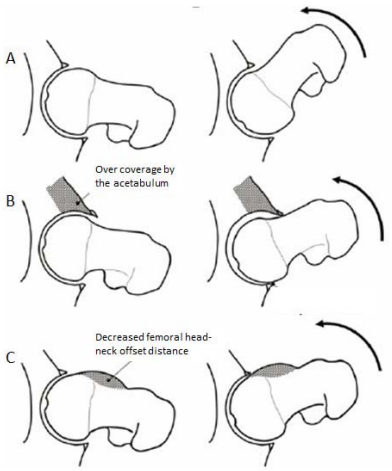
Sacro-iliac Pain



Femoral Acetabular Impingement

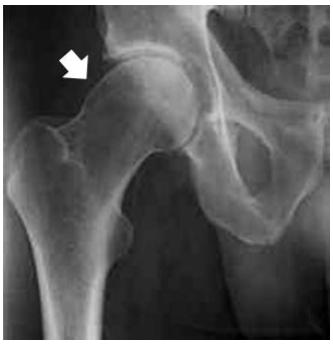
- Hip Pain in Athletes
  - 3 to 8% of sports injuries (30-80/1000)
    - Labral tears in 22-55% of athletes with hip complaints (7-44/1000)
  - It is not always clear that the Labral tear in the cause of the hip pain.

Femoral Acetabular Impingement



MAYO CLINIC

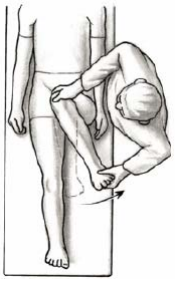
Femoral Acetabular Impingement



MAYO CLINIC

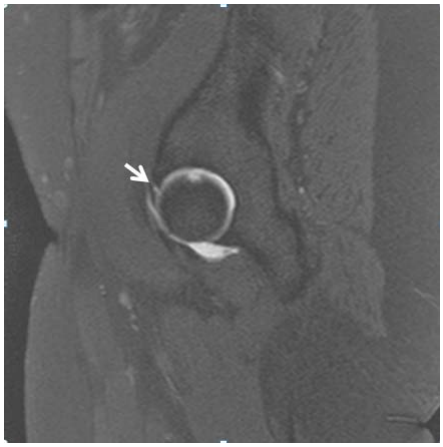
Hip Exam

- Flex hip > 90 degrees
- Adduct and Internally rotate the hip
- Anterior groin pain = positive test for Femoral acetabular impingement or labral tear
- Scouring Maneuver
- Abducted and Externally Rotated
- To
- Adducted and Internally Rotated



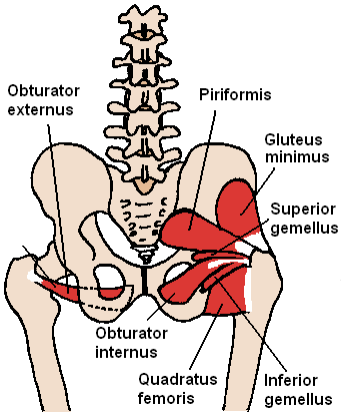
MAYO CLINIC

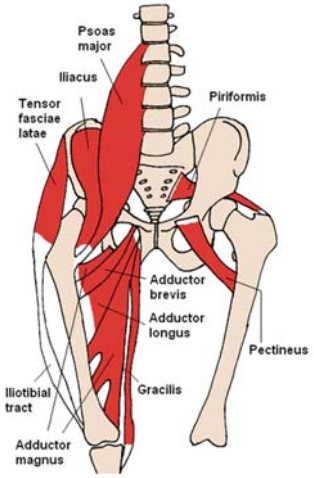
Hip Labral Tear



MAYO CLINIC

Hip girdle muscles





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Hip Pain

- Pain Relief
  - Cane in opposite hand
  - Injections
    - Interarticular hip joint
    - Diagnostic
      - Sacro-iliac joint
      - Bursae
  - Surgery
    - Hip replacement vs resurfacing/hemi-arthroplasty

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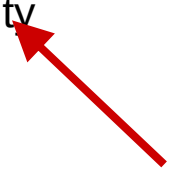
Hip Pain

Flexibility



Pain Relief

Hip Pain

Flexibility

- Stretch Hip Flexors
- Stretch Hip Abductors
- Stretch Hip Rotators

Low Back Pain

Strengthening

Pain Relief

Hip Pain

Strengthening

- Strengthen hip girdle
  - Abductors
  - Gluteal Muscles
  - Closed-kinetic chain exercises
- Non-impact or non/minimal weight bearing exercise
  - Bikes
  - Pool based

Low Back Pain

Flexibility

Strengthening

Pain Relief

Return to Function

Physical Therapy

- Pain Control
- Re-establish Motion/ Posture
- Improve strength
- Return to desired activities

Physical Therapy

- May be difficult but shouldn't be painful
- Post exercise discomfort for less than 2 hours
- Takes 2 months for significant change in strength
- If this is not working, consider re-assessment

Physical Therapy
Reasons it won't work

- Wrong Diagnosis
- Wrong Treatment
- Not long enough treatment
- Patient doesn't "get it"

Return to Program Schedule

Diagnostic Utility Musculoskeletal Ultrasound in Rheumatology

Gurjit S. Kaeley, MBBS, MRCP, FACR
Division Chief,
Associate Professor of Medicine,
Director of Musculoskeletal Ultrasound,
Division of Rheumatology,
University of Florida College of Medicine, Jacksonville, Florida

Disclosures

- **None**

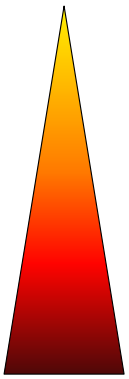
Return to Program Schedule

Objectives

- **Upon completion of this session, participants should be able to:**
  - Explain how ultrasound assists in the assessment and management of regional pain syndromes
  - Describe the utility of ultrasound in Rheumatoid Arthritis and Spondyloarthropathies.
  - Recognize sonographic features of crystalline arthropathies

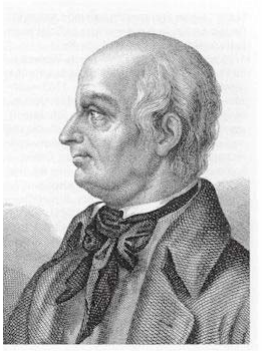
Ultrasound

Medical Ultrasound	1.0 - 20 MHz
Ultrasound	>20,000 Hz
Audible Sound	20Hz-20,000 Hz
Infrasound	0-20 Hz



Lazzaro Spallanzani

Born	January 10, 1729 Scandiano
Died	February 12, 1799 Pavia
Nationality	Italy



http://en.wikipedia.org/wiki/Lazzaro_Spallanzani

A brief history of musculoskeletal ultrasound: 'From bats and ships to babies and hips'
Kane et al
Rheumatology 2004; 43: 931-933

MAYO CLINIC

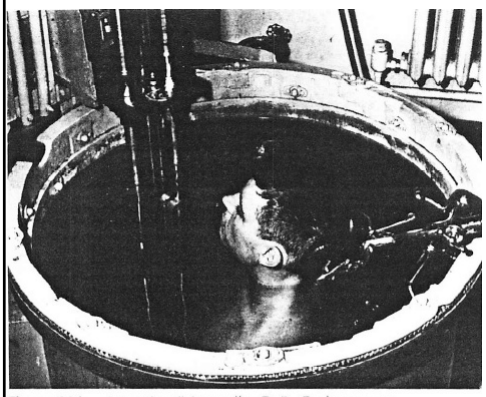


Figure 20A A "patient" (actually, C. R. Cushman, an electronic engineer working with Howry on the project) in position in the B-29 scanner, prepared for taking a scan of the neck. Lead weights on the patient's stomach ensured a consistent immersion level.

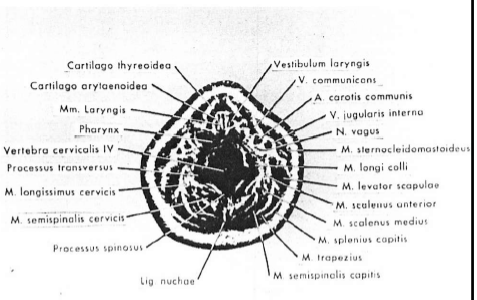


Figure 20B Cross-section of the neck of C. R. Cushman, made in the "gun-turret" scanner in 1956. Ten minutes were required to construct the image onto photographic film. The ability to image anatomical structure within the neck in such detail was a technical breakthrough for the Howry team. [Photograph courtesy of G. J. Posakony.]

Medical Diagnostic Ultrasound: Retrospective on its 40th Anniversary

MAYO CLINIC

Contemporary Ultrasound Machines

Why Rheumatologists Should Perform Musculoskeletal Ultrasound

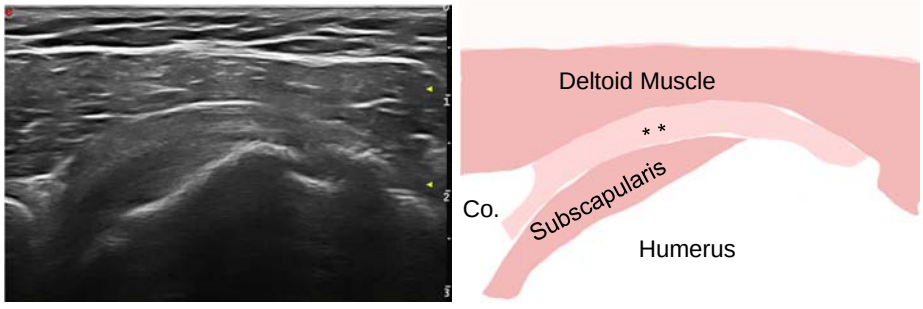
- Improve immediate diagnosis of joint and soft tissue disease ('extension of clinical examination')
- Early diagnosis of synovitis
- Early diagnosis of bone erosion and cartilage damage
- Objective monitoring of therapeutic response, disease status and outcome
- Improve interventional skills

Kane, D. et al. Rheumatology 2004 43:823-828; doi:10.1093/rheumatology/keh214

Indications For Musculoskeletal Ultrasound

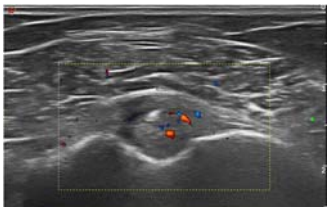
- Regional Pain
- Rheumatoid Arthritis
  - Damage
  - Synovitis
  - Extra-articular structures
- Spondyloarthropathy
- Crystalline Arthropathies
- Ultrasound Guidance for Procedures

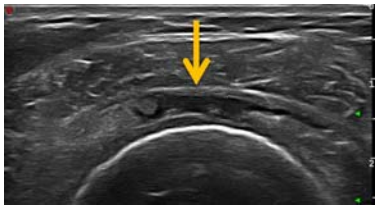
Regional Pain: Shoulder Pain

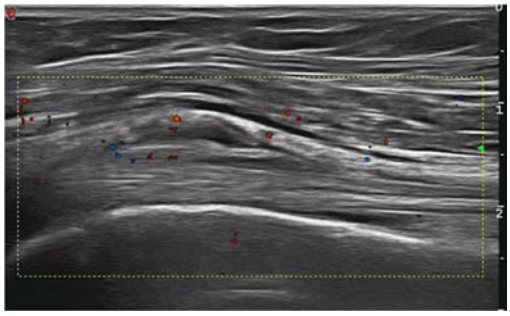


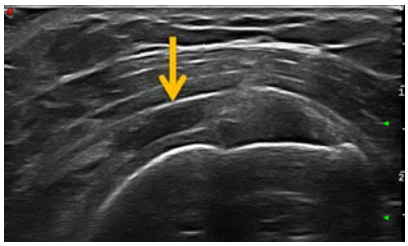
Dynamic testing reveals presence of subcoracoid/subdeltoid bursitis (**)

Regional Pain: Shoulder Pain





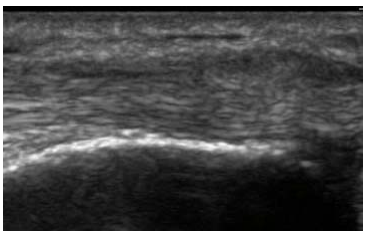


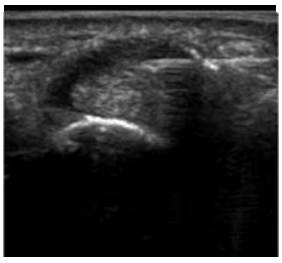


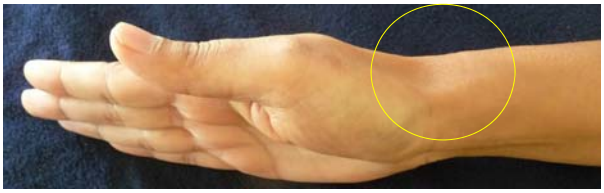
Supraspinatus Tear

Bicipital Tenosynovitis

Regional Pain: Lateral Wrist Pain





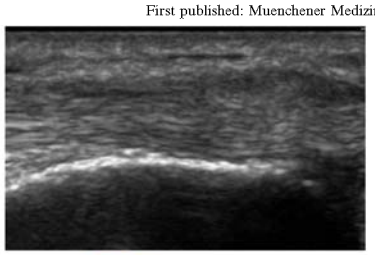


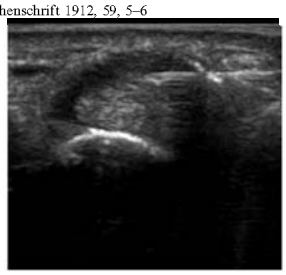
Translated Article

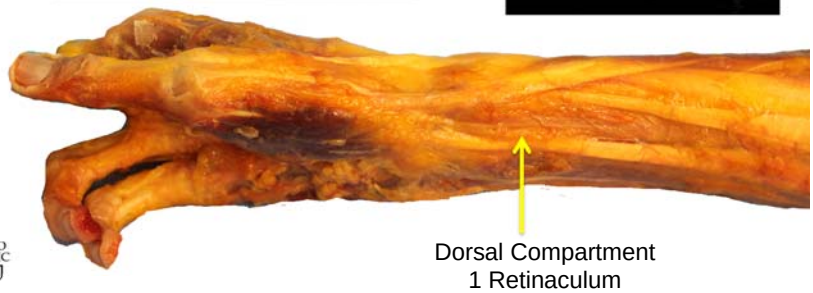
ON THE NATURE AND TREATMENT OF STENOSING TENDOVAGINITIS ON THE STYLOID PROCESS OF THE RADIUS

DR F DE QUERVAIN OF BASEL

First published: Muenchener Medizinische Wochenschrift 1912, 59, 5–6

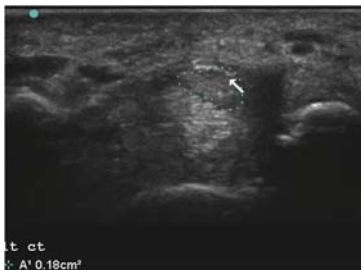


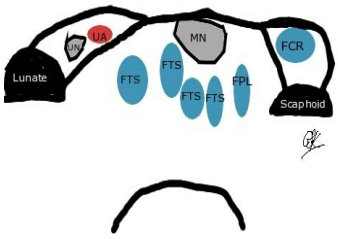




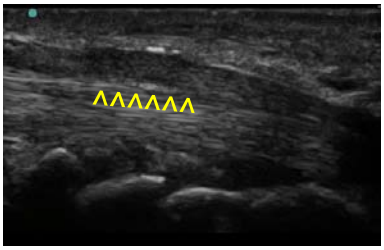
Dorsal Compartment
1 Retinaculum

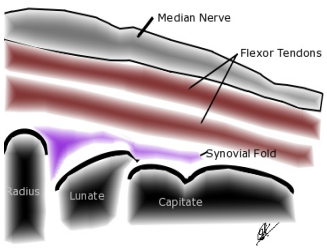
Carpal Tunnel Syndrome





Edema and Pre-stenotic Dilation of Median Nerve





Indications For Musculoskeletal Ultrasound

- Regional Pain
- Rheumatoid Arthritis
  - Damage
  - Synovitis
  - Extra-articular structures
- Spondyloarthropathy
- Crystalline Arthopathies
- Ultrasound Guidance for Procedures

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How Does Ultrasound Help in the Diagnosis of Inflammatory Arthritis?

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When to Consider US in RA

ERA

Diagnosis: confirm synovitis

Prognosticate: Doppler Activity and Erosion detection (Information may guide aggressiveness of therapy)

LDA **MDA** **HDA**

Established RA

Confirm Doppler remission

Consider when additional evidence for ongoing synovitis or damage is needed to escalate or de-escalate therapy

Consider when there is discrepancy between physician and patient global tender and swollen joint counts

Consider for evaluation of symptomatic areas where clinical exam is not clear, eg, at shoulders, elbows, hips, ankles and feet

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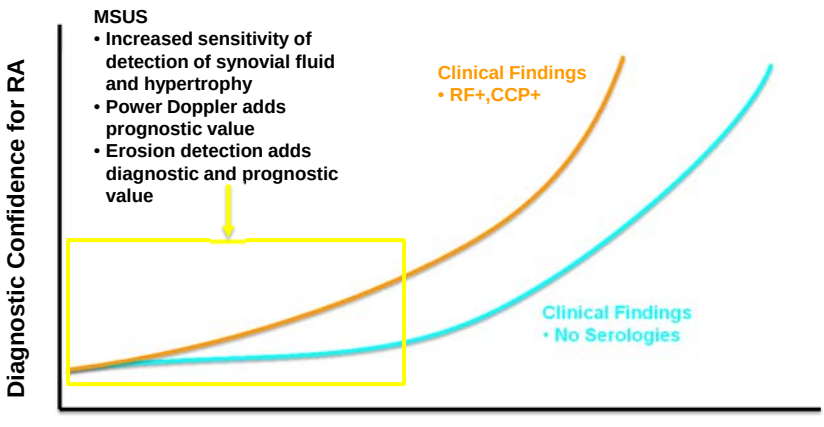
LDA = low disease activity; MDA = moderate disease activity; HDA = high disease activity

Written communication: Gurjit Kaeley, MD, October 2013.

Use of Sonography in ERA



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RF = rheumatoid factor
CCP = anticyclic citrullinated peptide

Personal Communication Gurjit S Kaeley Oct 2013
Colebatch AN et al. *Ann Rheum Dis*. 2013;72(6):804.

MSUS – Role in Diagnosis of Early Inflammatory Arthritis

- Prognostication?
  - In patients seronegative for RF, CCP, baseline sonographic findings of synovial hypertrophy, PD, and erosions predicted a diagnosis of Inflammatory arthritis at one year.
  - Van Stadt et al – patients seropositive for RF and or CCP – B-mode synovitis and PD predicted future inflammatory arthritis at the joint level.

MAYO CLINIC

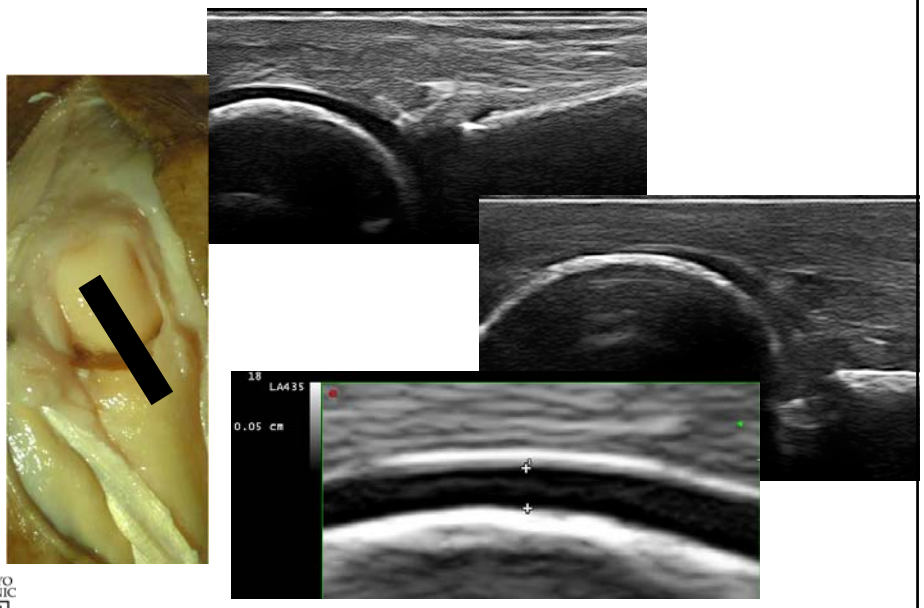
Freeston JE et al Annals of the rheumatic diseases 2009:ard.2008.106658.
van de Stadt LA *et al.. Arthritis research & therapy 2010; 12:R98*

Use of MSUS in RA: Joint Assessment

- Disease activity evaluation
  - Estimation of joint destruction
    - Cartilage degradation
    - Erosion detection
  - Estimation of ongoing activity
    - Synovial hypertrophy and fluid
    - Activity of synovial hypertrophy inferred by estimating blood flow – doppler techniques

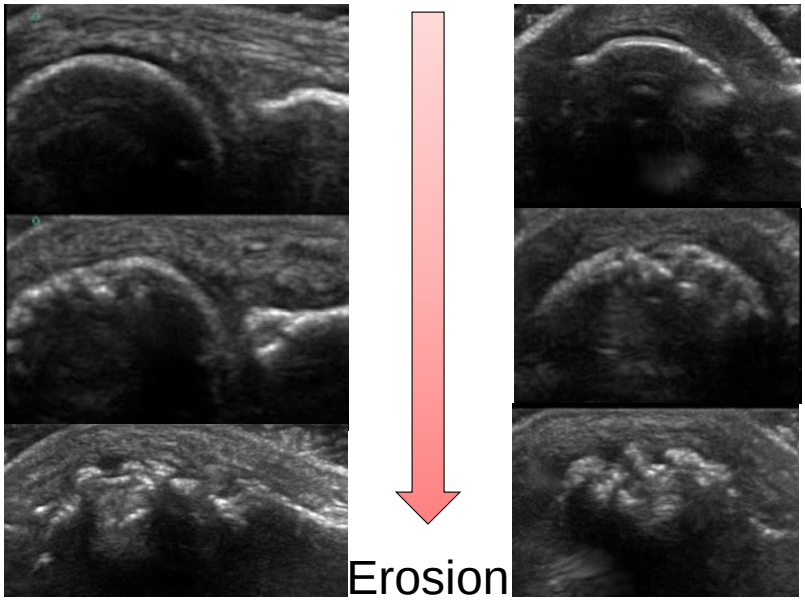
MAYO CLINIC

Metacarpal Head Cartilage



MAYO CLINIC

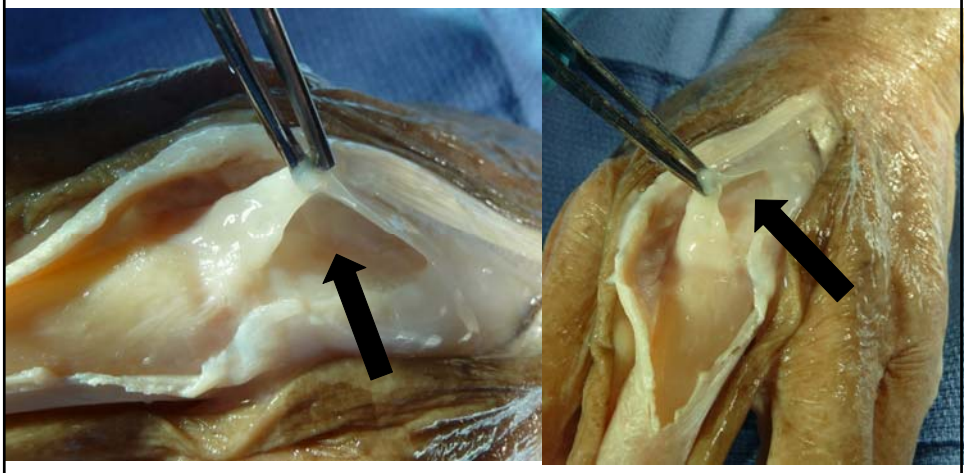
RA Cartilage Degradation



MAYO CLINIC

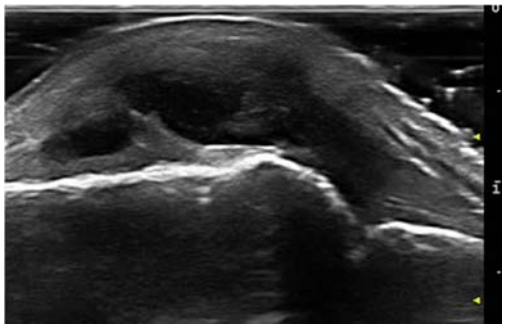
Evaluating Activity

MCP Joint Dorsal Recess

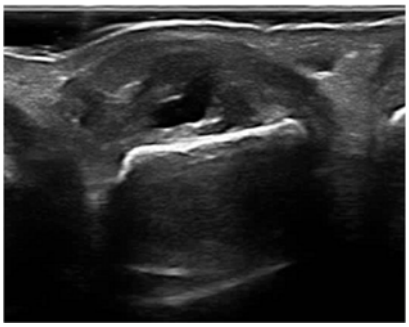


Evaluation of Effusion

- Synovial Fluid (Anechoic compressible material)

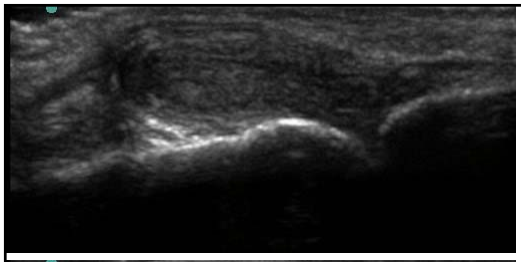


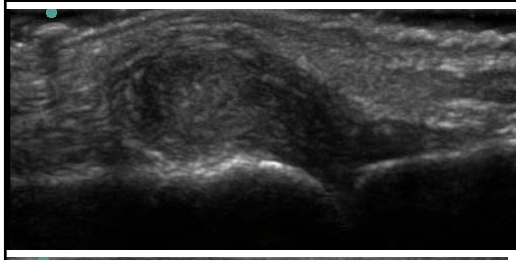
2nd MCP Longitudinal View

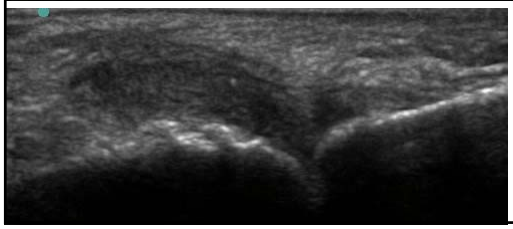


2nd MCP Short View

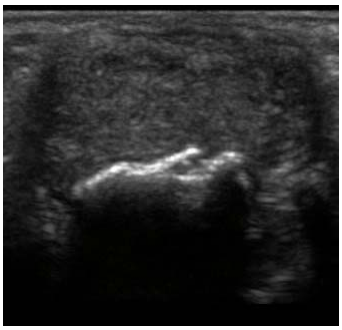
MAYO CLINIC



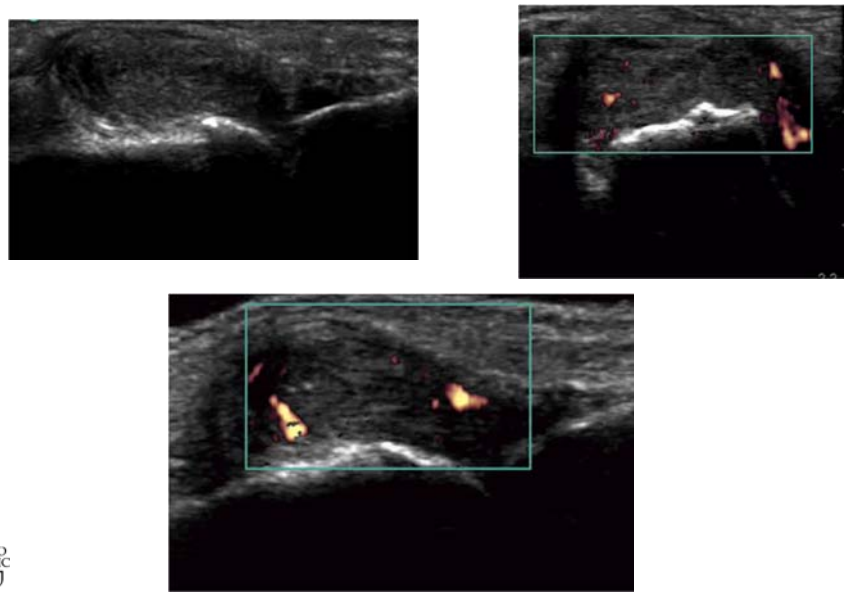




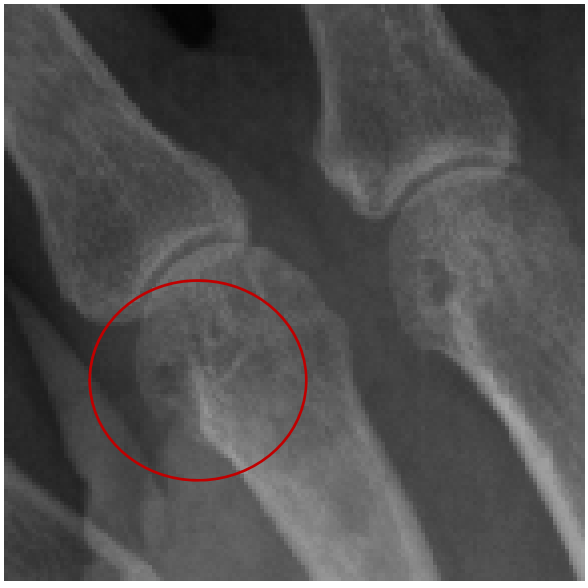
RA –MCP Joint Synovial Hypertrophy



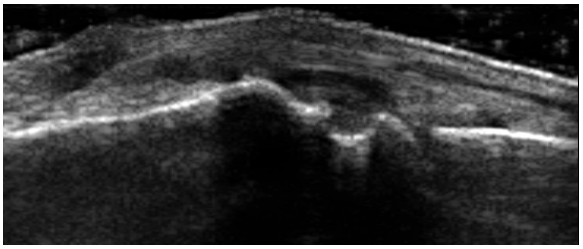
RA –MCP Joint Synovial Hypertrophy

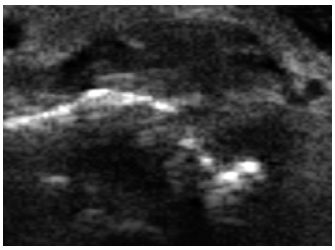


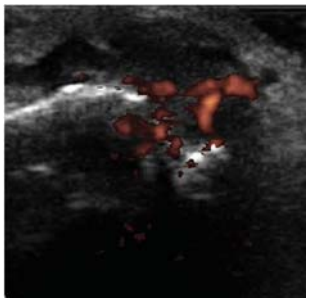
RA – MCP 2 Erosion – Is it Active?



RA – MCP 2 Erosion – Is it Active?







Use of MSUS in RA - 2

- Evaluation of extra-articular structures
  - Evaluation of tendons
  - Evaluation of nerves for entrapment neuropathy
- Evaluation of large joints / Regional Pain
  - Commonly a source of pain and disability.
  - Eg Shoulder, Ankle

Tendon Involvement in RA

- Extensor Compartment

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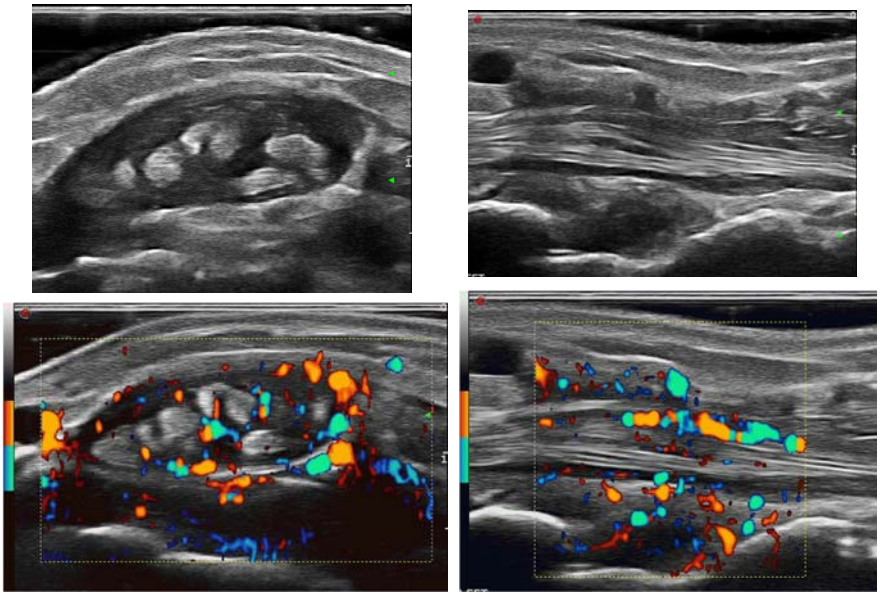
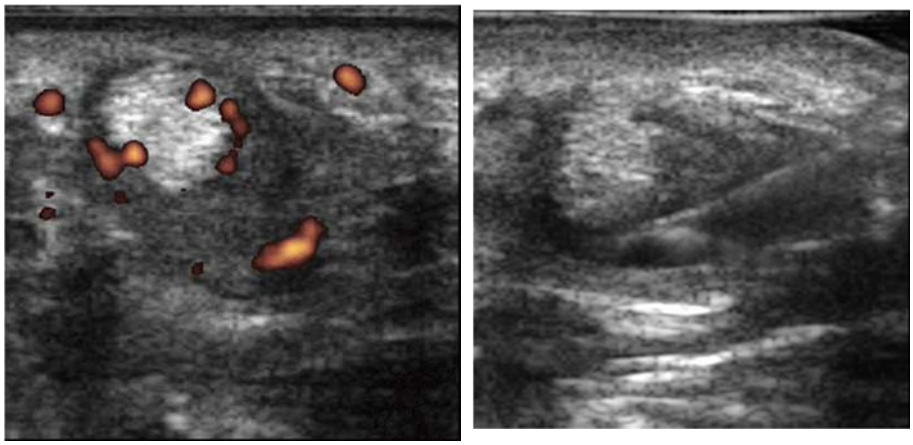
Extensor Tenosynovitis



MAYO CLINIC

Right 3rd Flexor Tendon Sheath

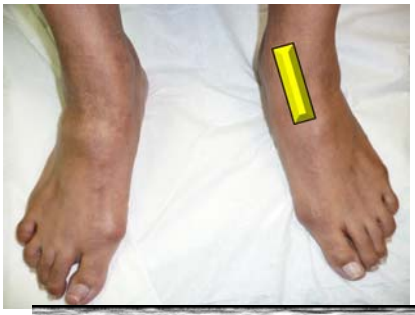


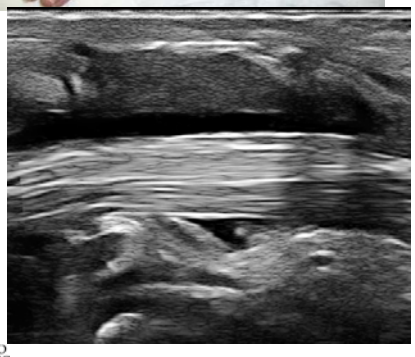
MAYO CLINIC

Use of MSUS in RA - 2

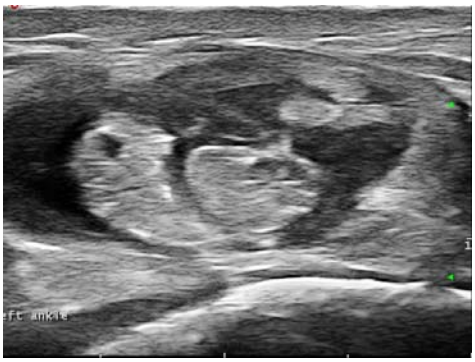
- Evaluation of larger joints / Regional Pain
  - Commonly a source of pain and disability.
  - Eg Shoulder, Ankle

MAYO CLINIC

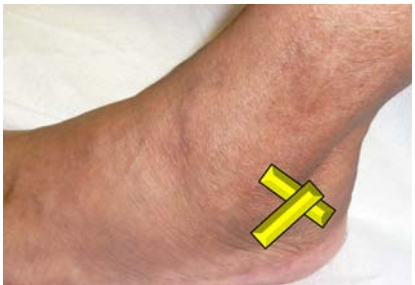


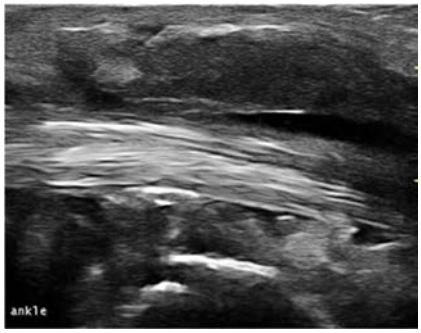


Left Ankle Pain

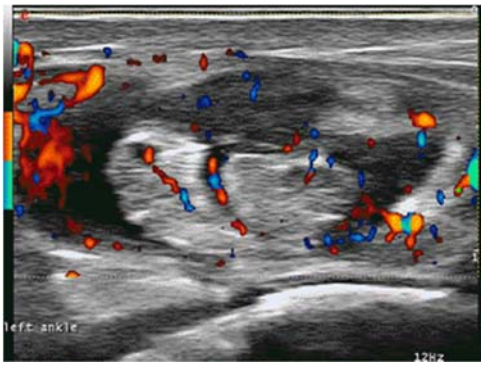


MAYO CLINIC





Left Ankle Pain



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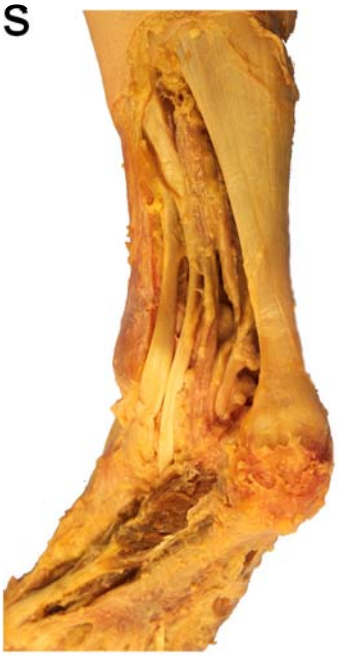
Indications For Musculoskeletal Ultrasound

- Regional Pain
- Rheumatoid Arthritis
  - Damage
  - Synovitis
  - Extra-articular structures
- Spondyloarthropathies
- Crystalline Arthopathies
- Ultrasound Guidance for Procedures

MAYO CLINIC

Le Premier Enthesis

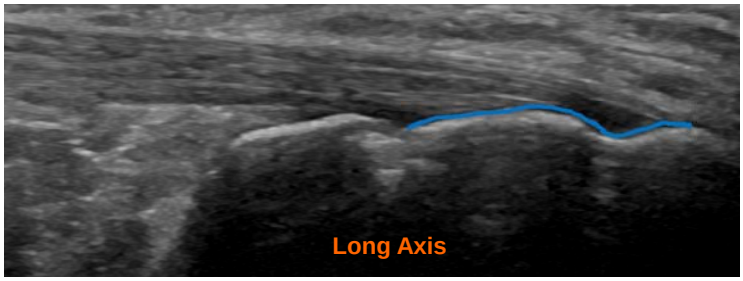
- Achilles Tendon
  - Strongest
  - Fan like insertion
  - Superficial fibres run into plantar fascia
- Retrocalcaneal Bursa
  - Lined anteriorly and posteriorly by fibrocartilage
  - “Half joint, Half bursa”



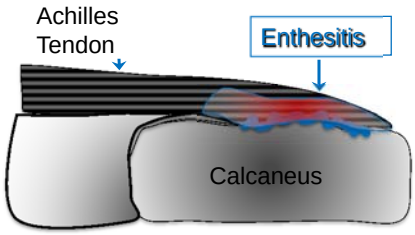
MAYO CLINIC

Canoso JJ. J Rheumatol 1998; 25:1254-6.

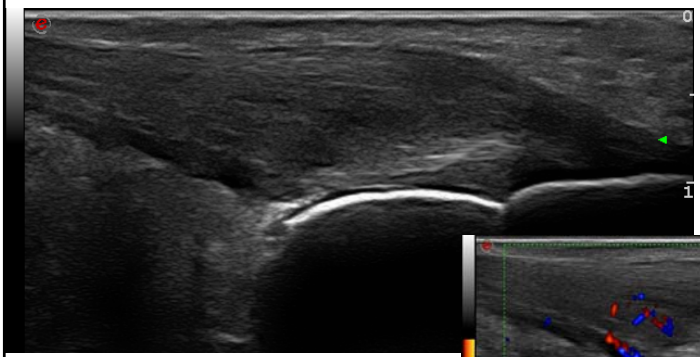
Enthesitis -Traditional View



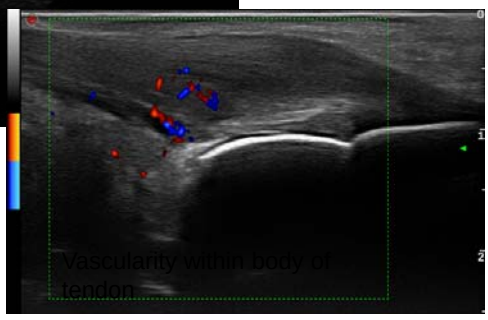
Achilles Tendon



McGonagle D. *Arthritis Rheum.* 1999;42:1080-1086

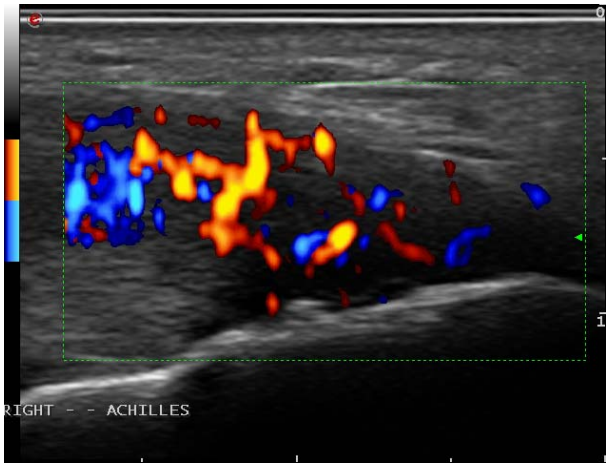


Hypoechogenecity and increased thickness



Achilles Enthesitis

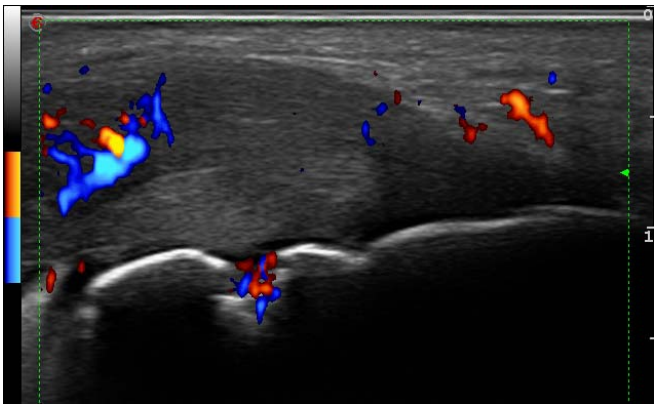
Doppler Signal at Enthesis



Achilles Enthesitis

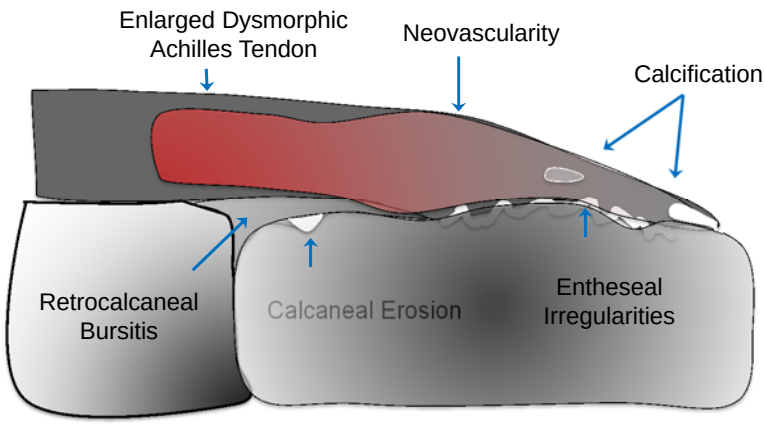
D'Agostino MA, et al. Arthritis Rheum. 2003;48(2):523-33.

Calcaneal Erosion

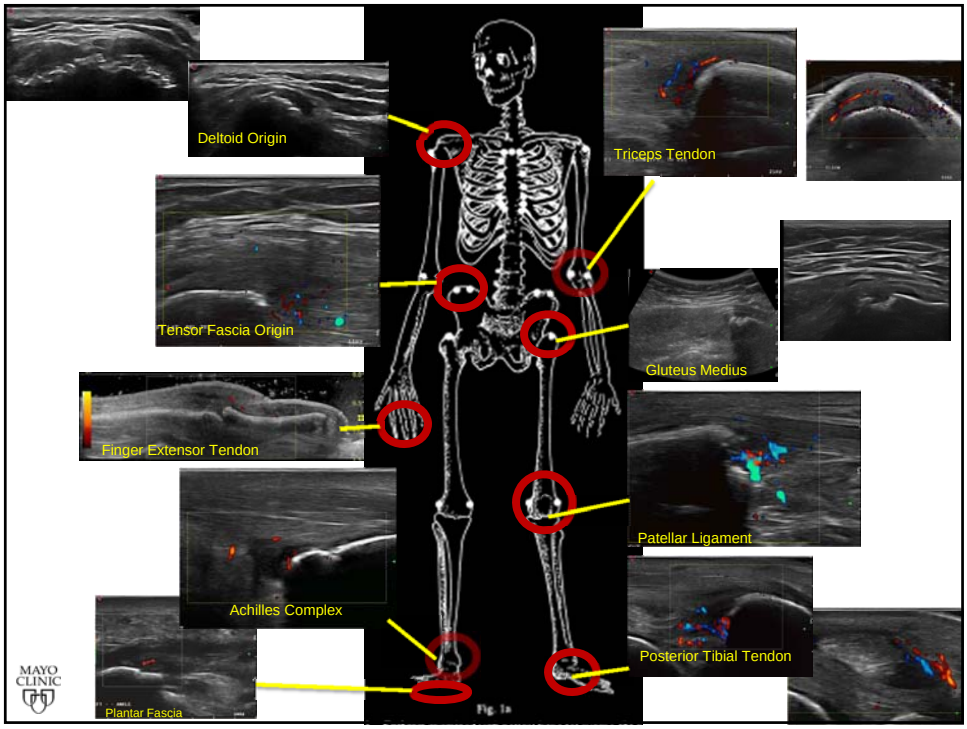


Achilles Enthesitis

Enthesitis – Composite View



Achilles Tendon Enthesis Complex



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- Crystalline Arthopathies
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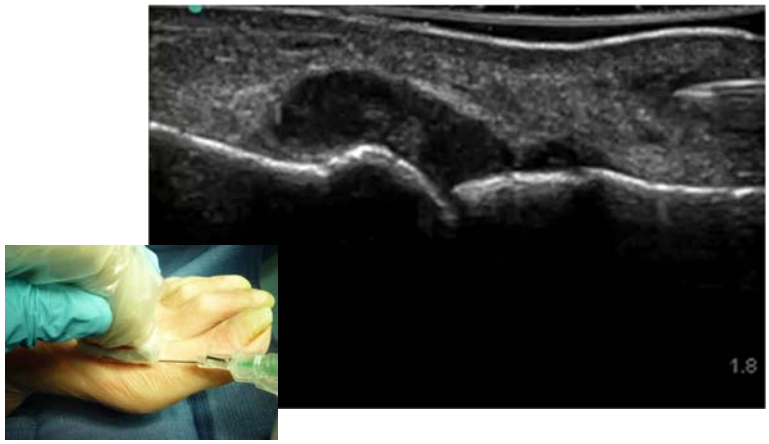
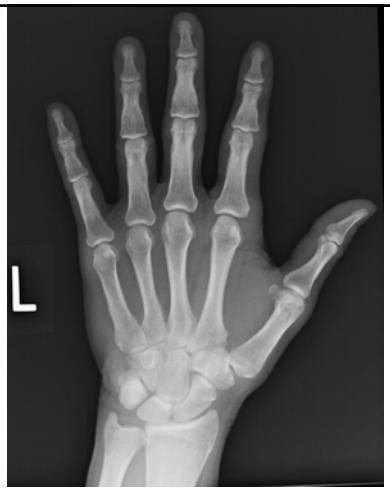
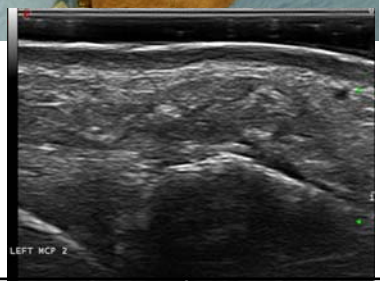
Acute Podagra

- How would you aspirate the 1st MTP?



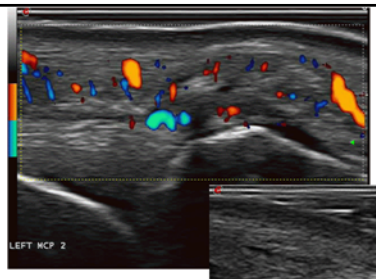
MAYO CLINIC

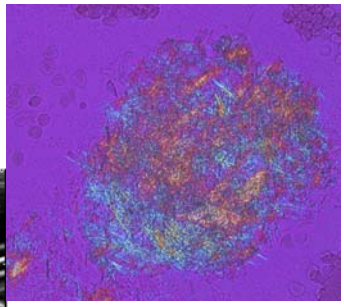


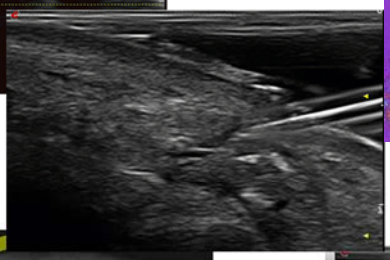


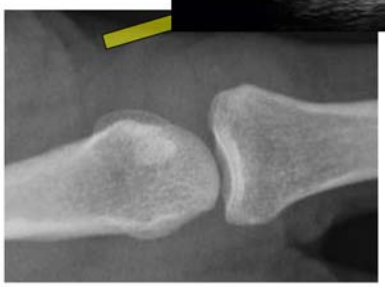
Chronic Arthralgia

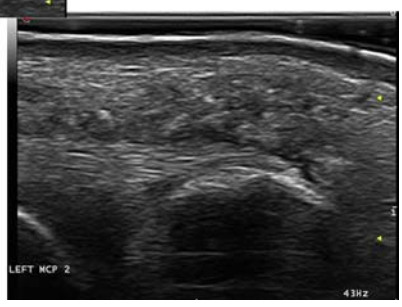
MAYO CLINIC











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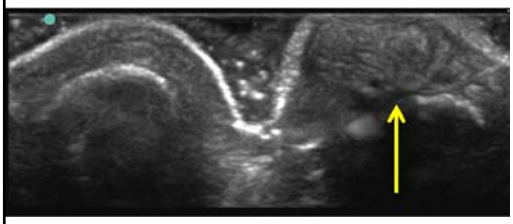
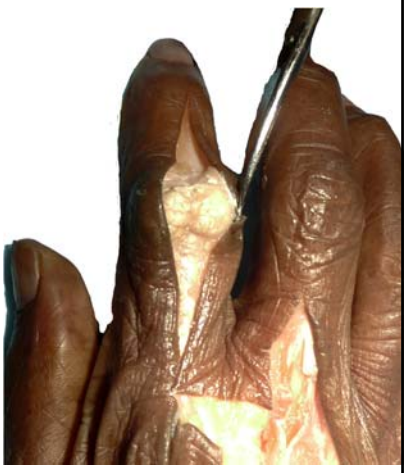
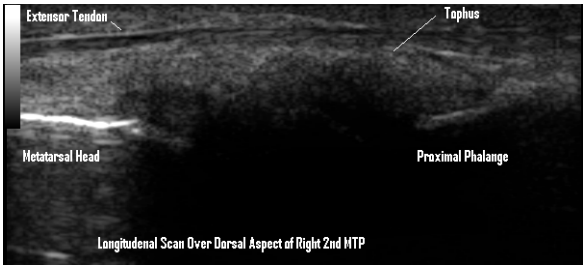
Tophaceous Gout

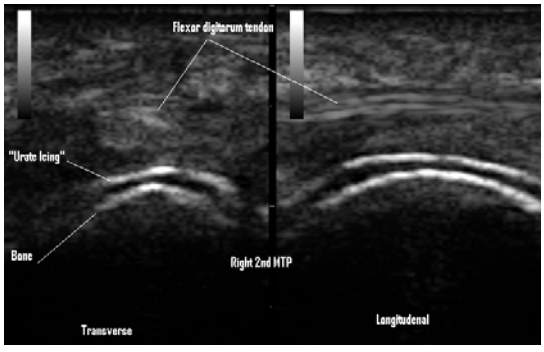


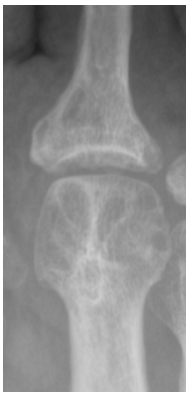


MAYO CLINIC

Tophaceous Gout







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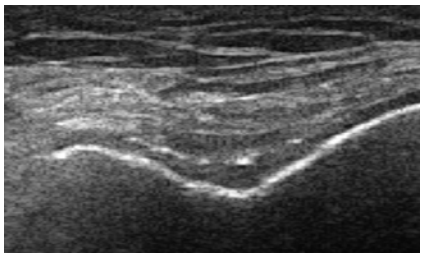
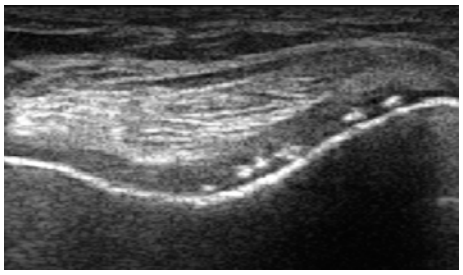
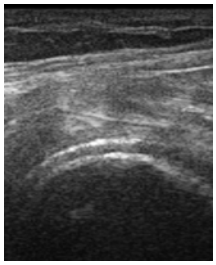
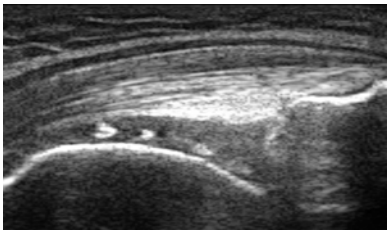
Gout – Double Contour Sign

Chondrocalcinosis





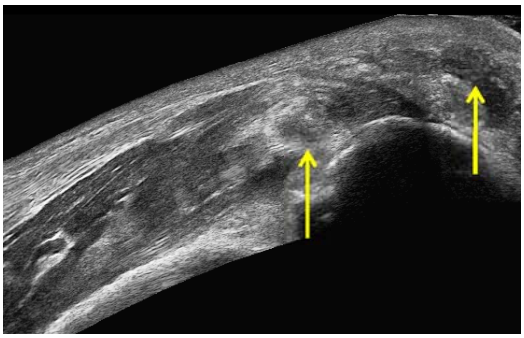




Filippucci, E., et al (2009). *Osteoarthritis Cartilage, 17(2), 178-181.*

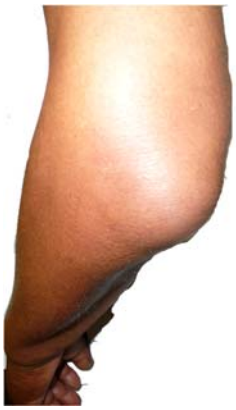
Acute Gout

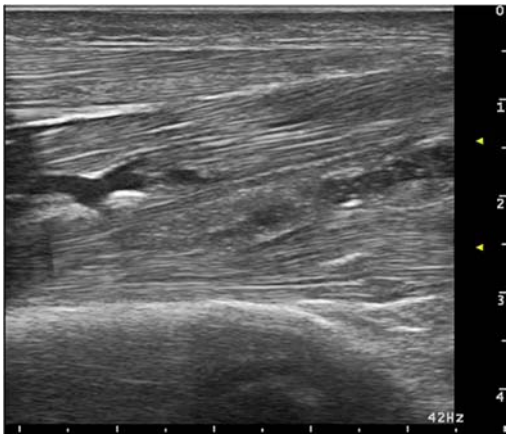

Normal Contralatral Posterior Long View Elbow

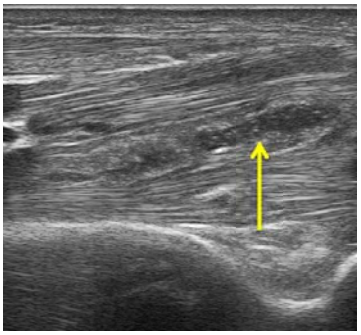


Tophaceous deposits in the triceps tendon and olecranon bursa.

Soft Tissue Tophaceous Deposits – Elbow







Intramuscular Tophaceous deposits.

CPPD

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Sonographic Features of CPPD

- Thin hyperechoic bands, parallel to the surface of the hyaline cartilage (frequently in the knee)
- ‘‘Punctate’’ pattern -several thin hyperechoic spots, more common in fibrous cartilage and in tendons
- Homogeneous hyperechoic nodular or oval deposits localised in bursae and articular recesses (frequently mobile)

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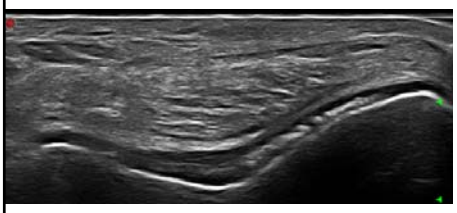
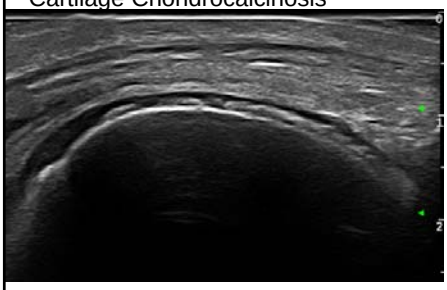
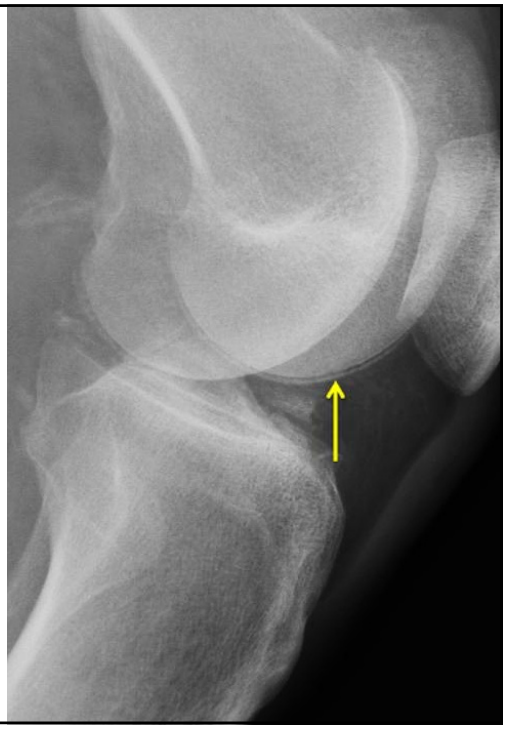
Frediani B, *et al. Annals of the rheumatic diseases 2005; 64:638-640.*

CPPD - Knee



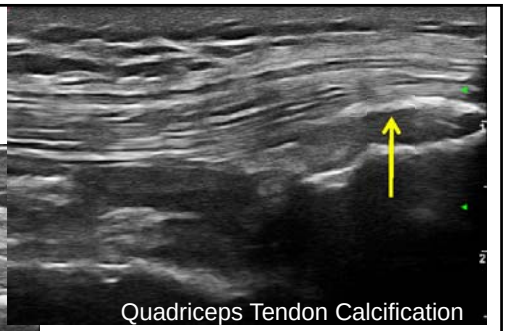
Cartilage Chondrocalcinosis



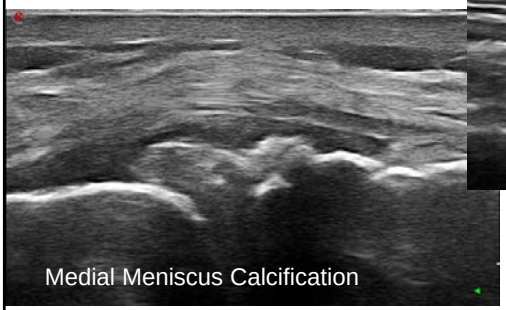


MAYO CLINIC

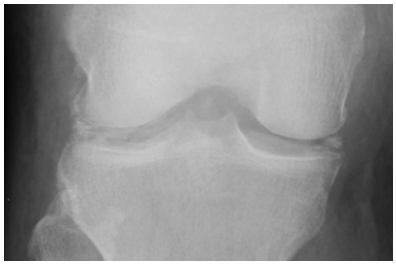
CPPD - Knee



Quadriceps Tendon Calcification



Medial Meniscus Calcification



Lateral Meniscus Calcification

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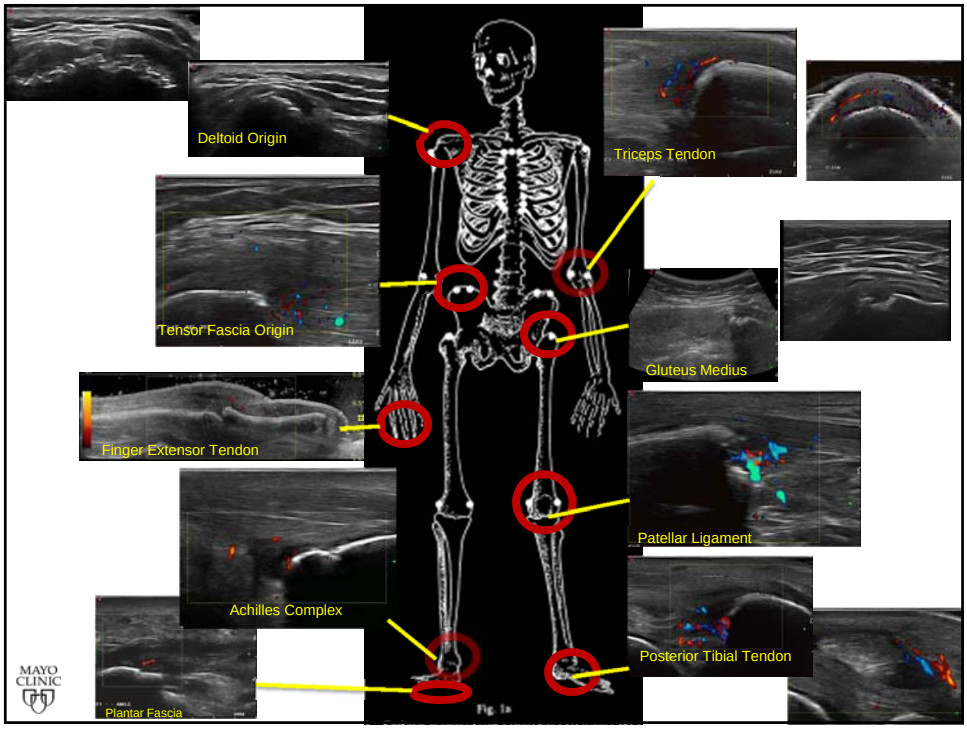
Summary

- Sonography can effectively be used in the evaluation and followup of inflammatory arthropathies.
- Ultrasound is effective in evaluating extra-articular structures that may be painful.
- Sonographic is useful in the evaluation of crystalline arthropathies.



Return to Program Schedule

MAYO CLINIC
HEALTH SYSTEM

Behçet's (Syndrome) Disease

Kenneth T. Calamia, M.D.
calamia@mayo.edu

Disclosure

- Research support: Celgene

There are no approved agents for the treatment of Behçet's Disease.

- This presentation will contain discussion of unapproved agents in the treatment of Behçet's disease.

MAYO CLINIC
HEALTH SYSTEM

Return to Program Schedule

Learning Objectives

- Recognize the clinical manifestations of BD in the USA and understand differences from those from the Silk Road.
- Identify other disorders with mucocutaneous and ocular manifestations that may mimic Behçet's Disease.
- Recommend empiric and evidence-based treatments for Behçet's Disease.

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Morbus Behçet

- Hippocrates; Adamantiades (1931)
- H. Behçet (1937)
  - oral ulcers
  - genital ulcers
  - hypopyon-uveitis
- Distinctive multisystem vasculitis
  - large and small vessels
  - arteries and veins
- "silk road" but worldwide in distribution

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Behçet's Disease
International Study Group Criteria

- recurrent oral ulceration (3x/yr)

  plus 2 of the following:
- recurrent genital ulceration
- eye lesions
- skin lesions

  EN, pseudofolliculitis, papulopustules, acneform
- positive pathergy test

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Lancet,1990

Behçet's Disease in US
Sensitivity of "Diagnostic" Criteria

	Total group n=164 (%)	With pathergy test n=27 (%)	No pathergy n=137 (%)
Mason & Barnes	77.4 ± 6.4	70.4 ± 17.2	78.8 ± 6.8
O'Duffy	88.4 ± 4.9	88.9 ± 11.9	88.3 ± 5.4
Dilsen	82.4 ± 5.8	77.8 ± 15.7	82.5 ± 6.4
Japan	84.8 ± 5.5	70.4 ± 17.2	86.9 ± 5.7
ISG	75.6 ± 6.6	77.8 ± 15.7	74.5 ± 7.3
Iran (traditional)	82.9 ± 5.8	77.8 ± 15.7	83.2 ± 6.3
Classification Tree	91.5 ± 4.3*	88.9 ± 11.9	91.2 ± 4.7

(* p=0.001)

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Calamia, Davatchi, 2000

Behçet's Disease
ISG criteria

- The diagnosis of BS is clinical
- The clinician should consider other manifestations of the disease
  - large vessel disease
  - meningoencephalitis
  - arthritis, gastrointestinal disease

especially in Western countries

where pathergy is less common & pathergy testing is less often performed

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Schirmer, Calamia, O'Duffy, 1999

Behçet's Disease
New International Criteria for Behçet's Disease (ICBD)

ICBD scoring: score ≥ 4 indicates BD

Symptom	Points
Ocular lesions	2
Oral aphthosis	2
Genital aphthosis	2
Skin lesions	1
Central nervous system	1
Vascular manifestations	1
Positive pathergy test*	1

*Though the main scoring system does not include pathergy test, where pathergy testing *is* conducted, a positive result may be included for one extra point.

Distribution of scores in cases and controls

Score*	% cases	% controls	Plausibility of BD	Classification
≤1	<1%	11%	Highly unlikely	No BD
2	1%	72%	Very unlikely	
3	4%	9%	Possible	
4	14%	5%	Probable	BD
5	32%	3%	Highly probable	
≥6	48%	<1%	Almost certain	

*This table does not incorporate any pathergy test results

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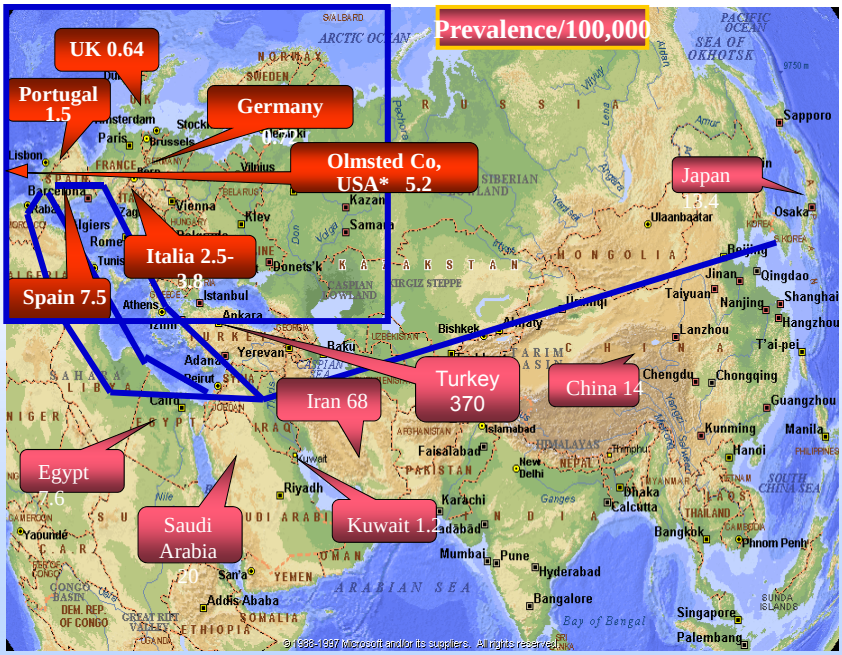
International Team for Revision , International Congress on BD, London, 2010



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*Calamia, Arthritis Care & Res, 2009

Behçet's Disease
Regional Differences

Silk Road	America & W. Europe
Men ≥ Women	Women > Men
Intractable eye disease	Treatable eye disease
CNS ≤ 10%	CNS ≥ 20%
HLA-B51 in 50-80%	HLA-B51 in 15%
Regional differences	HLA-DRB1*04

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Behçet's Disease
Regional Differences

GI disease	~30-50% in Far East
Vascular	40% Middle East, 5-10% Far East
Aortic Valve	Mainly Far East
Endomyocardial	Mainly in France

MAYO CLINIC HEALTH SYSTEM

Behçet's Syndrome

The cause of the disorder is unknown

There is no "gold-standard" for the Dx

There are sporadic, non-silk road cases

- lack genetic and ancestral similarities
- mucocutaneous syndromic presentations
- milder, females
- often attributed to other entities:

  CUC, Crohn's, Reiter's, SLE

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Behçet's Syndrome or ?

- The importance of the diagnosis of Behçet is related to the presence or risk of uveitis, CNS disease, and vascular manifestations
- Younger patients and males are at greatest risk of complications
- In patients at low risk, with mucocutaneous disease, it may be appropriate to avoid diagnosis of BD

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Behçet's Disease
Epidemiology

- prevalence
  - 100-370/100,000 Turkey and Iran
    - Lower rates for ethnic Armenians in Istanbul
  - 13-17/100,000 Japan, Korea, China
    - very low rates in Japanese-Americans
  - 0.3-7.5/100,000 Europe and USA
    - higher in German Turks, but < than in Turkey

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Environmental Agents Implicated in BD

- Viruses, esp HSV
- Bacteria
  - Streptococci: tonsillitis, dental caries
  - Acneform lesions not sterile
    - Familial clustering of acne/arthritis
  - Therapeutic effect of antibiotics
- BD assoc/w ↓ socio-econ status in Turkey
- ↓ in incidence & severity of BD in Japan
  - c/w ↑ atopic diseases (↑Th 2)
  - c/w ↓ in dental infections

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Direskeneli, Clin & Experimental Rheumatology, 2010

BD: A Seronegative Spondyloarthropathy?

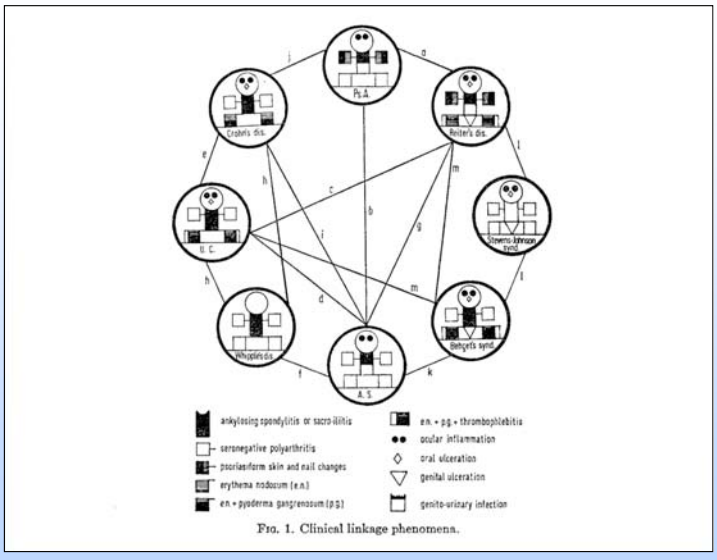

FIG. 1. Clinical linkage phenomena.

MAYO CLINIC HEALTH SYSTEM

Moll, *Medicine*, 1974

BD: an autoimmune disease?

- No evidence of B or T cell hyperreactivity or transfer by Ab or pathogenic T cells
- Female predilection
- No immune cytopenias, Raynaud's, Sjogren's, vitiligo, nephritis, neuropathy
- No premature atherosclerosis
- Skin and mucosal disease distinct
- Cessation of disease activity over time in BD

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BD: an autoinflammatory disease?

- Apparently unprovoked inflammatory episodes
- Innate immunity abnormalities
- Several differences between BD and classic autoinflammatory disorders:
  - Polygenetic
  - Family history only present in about 10%
  - Age of onset in 2nd-4th decades
  - Uveitis different

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Different organ responses to Rx in BD

- Thalidomide ↓ skin/mucosa ↑EN
- Colchicine ↓ EN and arthritis
- Etanercept ↓ skin/mucosa, no pathergy effect
- Gevokizumab (IL 1-β blocker) ↓ eye disease, not for ulcers
- Tocilizumab ↓ eye disease, not for ulcers

Suggests >1 inflammatory pathway

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Yazici, *Clin Rev Allerg Immunol*, 2012

Pathergy

- Unique to Behcet's Disease
- Hyperactive neutrophils after trauma
- Tested for by needle prick
- More common along Silk Road
- Not common in the USA
- Testing not commonly done, but easy to perform:
  - 3 sticks with sterile 20g needle
  - "read" at 48 hours

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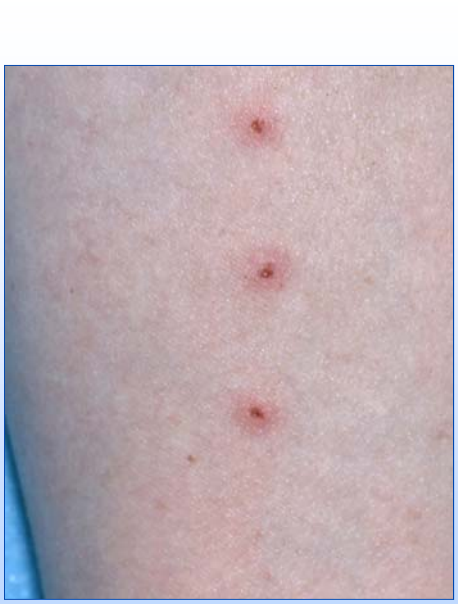

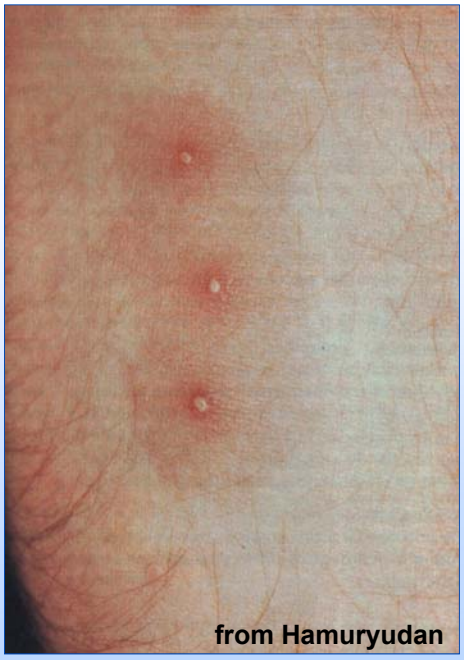

from Hamuryudan

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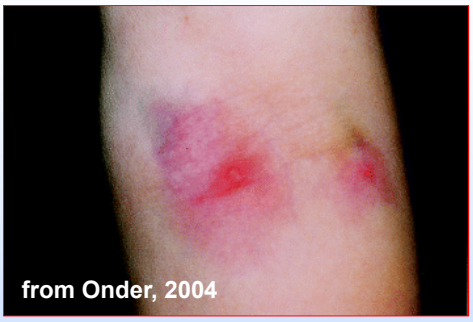
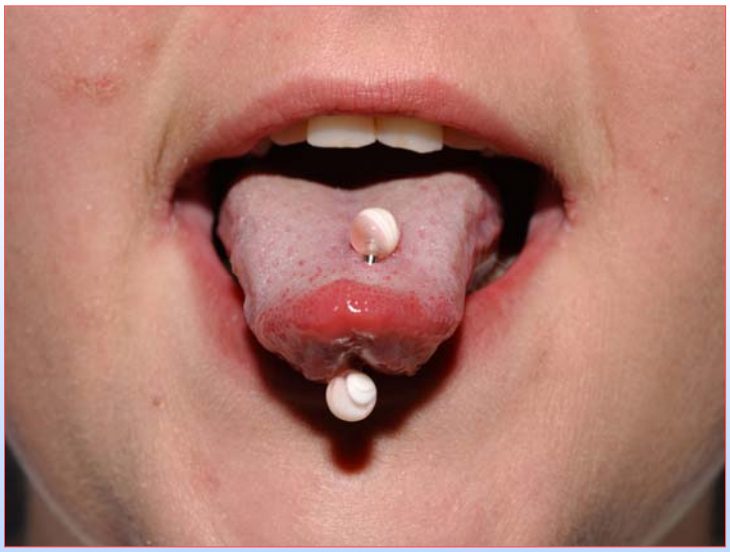
Pathergy Equivalents



from Onder, 2004

Skin reaction, thrombosis after venipuncture
Flare of uveitis after cataract surgery
Flare of arthritis after arthrocentesis or carpal tunnel release
Bumps after acupuncture or EMG
Aneurysm formation after arterial puncture

MAYO CLINIC HEALTH SYSTEM



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Behçet's Disease - USA
164 Mayo Clinic patients, 1985-1997

Manifestation	#	%	% female
Oral ulcers	161	98	70
Genital ulcers	131	80	
Uveitis	83	51	
Retinal vasculitis	32	20	
Skin	108	66	
Pathergy	8/27	30	
Large vessel	31	19	
CNS	37	23	
Arthritis	44	27	

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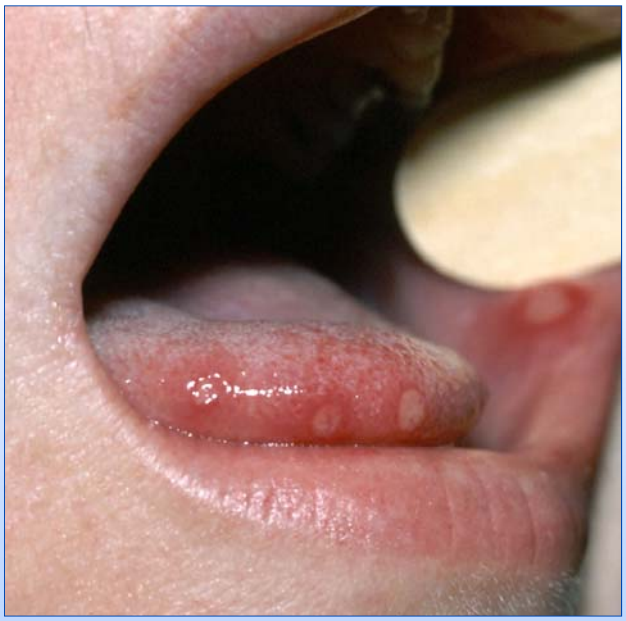
76% patients met ISG criteria

Calamia, 2000



MAYO CLINIC HEALTH SYSTEM

Recurrent Aphthous Stomatitis
Clinical Classification

Simple aphthosis

- episodic, short-lived
- few lesions, recur 3-6 times/year
- painful, then aching
- non-keratinized mucosa affected

Complex aphthosis

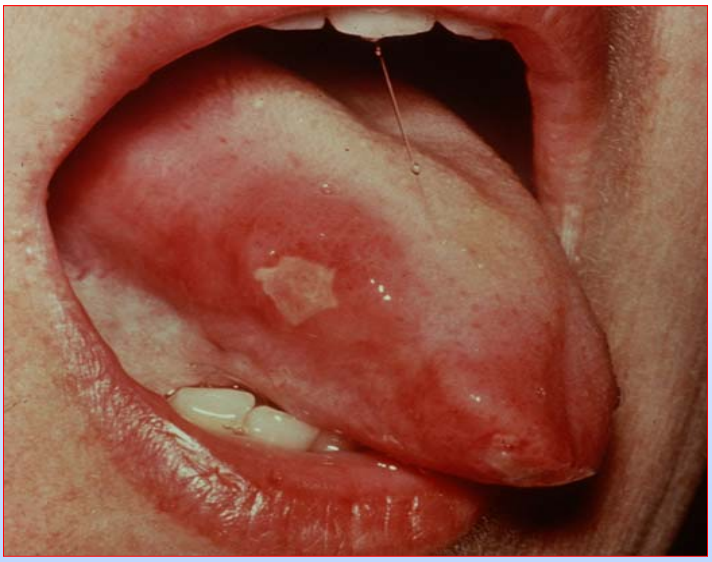
- episodic or continuous
- few to many lesions, small to large aphthae
- slow healing, greater pain and disability
- genital aphthae: a *forme fruste* of Behçet's?

Both: minor (<1cm), major (>1 cm, Sutton's disease), and herpetiform (grouped) varieties

MAYO CLINIC HEALTH SYSTEM

Rogers, Seminars in Cutaneous Medicine and Surgery, 1997

Major Aphthous Ulcer (Sutton's Ulcer)



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Recurrent Aphthous Stomatitis
Associated disorders

- Menstruation; smoking cessation
- Celiac disease ("sprouw"= ulcer)
- Inflammatory bowel disease
  - Ulcus vulvae acutum
- AIDS associated aphthosis
- ↓ B_1 , B_2 , B_6 , B_{12} , folate, iron, zinc
- Hematological disorders
  - Anemia, Cyclic neutropenia, ↓IgA
  - Myelodysplasia / myeloproliferation

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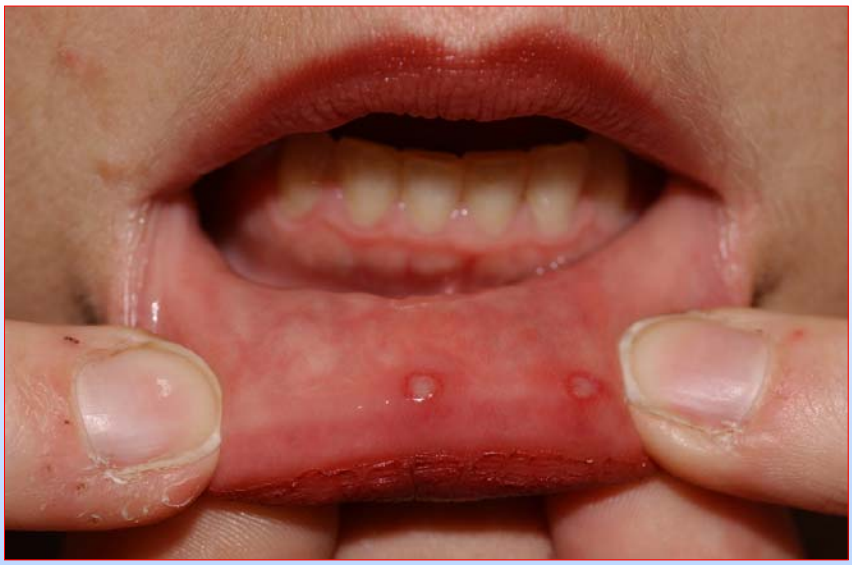
IBD



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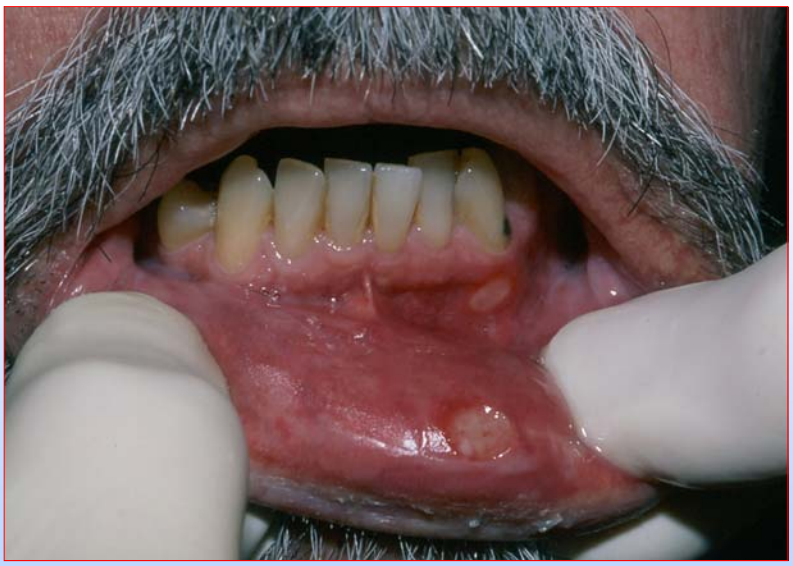
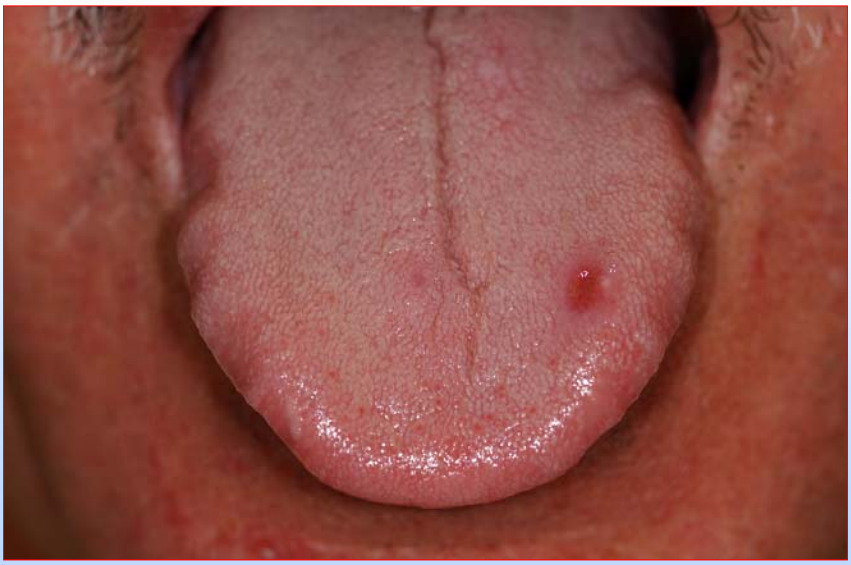
CMML



MAYO CLINIC HEALTH SYSTEM

Myelodysplastic Syndrome



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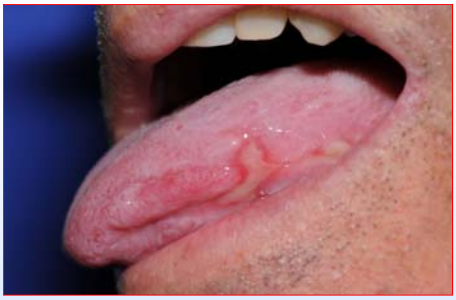
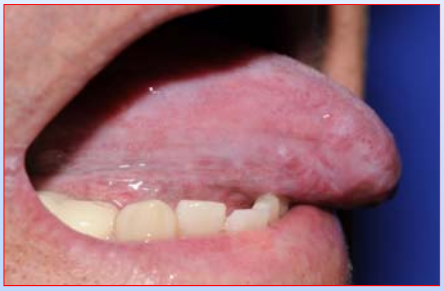
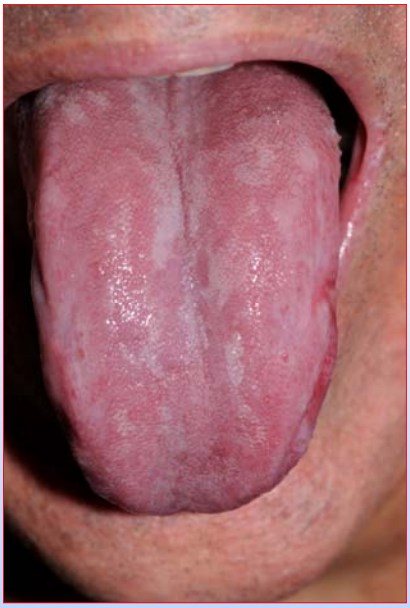
IgA Deficiency







MAYO CLINIC HEALTH SYSTEM

Complex Aphthosis
Associated Disorders in 269 Patients

- Female 152 (57%)
- Genital ulcers 39 (16%)
- Started as simple aphthosis in 50%

Anemia	25%	Mucosal dz	6%
GI disease	16%	DC'd smoking	4%
Behçet Dis.	9%	Drugs	3.3%
Hematologic	5%	NSAIDs, captopril	

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Rogers, 2003

Recurrent Aphthous Stomatitis
Differential Diagnosis

- Recurrent intraoral HSV
- Wegener's
- SLE, DLE
- Oral Crohn's
- Pyostomatitis vegitans (CUC)
- Erythema multiforme
- Lichen planus
- Mucous membrane pemphigoid
- Pemphigus vulgaris
- Linear IgA disease

Differences include morphology, diffuse mucositis, location, chronicity
Biopsy with IF!

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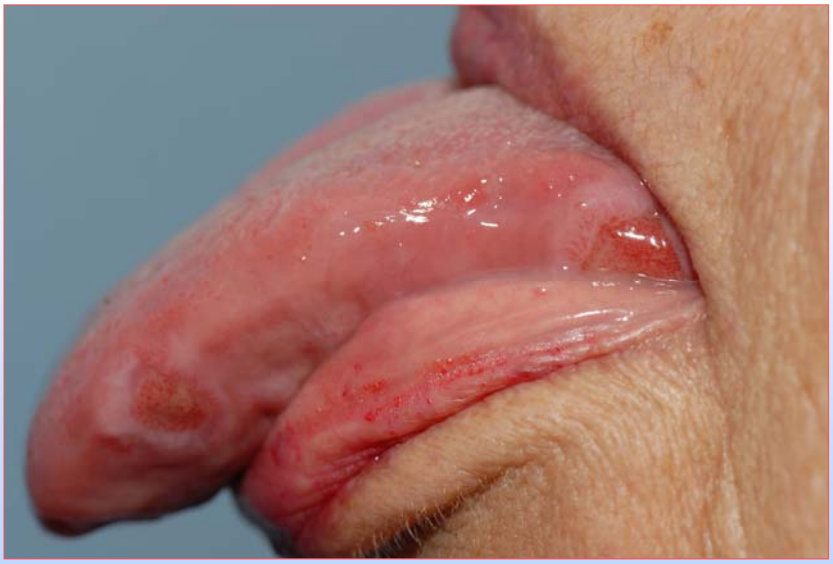
Wegener's



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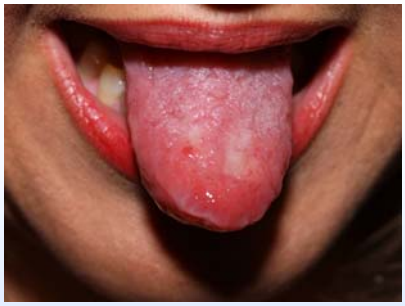

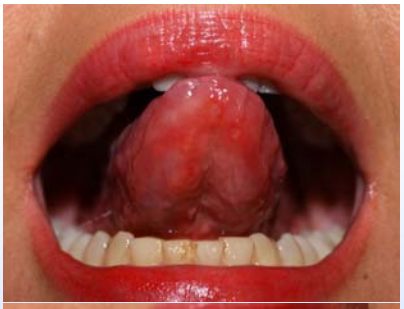

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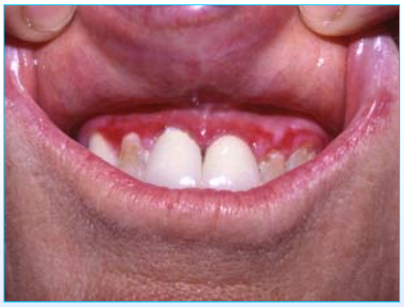
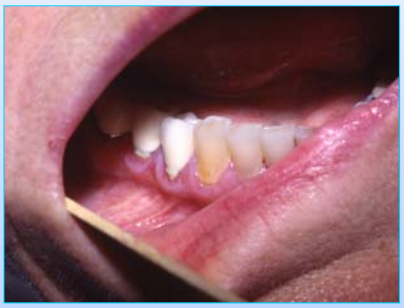
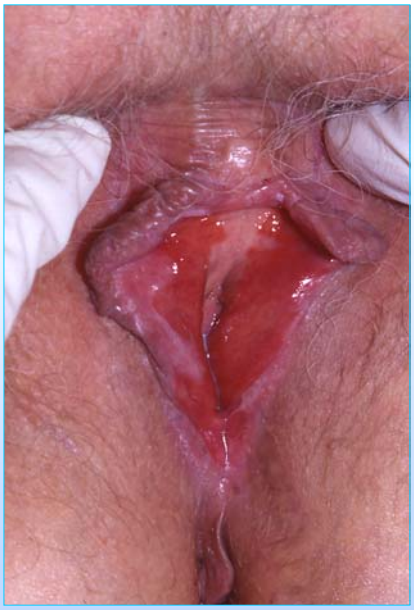
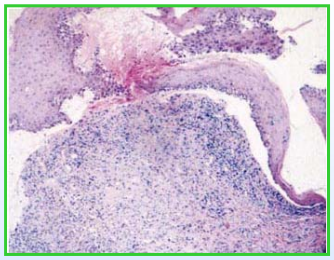


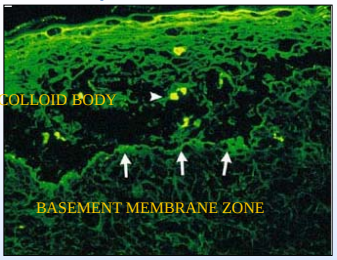


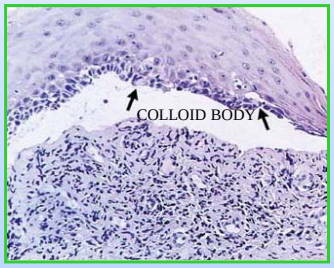


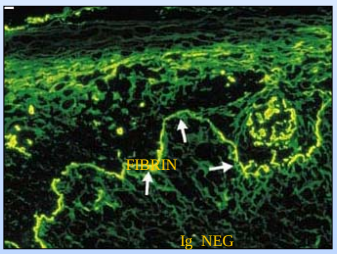
MAYO CLINIC
HEALTH SYSTEM

Erosive Lichen Planus- Cell mediated cytotoxicity to basal cells of the stratified squamous epithelium









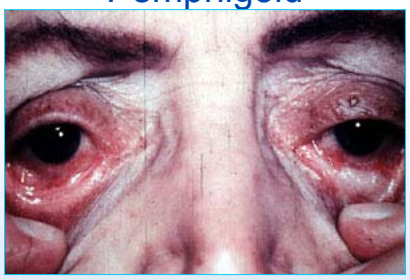
MAYO CLINIC
HEALTH SYSTEM

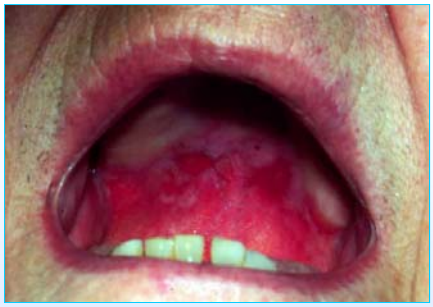
Diseases with Oculo-Oro-Genital Manifestations

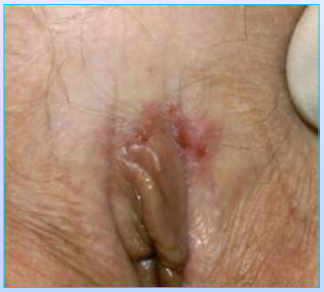
- Behçet's Disease
- Vulvovaginal-gingival form of erosive LP
- Reiter's syndrome
- Crohn's disease
- Erythema multiforme
- Mucous membrane pemphigoid
- Pemphigus vulgaris

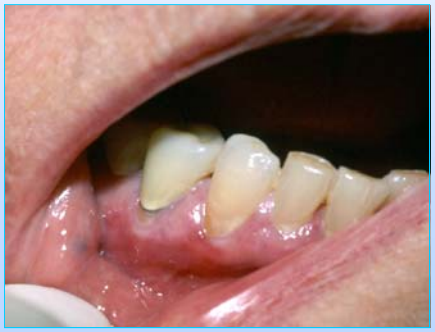
MAYO CLINIC HEALTH SYSTEM

Mucous Membrane Pemphigoid









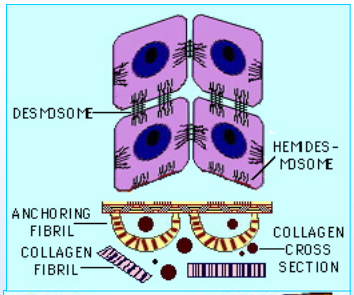
MAYO CLINIC HEALTH SYSTEM

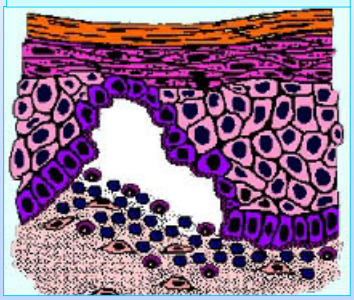
Mucous Membrane Pemphigoid

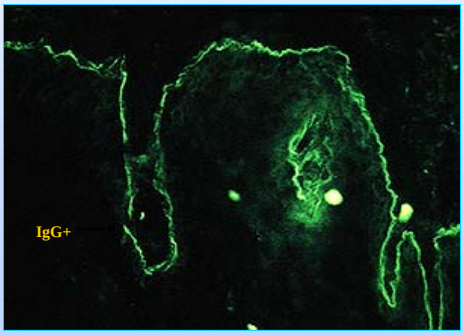
- Extensive vesiculobullous mucositis
  - Desquamative gingivitis
- Chronic progressive scarring conjunctivitis
- Skin involvement 20%
- Middle age or elderly adults: females
- Ab to epithelial basement membrane Ag

MAYO CLINIC HEALTH SYSTEM

Mucous Membrane Pemphigoid

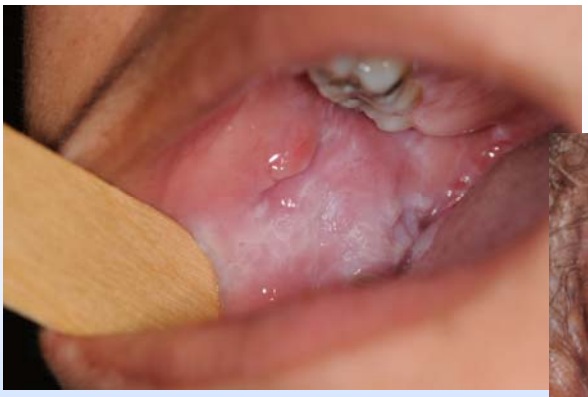


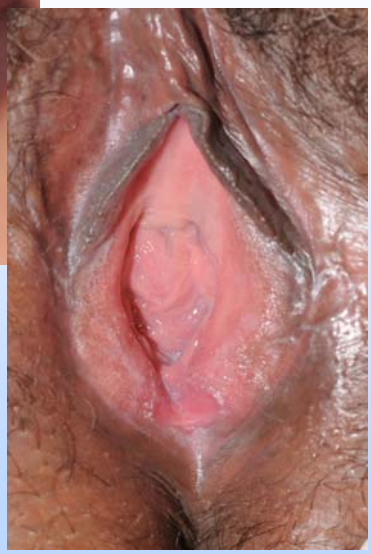




MAYO CLINIC HEALTH SYSTEM

Pemphigus vulgaris

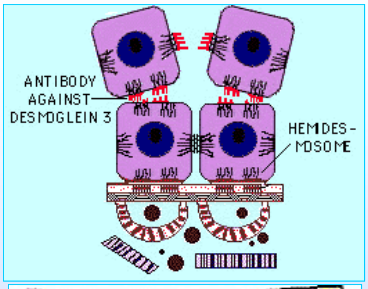


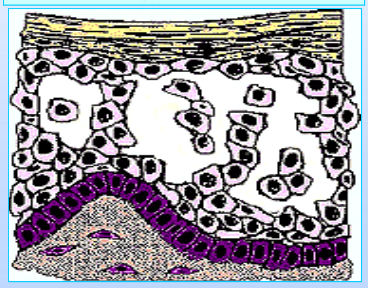


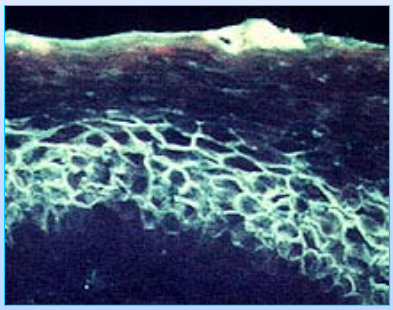
Ab to intracellular adhesion molecules
May have serum Ab to desmoglein 3
Young adults of both sexes
Oral involvement at sites of movement or folding

MAYO CLINIC HEALTH SYSTEM

Pemphigus vulgaris

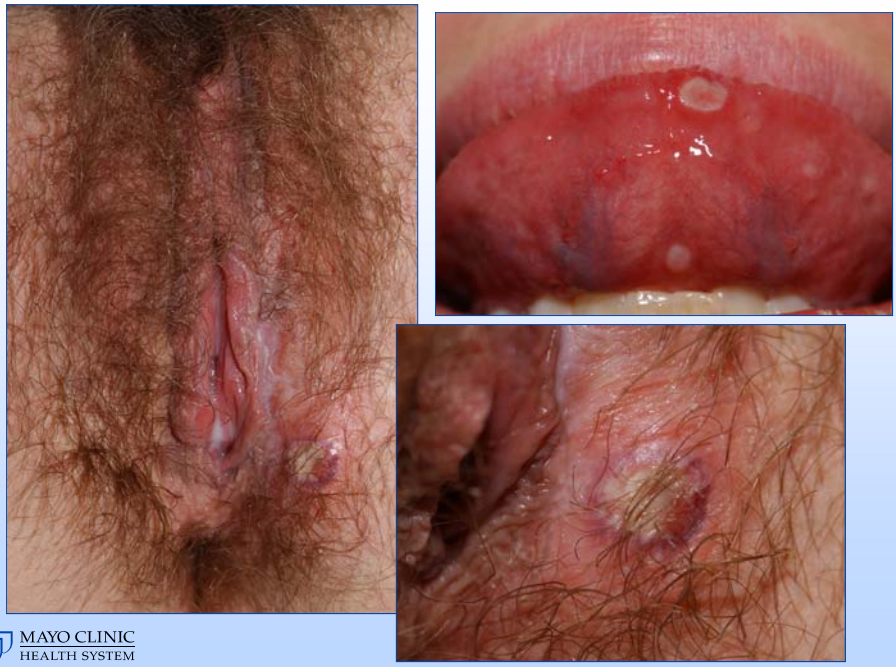






MAYO CLINIC HEALTH SYSTEM

MAYO CLINIC
HEALTH SYSTEM



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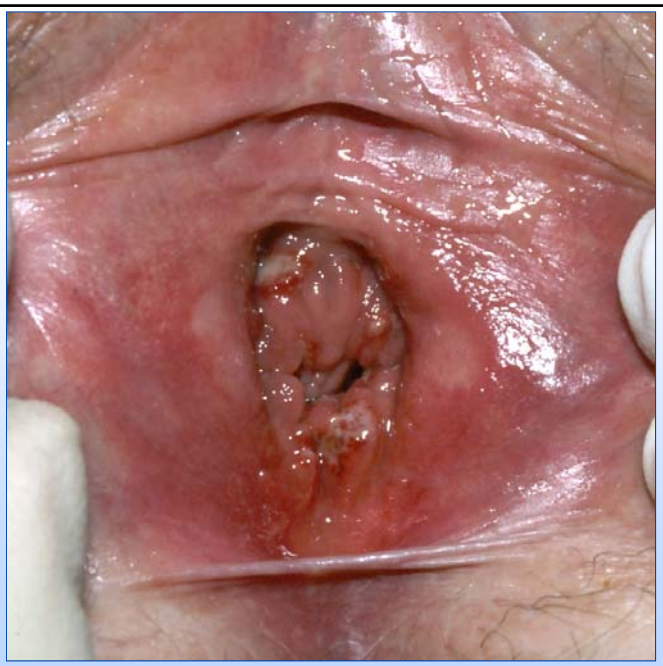
HEALTH SYSTEM



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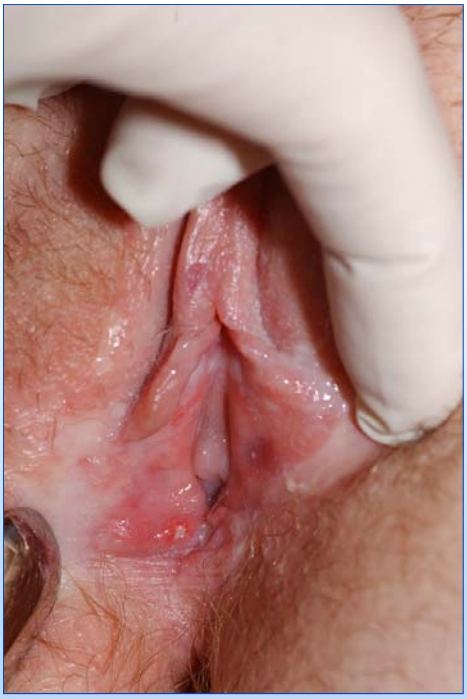
HEALTH SYSTEM



MAYO CLINIC
HEALTH SYSTEM

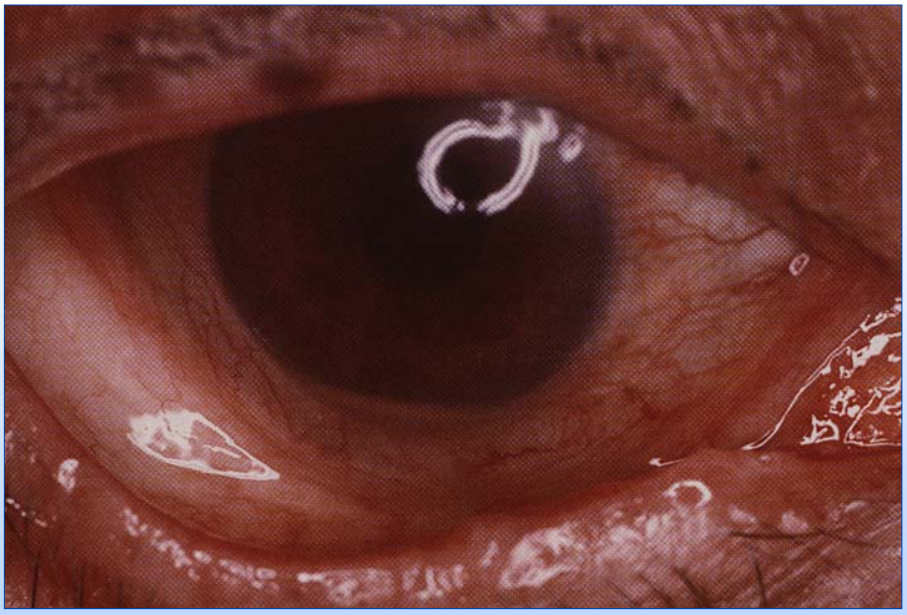
Behçet's Disease
Ocular disease

- anterior uveitis
- posterior uveitis

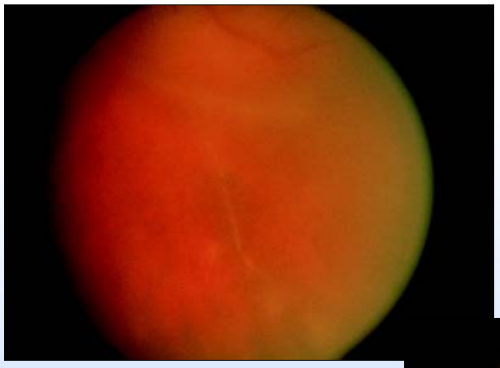
panuveitis

- retinal vasculitis
- asymptomatic eye disease
- conjunctival ulcers (~3%)

MAYO CLINIC HEALTH SYSTEM



MAYO CLINIC HEALTH SYSTEM



Retinal vasculitis:
inflamed retinal vessel
Vitritis

Retinal vasculitis:
retinal hemorrhages &
cotton wool spots

MAYO CLINIC HEALTH SYSTEM

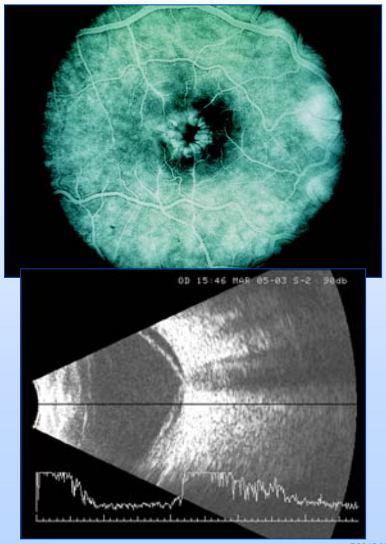
Characteristics of Uveitis in Systemic Diseases

Disease	Ant	Int	Post	RV	Unilat	Bilat	< 3mo	>3mo	Characteristics
HLA-B27 (AS, RD)	+				+		+		Hypopyon
IBD	+	+			+ or +		+	+	
PSA	+	+			+ or +		+	+	
Sarcoid	+	+	+	+		+		+	Granulomatous
JRA	+					+		+	Band Keratop.
MS	+					+		+	Granulomatous
MS		+		+		+		+	Snow bank
Behçet	+	+	+	+		+	+	+	Hypopyon

MAYO CLINIC HEALTH SYSTEM

Ocular inflammation: Complications

Macular edema
Glaucoma
Retinal ischemia
Neovascularization
Retinal detachment
Cataract



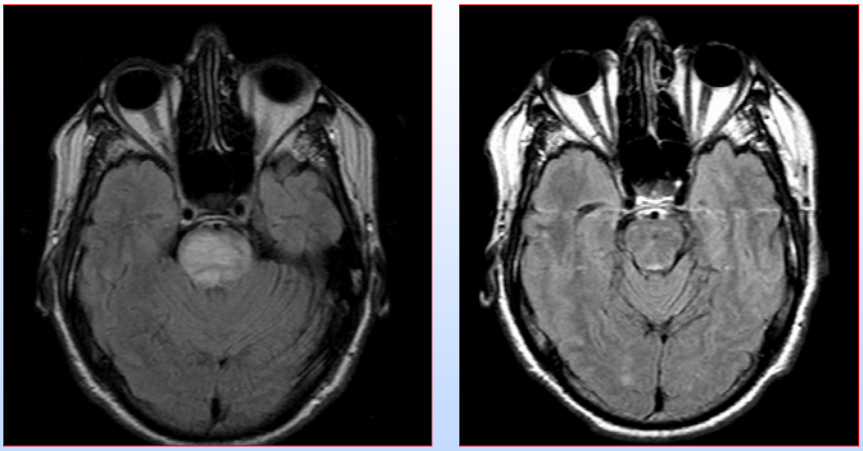
MAYO CLINIC HEALTH SYSTEM

Behçet's Disease
Central nervous system disease

- Aseptic meningitis-meningoencephalitis
- Focal / multifocal parenchymal CNS disease (~80%)
  - brain stem & diencephalic regions
  - periventricular white matter, spinal cord
- Cerebral venous thrombosis (~20%)
  - headache, papilledema
  - 65% had DVT elsewhere (vs 19%)*

MAYO CLINIC HEALTH SYSTEM

***Tunc, ARD, 2004**



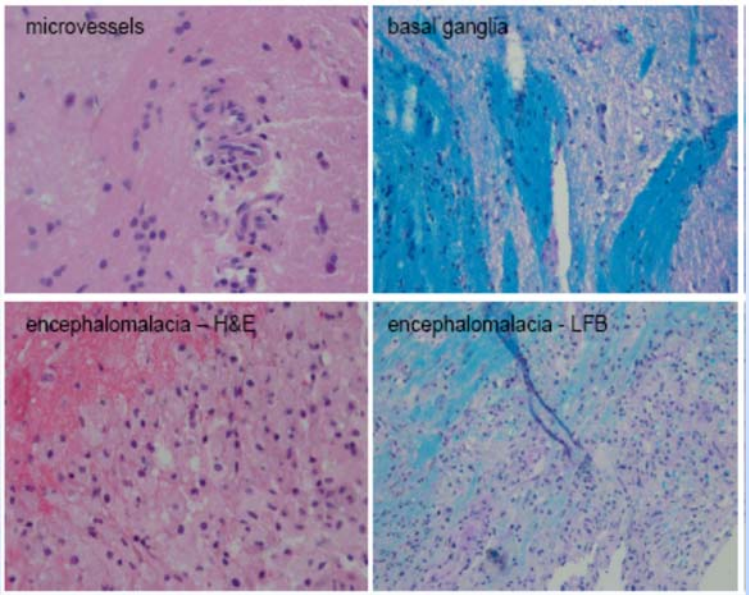
7-1-2004

4-27-2005

after chlorambucil 6 mg/d

MAYO CLINIC HEALTH SYSTEM

Neuropathology in CNS BD



MAYO CLINIC HEALTH SYSTEM

Natural History

- No prospective studies
- 1/3 have single attack
  - Recovery usually good / complete with steroids alone
- 1/3 have recurrent attacks
- 1/3 have a progressive course
- Prognosis less good with progressive disease, frequent relapses, brainstem & spinal cord involvement, high CSF protein & cells

MAYO CLINIC HEALTH SYSTEM

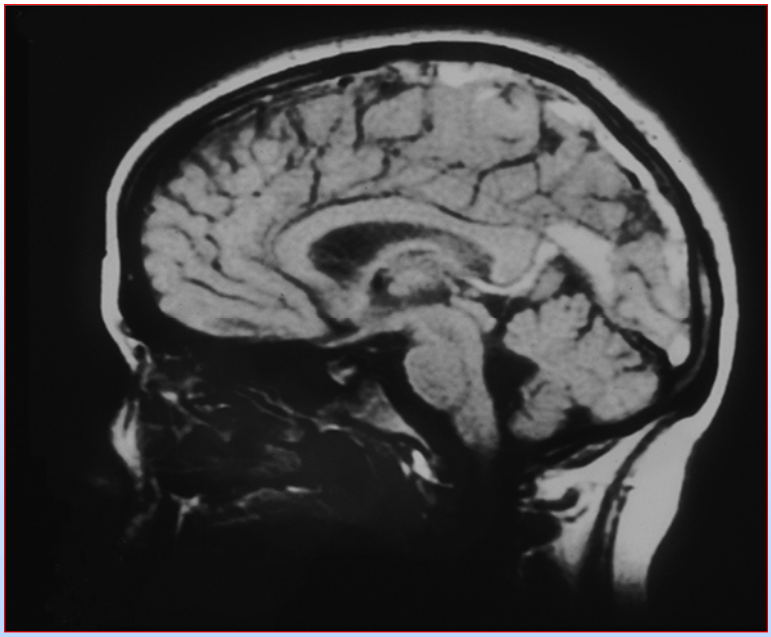
Al-Araji, *Lancet Neurology*, 2009

CNS Behcet's Disease at Mayo Clinic

- Eight patients seen 2002-2007
- 6 males, 2 females age 20-47
- 5 Caucasians, 2 Middle Easterners, 1 Creole
- HLA-B51 in 4 patients
- Motor/sensory stroke-like deficits in 65%
- Headache in 50%, usually w/ aseptic meningitis
- T2/FLAIR changes MRI seen in brainstem (5), sub-cortical white matter (4), basal ganglia (3)
- Aphthous ulcers & acneiform lesions were most common non-neurological symptom.

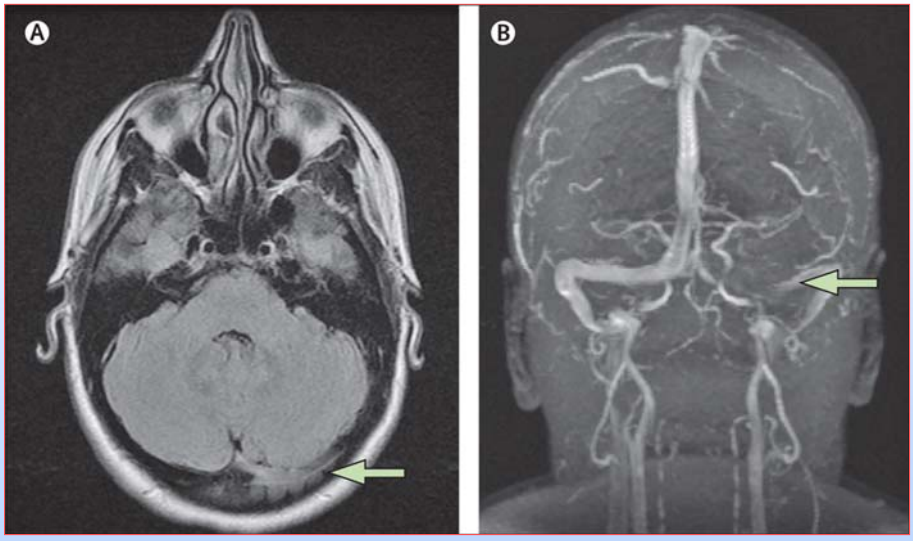
MAYO CLINIC HEALTH SYSTEM

Konieczny, Int'l Congress on Behcet's Disease, 2008



MAYO CLINIC HEALTH SYSTEM

Transverse Venous Sinus Thrombosis in BD



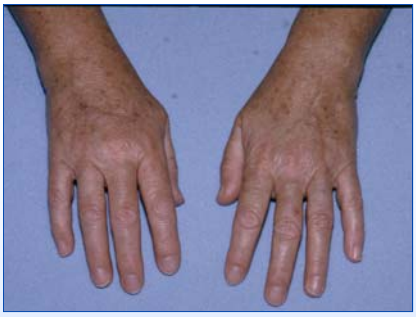
MAYO CLINIC HEALTH SYSTEM

Al-Araji, *Lancet Neurology*, 2009

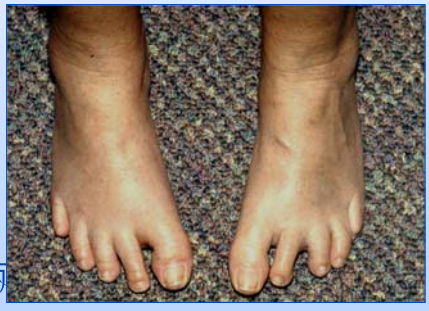
Behçet's Disease
Musculoskeletal

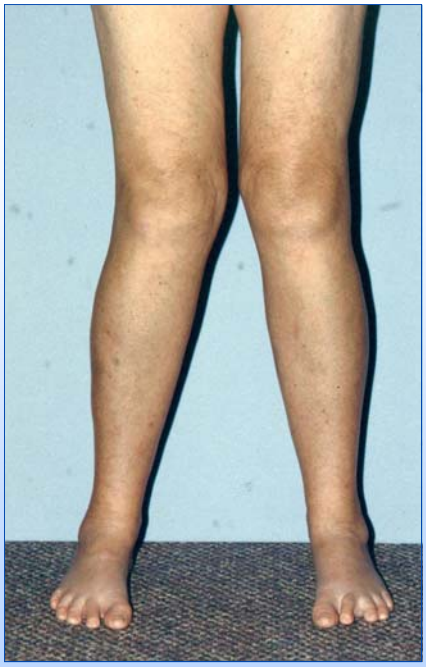
- Oligoarthritis (40-50%)
  - monoarthritis or polyarthritis possible
- Fibromyalgia (16% of females in Turkey)
- Spondylitis?

MAYO CLINIC HEALTH SYSTEM



Polyarthritis in Behcet's Disease



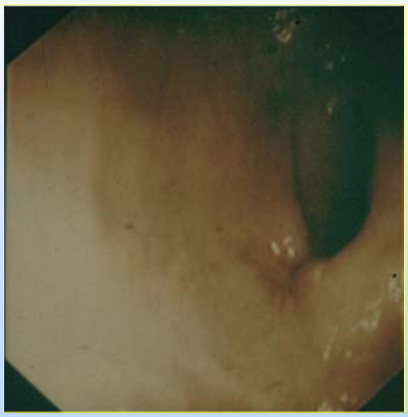


Behçet's Disease
Gastrointestinal

- Ulcers in colon, ileum
  - Superficial, multiple
  - No diffuse inflam.
- Melena, abdominal pain, diahrrea
- Consider NSAIDs

In Japan:

- Perforate or bleed
- Recur post-op in 50%



MAYO CLINIC HEALTH SYSTEM

Behçet's vs Crohn's Disease

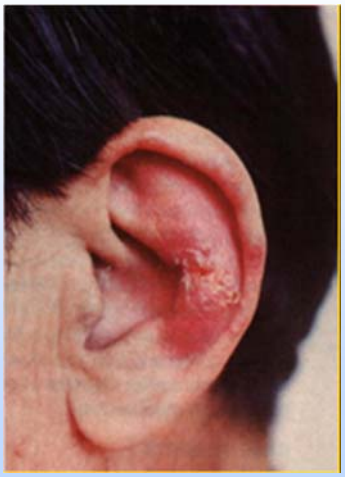
Both: Oral lesions, arthritis, phlebitis, EN

	Behçet's	Crohn's
Genital Ulcers	+++	rare
CNS disease	++	rare
Uveitis	panuveitis	anterior
Perianal dz.	Rare (<1%)	10-15%
Strictures	Rare (8%)	17%
Granulomas	<1%	10-15%
Saccharomyces Ab	29-49%	41-62%

MAYO CLINIC HEALTH SYSTEM

MAGIC Syndrome

Mouth
And
Genital Ulcers
Inflammed
Cartilage
-Behçet Syndrome
-Relapsing Polychondritis



MAYO CLINIC HEALTH SYSTEM

Firestein, 1985

Behçet's Disease
Large vessel involvement

- Occurs in about 1/4 patients with BD
- Cause of significant morbidity/mortality
- Affects prognosis
- Treatment unclear

MAYO CLINIC HEALTH SYSTEM

Large Vessel Involvement in Behçet's
Classification

- Systemic arterial vasculitis
  - aneurysms/occlusions/stenoses
- Pulmonary arterial vasculitis
  - aneurysms/occlusions/stenoses
- Venous occlusions
  - superficial venous thromboses
  - deep venous thromboses
  - vena cava thromboses
  - cerebral venous thromboses
  - Budd-Chiari syndrome
  - portal vein thrombosis
  - right ventricular thrombi
  - pulmonary emboli
- Varices

MAYO CLINIC HEALTH SYSTEM

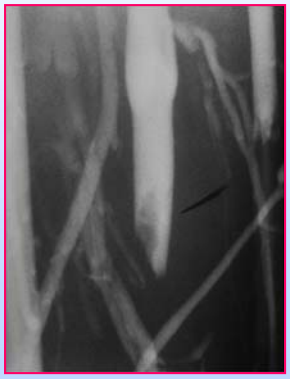
Calamia, *Curr Opin Rheum*, 2011

Behçet's Disease in USA
Venous Lesions

27 patients (13% of 164 US patients)

#	lesion
15	deep venous thrombosis
7	superficial thrombophlebitis
3	caval thrombosis
2	cerebral venous thrombosis
1	central retinal vein thrombosis
1	pulmonary embolus

8 recurrent/progressive DVT on ACs



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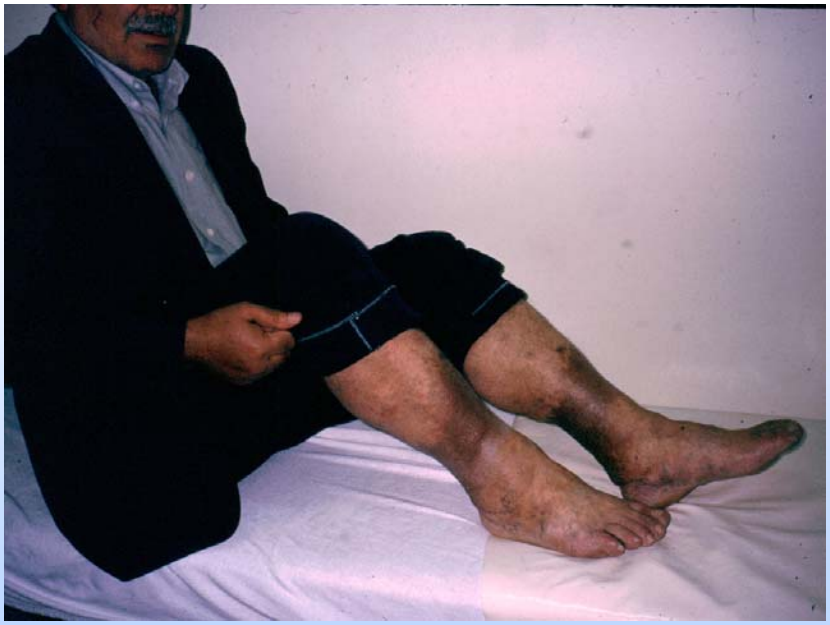
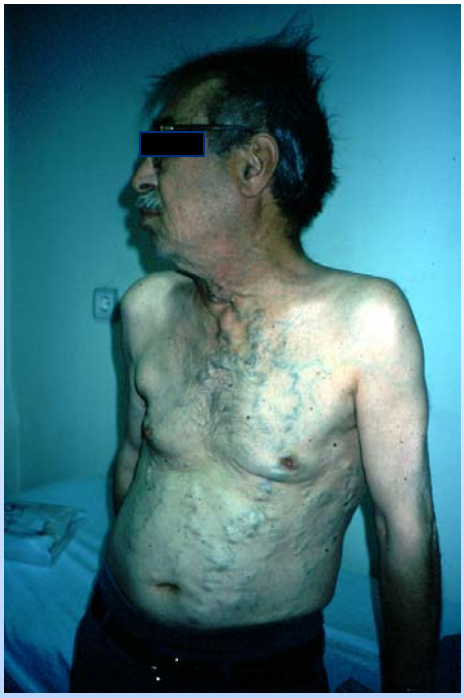


MAYO CLINIC
HEALTH SYSTEM

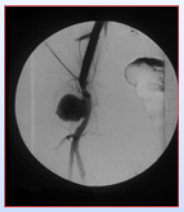


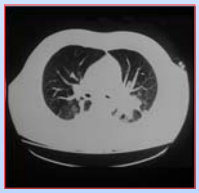
MAYO CLINIC
HEALTH SYSTEM

Behçet's Disease in USA
Arterial Lesions

12 aneurysms in 5 patients

- aortic (+ IVC thrombosis)
- multiple extremity (2) (+ DVT)
- femoral artery, anast. x 4 (+ IVC)
- pulmonary artery and femoral art.
- pulmonary artery and aorta





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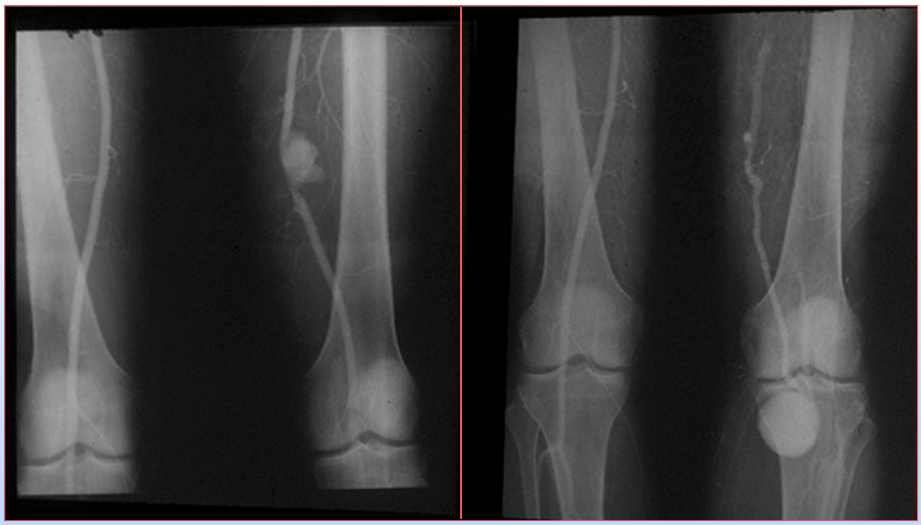

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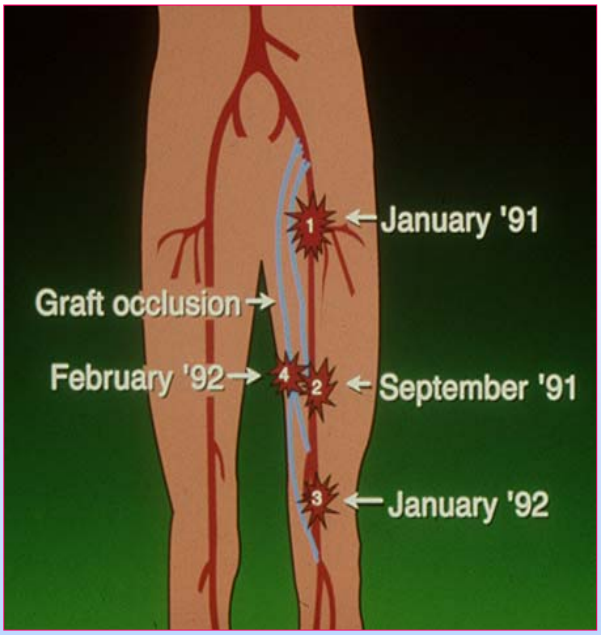

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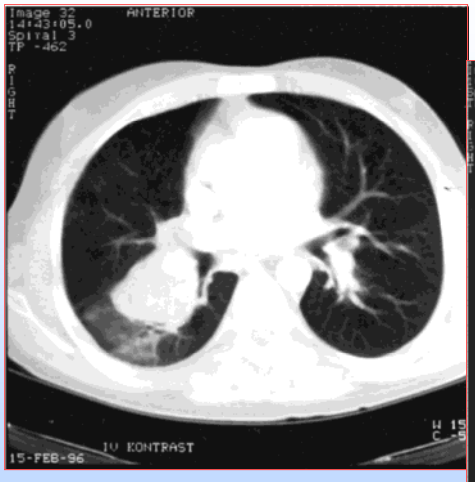
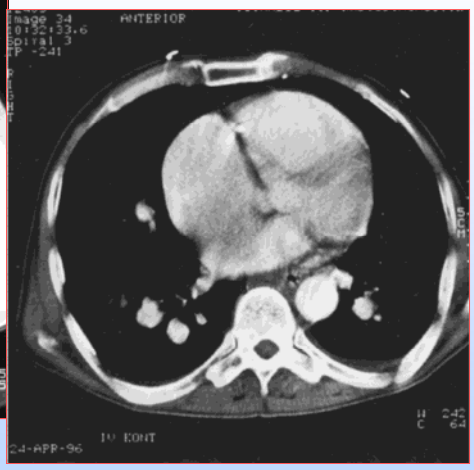
Pulmonary Artery Aneurysms





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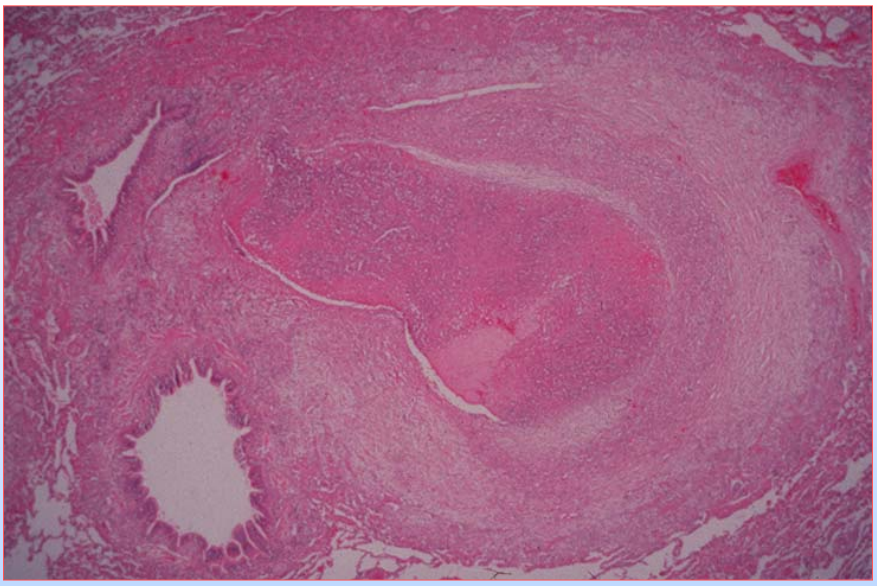
Erkan, *Thorax*, 2001



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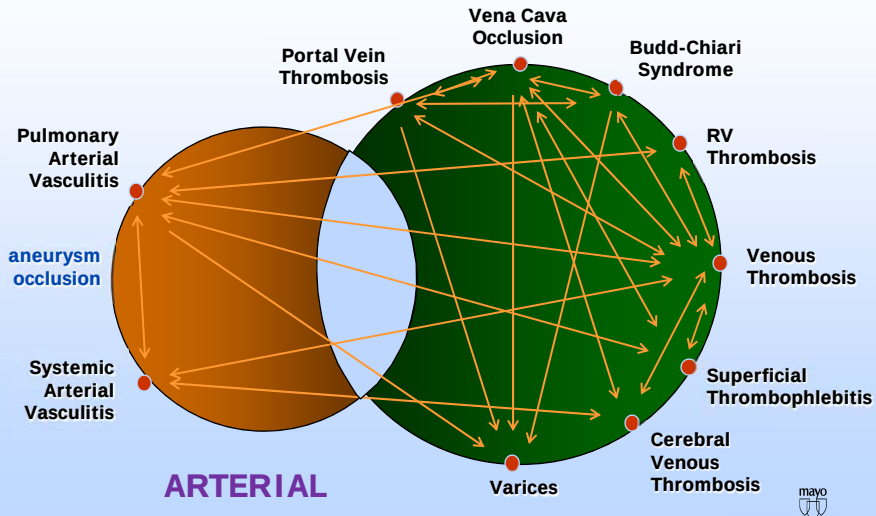
Vasculo-Behçet



MAYO CLINIC HEALTH SYSTEM

Behçet's Disease
Types of Skin Lesions

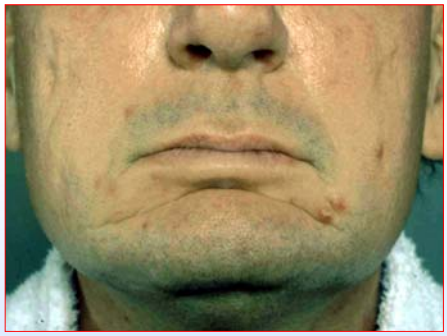
ISG Criteria

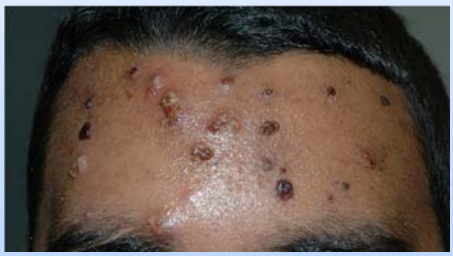
- EN
- pseudofolliculitis
- papulopustular lesions
- acneiform nodules

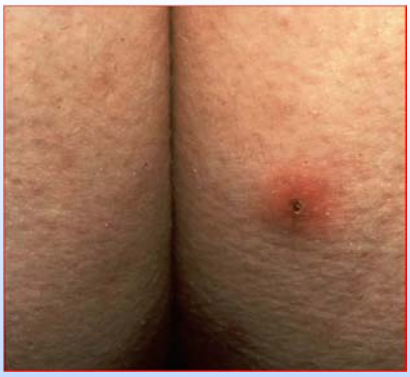
Other lesions

- superficial thrombosis
- folliculitis
- Sweet's-like lesions
- pyoderma
- extragenital ulcers
- erythema multiforme
- acral nodules

MAYO CLINIC HEALTH SYSTEM







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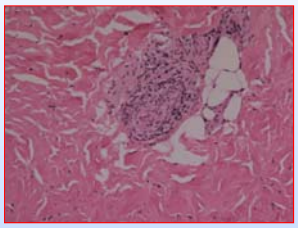
Behçet's Disease in the USA
Cutaneous Manifestations

Histopathologic findings

Total # with skin biopsy (excludes oral or genital ulcers)	41
Biopsy at evaluation	18
Previous biopsy, ew	28
Vasculitis on biopsy	13

Remainder nonspecific



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Balabanova, JAAD, 1999

Behçet's Disease
Treatment guidelines

- Treatment of BS depends on the clinical expression and prognosis, determined by age, gender, and disease duration
- Morbidity of disease determined by eye involvement, vascular, CNS disease
- Mortality primarily determined by vascular disease & CNS disease

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Behçet's Disease
Disease activity

- Laboratory tests usually not helpful:
  - Acute phase response correlates with thrombophlebitis, arthritis, EN
- Fever: infection vs large vessel disease

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Twenty Year Prognosis in Behçet's Syndrome

- 428 patients, seen 1978-1983
- 41 patients died (9.6%), 39 M, 2 F
  - PAA 10
  - Vena Cava Thrombosis 5
  - Budd Chiari 3
  - CNS disease 5
- 50% males with eye disease: blind

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Kural-Seyahi, *Medicine,* 2003

Management of Behçet's disease

EULAR recommendations for the management of Behçet disease

G Hatemi,[1] A Silman,[2] D Bang,[3] B Bodaghi,[4] A M Chamberlain,[5] A Gul,[6] M H Houman,[7] I Kötter,[8] I Olivieri,[9] C Salvarani,[10] P P Sfikakis,[11] A Siva,[12] M R Stanford,[13] N Stübiger,[14] S Yurdakul,[1] H Yazici[1]

Ann Rheum Dis, 2008; 67:1656-62

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EULAR recommendations for the management of Behcet's disease

- Patients with inflammatory eye disease of the posterior segment should be on a Rx includes azathioprine & systemic steroids
- Patients with severe eye disease, ↓ >2 lines drop in VA +/or retinal disease cyclosporine A or infliximab should be used in combination with aza & steroids or interferon-α +/- steroids

2014*- infliximab (++) or adalimumab (+) considered 1st or 2nd line steroid sparing Rx or for treatment for acute exacerbations

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***Levy-Clarke, *Ophthalmology*, 2014**

EULAR recommendations for the management of Behcet's disease

- **For parenchymal CNS disease: corticosteroids, interferon α, azathioprine, cyclophosphamide, MTX and TNF-α antagonists.** ***Chlorambucil (O'Duffy, 1976)***
- **CSA should be avoided unless essential for intraocular inflammation**
- **For dural sinus thrombosis: corticosteroids Anticoagulants controversial**

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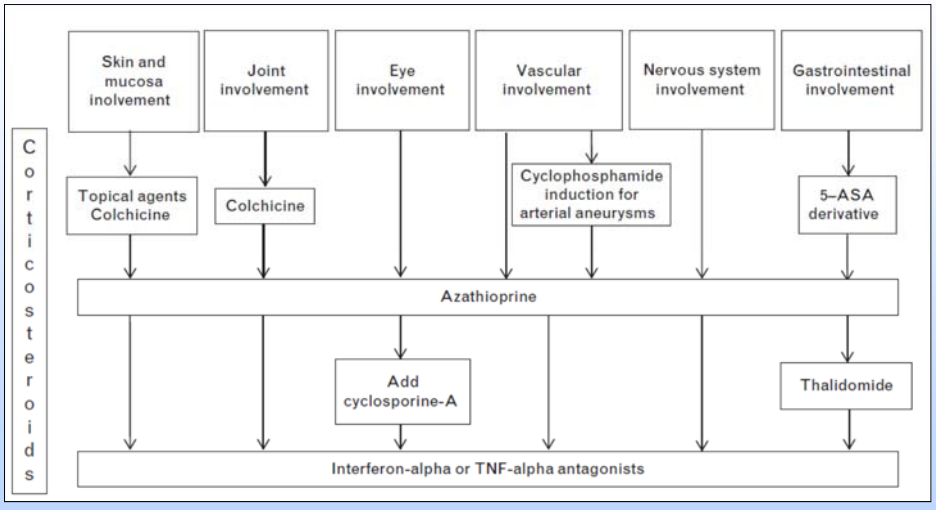
Hatemi, *Ann Rheum Dis, 2008; 67:1656-62*

Management of Behçet's Syndrome



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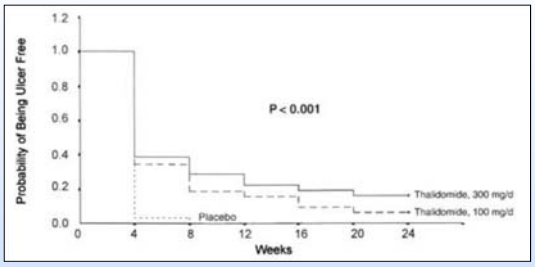
Ozguler, *Current Opin Rheumatol*, 2014

Thalidomide in BD



Males only
Neurotoxicity- 6%

Yazici, Ann Intern Med, 1998

"Grand-round cases divert us from the humdrum of everyday practice, but diagnostic eurekas must be tempered by therapeutic sobriety. Let us not kill a potentially useful drug, given a second chance, by injudicious prescribing."

Ehrlich, Ann Intern Med, 1998

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Use of anti-TNF agents in ocular BD

- Meta-analysis (369 pts)- 90% response rate in pts inadequately controlled by conventional Rx
- With F/U 16-36 mo- INFlix effects sustained, relapse rates <50% of baseline, stabilization of VA
- Fewer exacerbations INFlix (0.4/yr) compared to CSA (1.2/yr) in retrospective studies (3/yr baseline)
- 67.7% of 124 refractory patients inactive at 1 year
- Retinal vasculitis: lower relapse rate & VA with INFlix compared to standard Rx (mean F/U 36 mo)

Arida, 2011; Levy-Clarke, 2014; Yamada, 2010, 2011; Calvo-Rio, 2014 Tabbara, 2008

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INF-α in posterior or panuveitis in BD

- Multiple open studies since 2003
- Effective in >90% of patients refractory to steroids, AZA and CSA
- Evolving experience with lower doses, 3MU tiw
- Do not use with AZA because of myelosuppression risk

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Gevokizumab (Xoma 052) in Behçet's Uveitis

- IL-1B inhibitor
- Orphan drug designation after a phase 2 trial of a single dose IV gevokizumab (0.3 mg/kg), in 7 patients with Behçet's uveitis.
  - All patients experienced complete reduction of inflammation, median of 14 days.
  - Duration of response 49 days, median
  - 5 patients with recurrent oral ulcers & folliculitis experienced recurrences during the study

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Gul, *Ann Rheum Dis*, 2012

EULAR recommendations for the management of Behcet's disease

- **The management of DVT in BD should include IS agents: steroids, AZA, CTX or CSA.**
- **There is no evidence of benefit from anticoagulants in the management of DVT**
  - ***Beware of coexisting pulmonary art. aneurysms!***
- **CTX & steroids recommended for pulmonary & peripheral arterial aneurysms**
  - ***Embolization for PAAs, surgical mortality ↑***
  - ***Surgery for peripheral or AAA***

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Hatemi, *Ann Rheum Dis, 2008; 67:1656-62*

Other biologic agents in Rx of BD

44 BD cases Rx'd with non anti-TNF biologics:

- 24 patients on IL-1 inhibitors:
  - 13- anakinra; 4- canakinumab ; 7- gevokizumab
- 7 patients treated with the IL-6 RA tocilizumab
- 1 pt.- anti-IL-12/23R agent ustekinumab
- 12 pts.- anti-CD-20 agent rituximab

Secukinumab (anti-IL-17), N=118 & Daclizumab (anti-IL-2 RAb), N=17 not superior to placebo for ocular BD in controlled trials

MAYO CLINIC HEALTH SYSTEM

Caso, *Mediators of Inflammation*, 2014; Arida, Clin & Exp Rheum, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apremilast for Behçet's Syndrome — A Phase 2, Placebo-Controlled Study

Gulen Hatemi, M.D., Melike Melikoglu, M.D., Recep Tunc, M.D., Cengiz Korkmaz, M.D., Banu Turgut Ozturk, M.D., Cem Mat, M.D., Peter A. Merkel, M.D., Kenneth T. Calamia, M.D., Ziqi Liu, Ph.D., Lilia Pineda, M.D., Randall M. Stevens, M.D., Hasan Yazici, M.D., and Yusuf Yazici, M.D.

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April 16, 2015

Apremilast in Behçet's Syndrome

Apremilast- PDE-4 inhibitor, ↑ intracellular cAMP
↓ TNF-α, interleukin-23, interferon-γ
↑ interleukin-10

- Phase 2, multicenter, placebo controlled study
- 111 patients with BD ulcers
- Apremilast 30 mg BID vs placebo x 12 weeks
- 1º endpoint- # ulcers at week 12
- 2º endpoints- pain, genital ulcers, dis.activity, QoL

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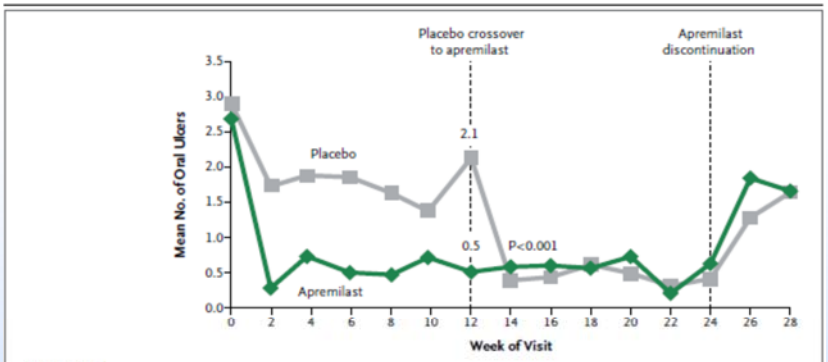
Hatemi, *New Eng J Med*, 2015



No. at Risk															
Placebo	56	56	53	51	44	42	45	45	36	45	36	34	45	38	54
Apremilast, 30 mg	55	55	50	53	48	47	50	49	41	49	38	37	47	40	54
Mean No. of Oral Ulcers															
Placebo	2.9	1.7	1.9	1.9	1.6	1.4	2.1	0.4	0.4	0.6	0.5	0.3	0.4	1.3	1.6
Apremilast, 30 mg	2.7	0.3	0.7	0.5	0.5	0.7	0.5	0.6	0.6	0.6	0.7	0.2	0.6	1.9	1.7

Figure 1. Mean Number of Oral Ulcers Per Patient, According to Study Group.
The mean number of oral ulcers per patient was significantly lower in the apremilast group than in the placebo group during the placebo-controlled phase (baseline to week 12). At week 12, patients in the placebo group were switched to apremilast therapy, after which the mean number of oral ulcers in those patients decreased. After apremilast was discontinued at week 24, the mean number of oral ulcers started to increase within 2 weeks. A repeated-measures analysis performed with data from baseline to week 12 showed consistent results.

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Hatemi, *New Eng J Med*, 2015

ISBD
INTERNATIONAL SOCIETY FOR BEHÇET'S DISEASE

Dr. Hulusi Behçet
1889-1948

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Return to Program Schedule

Periodic Fever Disorders

Rheumatology Update 2015

L.e. Mertz MD
Rheumatology Division
Mayo clinic Arizona

Disclosure Statement

There are no financial conflicts to disclose.

Return to Program Schedule

Goals of Presentation

- Review basic pathophysiology of fever in humans.
- Identify several genetic disorders that lead to Autoinflammatory/Periodic Fever disorders.
- Demonstrate how knowledge of genetic causes of fever may apply to understanding gout and recurrent pericarditis.
- Identify resources available for understanding the genetics of Periodic Fever disorders and obtaining genetic testing confirmation.

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Potential Etiologies of Fever

- Infection
- Malignancy
- Drugs
- CNS hemorrhage or irritation
- Autoimmune disorders
  - Vasculitis, SLE, Still's disease.
- Autoinflammatory
  - Periodic Fever disorders
    - Familial Mediterranean Fever
    - TRAPS-TNF Receptor Associated Periodic Syndrome
    - CAPS-Cryopyrin Associated Periodic Syndromes.
    - Mevalonate kinase deficiency.
  - Non-Periodic Fever Disorders
    - Crohn's disease, Sarcoidosis. others.
- Crystal induce arthritis
  - Gout, Pseudogout.

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Potential Etiologies of Fever

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  - Gout, Pseudogout.

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Autoinflammatory Disorder

Characteristics

- Inflammation by symptoms, findings, laboratory tests, x-rays or biopsy.
- Episodic, less often periodic.
- Unprovoked by usual causes(infection, malignancy, etc).
  - Occasionally associated with apparently benign physical(cold, vaccination) or emotional stress
- Lack of significant auto antibody production by B cells (SLE, ANCA).
- Lack of antigen specific, activated T cells (viral illness).
- Often associated with fever, leukocytosis, rash, arthralgia, myalgia.
- Laboratory evidence of inflammation: elevated ESR and CRP.
- Due to inappropriate activation of the innate immune system through antigen independent inflammatory mechanisms.

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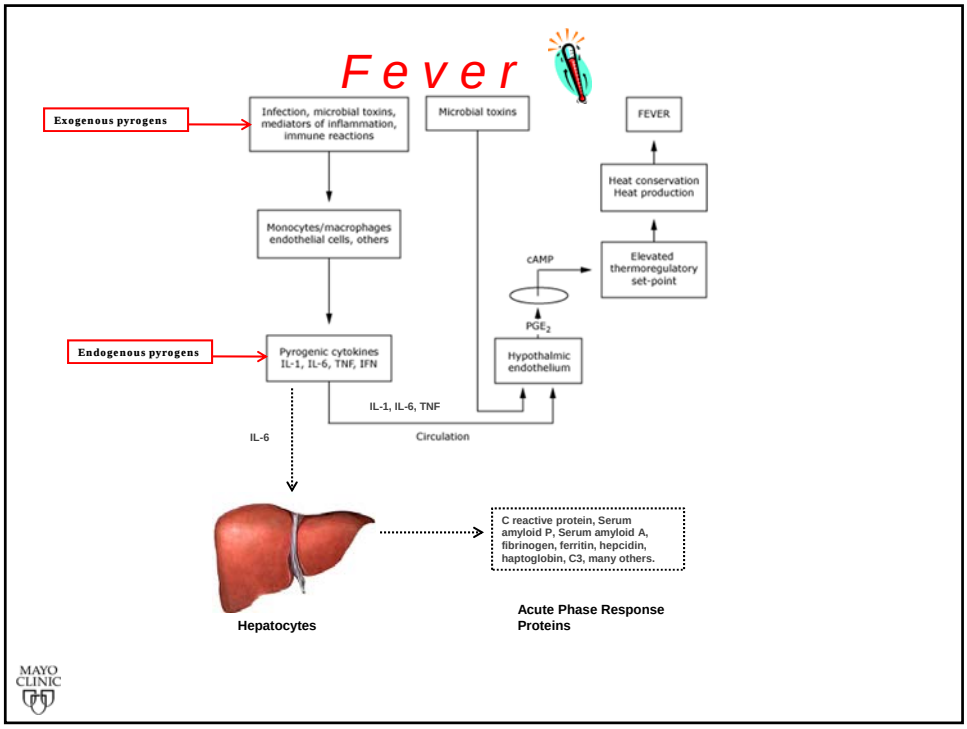
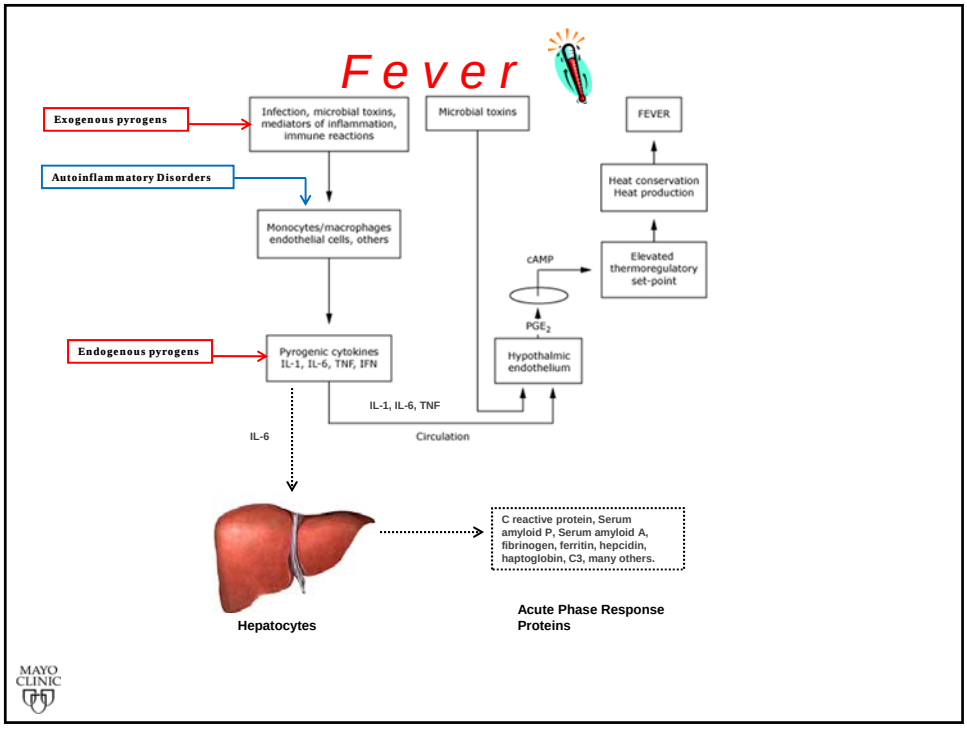

Fever
Exogenous pyrogens
Infection, microbial toxins, mediators of inflammation, immune reactions
Microbial toxins
FEVER
Heat conservation
Heat production
Monocytes/macrophages endothelial cells, others
cAMP
Elevated thermoregulatory set-point
PGE2
Endogenous pyrogens
Pyrogenic cytokines IL-1, IL-6, TNF, IFN
Hypothalmic endothelium
IL-1, IL-6, TNF
Circulation
IL-6
C reactive protein, Serum amyloid P, Serum amyloid A, fibrinogen, ferritin, hepcidin, haptoglobin, C3, many others.
Hepatocytes
Acute Phase Response Proteins
MAYO CLINIC


Fever
Exogenous pyrogens
Infection, microbial toxins, mediators of inflammation, immune reactions
Microbial toxins
FEVER
Autoinflammatory Disorders
Heat conservation
Heat production
Monocytes/macrophages endothelial cells, others
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Elevated thermoregulatory set-point
PGE2
Endogenous pyrogens
Pyrogenic cytokines IL-1, IL-6, TNF, IFN
Hypothalmic endothelium
IL-1, IL-6, TNF
Circulation
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C reactive protein, Serum amyloid P, Serum amyloid A, fibrinogen, ferritin, hepcidin, haptoglobin, C3, many others.
Hepatocytes
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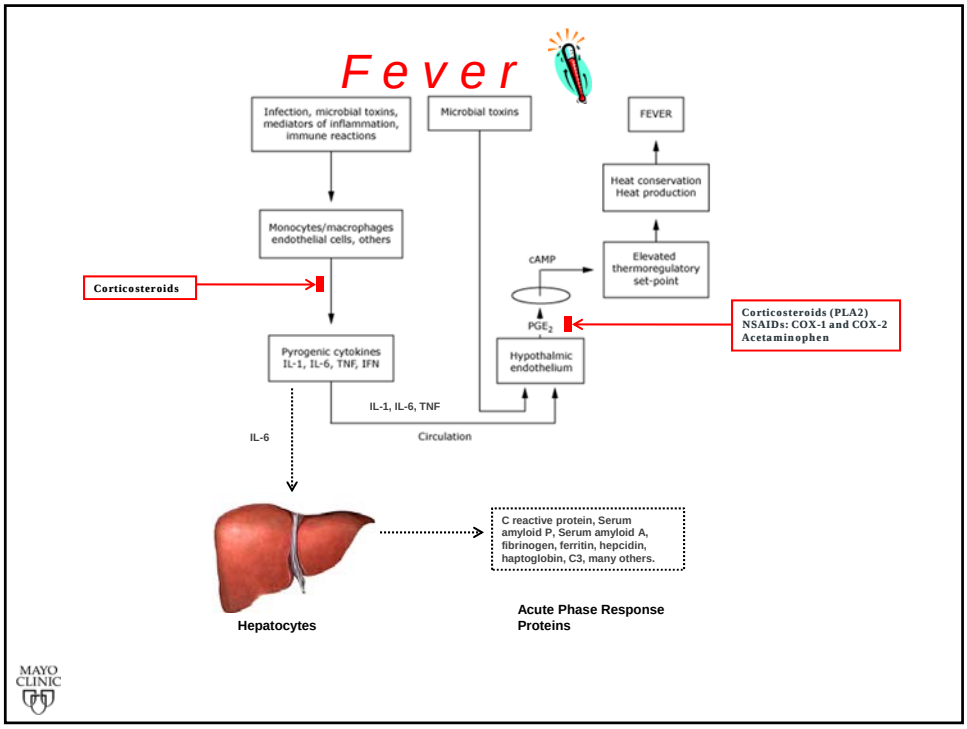
MAYO CLINIC


Fever
Infection, microbial toxins, mediators of inflammation, immune reactions
Microbial toxins
FEVER
Heat conservation
Heat production
Monocytes/macrophages endothelial cells, others
cAMP
Elevated thermoregulatory set-point
Corticosteroids
Corticosteroids (PLA2)
NSAIDs: COX-1 and COX-2
Acetaminophen
PGE2
Pyrogenic cytokines IL-1, IL-6, TNF, IFN
Hypothalmic endothelium
IL-1, IL-6, TNF
Circulation
IL-6
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Hepatocytes
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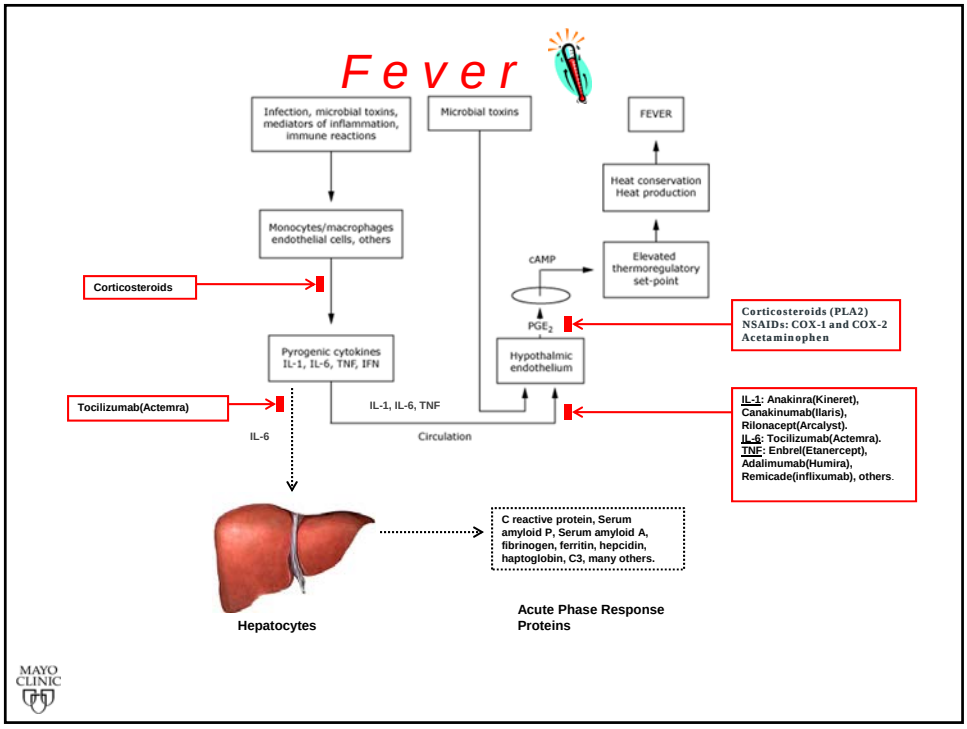
MAYO CLINIC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Acetaminophen
PGE2
Pyrogenic cytokines IL-1, IL-6, TNF, IFN
Hypothalmic endothelium
Tocilizumab(Actemra)
IL-1, IL-6, TNF
IL-1: Anakinra(Kineret), Canakinumab(Ilaris), Rilonacept(Arcalyst).
IL-6: Tocilizumab(Actemra).
TNF: Enbrel(Etanercept), Adalimumab(Humira), Remicade(infliximab), others.
Circulation
IL-6
C reactive protein, Serum amyloid P, Serum amyloid A, fibrinogen, ferritin, hepcidin, haptoglobin, C3, many others.
Hepatocytes
Acute Phase Response Proteins
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IL-1β in Autoinflammatory Disorders

	Viral URI	Gout	FMF	TRAPS
Stimulus	H1N1	Urate crystals Joint trauma	?Stress physical, emotional	?Stress physical, emotional
Fever	✓	✓	✓	✓
Fatigue	✓		✓	✓
Myalgia	✓		✓	✓
Arthralgia/itis	✓	✓	✓	✓
Erythroderma	✓	✓	✓	✓
Conjunctival inj.	✓			✓
Abd pain			✓	✓
IL-1 β⇧	✓	✓	✓	✓
ESR/CRP⇧	✓ episodic	✓episodic	✓episodic	✓persistent
Treatment	NSAIDs	Colchicine NSAIDs Corticosteroids Anakinra	Colchicine NSAIDs Corticosteroids Anakinra ?TNF inhibitors	Not Colchicine NSAIDs Corticosteroids Anakinra TNF inhibitors
Gene defect	None	None	MEFV (pyrin) AR	TNFRSF1A AD

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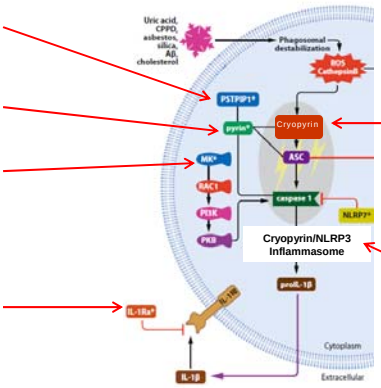
IL-1β production: The Inflammasome

PAPA(Pyogenic Arthritis, Pyoderma gangrenosum, Acne

Familial Mediterranean Fever

Mevalonate Kinase Deficiency (Hyperimmunoglobulin D Syndrome)

DIRA(Deficiency of Interleukin-1 Receptor Antagonist



CAPS(Cryopyrin Associated Periodic Syndromes)

1. FCAS(Familial Cold Autoinflammatory Syndrome.
2. MWS(Muckle-Wells Syndrome)
3. NOMID(Neonatal Onset Multisystem Inflammatory Syndrome)

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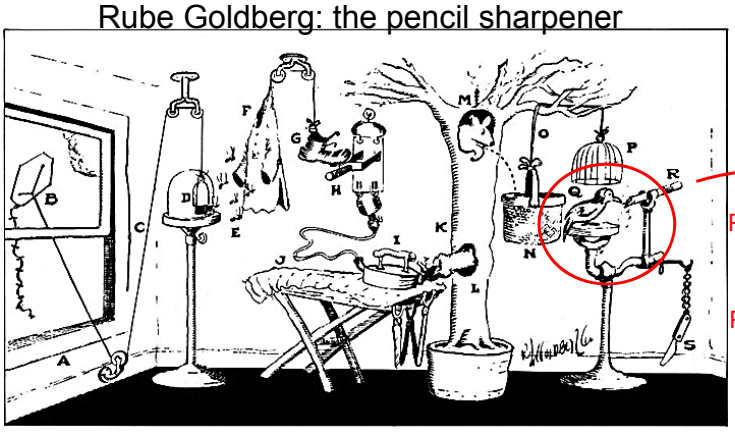
Annu. Rev. Immunol. 2009. 27:621–68

IL-1β production: The Inflammasome

Rube Goldberg: the pencil sharpener



Pro Caspase 1 ⇨ Caspase 1

Pro IL-1β ⇨ IL-1β

Inflammation & Fever

The Cryopyrin/NLRP3 Inflammasome

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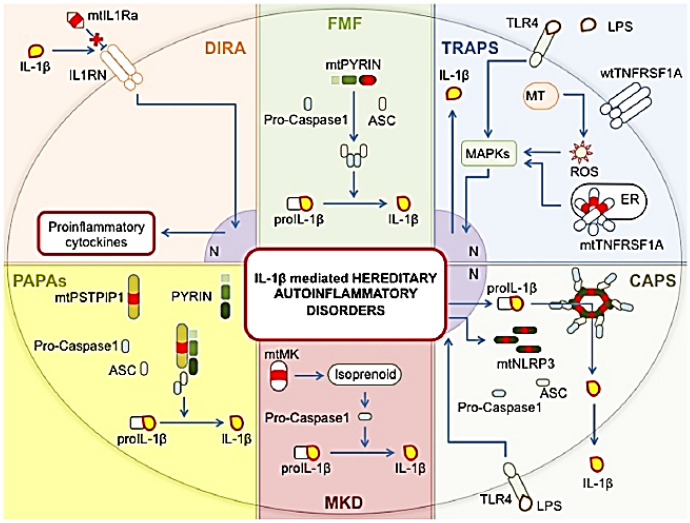
D. Rigante et al. / Autoimmunity Reviews 13 (2014) 892–900



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Familial Mediterranean Fever

- Commonly affected populations.
  - Turks
  - Armenians
  - Arabs
  - Non-Ashkenazie Jews
- Countries with reported cases
  - Mediterranean basin
  - North Africa
  - USA
  - Europe
  - Australia
  - Japan

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Clinical Case 11/23/2011

- 32 year old woman of Jordanian descent presents for follow up of Familial Mediterranean Fever (FMF) present since 3 months of age.
- Episodes of spontaneous fever, chest and abdominal pain, fatigue lasting approximately 3 days.
- Questions of tonsillitis and appendicitis lead to surgical removal without long term benefit.
- Episodes treated with bed rest until resolution.
- Colchicine 1 mg BIW started 4 years ago with complete resolution of episodes without med side effects.

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Clinical Case 11/23/2011

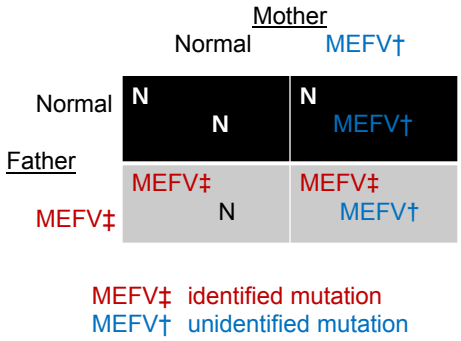
- Genetic Testing 8/19/2011 (ARUP Lab)
  - Only one pathogenic mutation detected in the MEFV gene.
  - This individual is a carrier of FMF.
  - MEFV mutation analysis
    - Mutation present in exon 10
    - Nucleic acid change: c.2080 A>G heterozygous.
    - Amino acid alteration: pMeth694Val
    - Analytic sensitivity 99%.
    - Clinical sensitivity 80%
    - Most highly associated with amyloidosis.

Clinical Case 11/23/2011

- Genetic Testing 8/19/2011.
  - Autosomal recessive inheritance(two abn. genes required).
  - Mutations in the MEFV gene are known to cause FMF. However, other genes may be involved as some affected patients do not have <u>any</u> identifiable MEFV gene mutations.
  - Affected individuals are usually <u>compound heterozygous</u> and carry <u>two</u> distinct MEFV gene mutations.
  - Approximately 80 MEFV gene mutations have been reported; the majority are in exon 10.

Clinical Case 11/23/2011

- Family history
  - Both parents reportedly asymptomatic.
  - 1/1 brother has FMF on colchicine.
  - 1/3 sisters has FMF on colchicine.
  - Consistent with autosomal recessive inheritance pattern.



MEFV‡ identified mutation
MEFV† unidentified mutation

Clinical Case: 2/14/2011

- 64 year old woman ill since 1 year of age.

"My Rheumatologist wants to know what I have".

- Dermatologic
  - Episodic, erythematous, painful macules of trunk.
  - Duration 7-10 days, weeks between, no visible sequellae.
  - Worsening of chronic fatigue and anorexia during episodes.
  - Bx: perivascular inflammation. Vasculitis questioned.
- Gastroenterologic
  - Episodic abdominal pain like "a towel twisted in abdomen".
  - Distant liver bx: minimal non-specific hepatitis.
- Musculoskeletal
  - Variable but daily proximal muscle soreness. Never joint swelling.
  - Distant muscle biopsy negative.

Clinical Case: 2/14/2011

- ENMT
  - Episodes of episcleritis, not with each episode of rash.
- Systemic
  - Daily fatigue, no fevers, weight stable.
- Investigations
  - GI w/u negative for celiac, Whipple's, inflam bowel disorders.
  - ESR and CRP frequently elevated during the rash.
  - Borderline elevated ANA once, recent positive anti thyroid peroxidase ab, but immune testing otherwise negative.
- Family history
  - Negative for similar symptoms and any other Rheumatologic disorders.
- Treatment
  - Corticosteroids relieve fatigue but did not affect the rash.

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Clinical Case: 2/14/2011

- Examination
  - Normal.
  - Cell phone pictures of skin confirm patchy erythema.
- Laboratory
  - Hgb 10.8 g/dl, WBC 12,800, Plt normal,
  - ESR 99 mm/hr, CRP 218.4 mg/L
  - CMP, muscle enzymes, urine normal.
  - Mild polyclonal hypergammaglob. with no monoclonal proteins
  - HCV, HBV, Lyme disease testing negative
- Immunologic tests
  - RF, anti CCP, ANA, ENA, ANCA panel negative.
  - C4, C1E Inh, cryos normal. C3 mildly elevated at 181 mg/dl.
  - IBD, celiac antibodies negative.
  - Anti TPO abs very high at 825.7 units (<9 units normal).

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Clinical Case 2/14/2011

- Genetic testing (GeneDx)
  - MEFV gene for Familial Mediterranean Fever.
    No mutation known to be associated with FMF was identified.
  - TNFRSF1A gene for TNF-Receptor Associated Periodic Fever Syndrome (TRAPS).
    - An autosomal dominant disorder.
    - This individual is heterozygous for a C>T nucleotide substitution in exon 3 (T50M mutation).This mutation has been reported previously in association with TRAPS (McDermott 1999, Absentijovich 2001) and its presence is consistent with this diagnosis in this patient. The analytic method used is expected to be 99% sensitive for mutations identifiable by sequencing.
- Minimal improvement on etanercept (Enbrel).
- Improved results with anakinra (Kineret).

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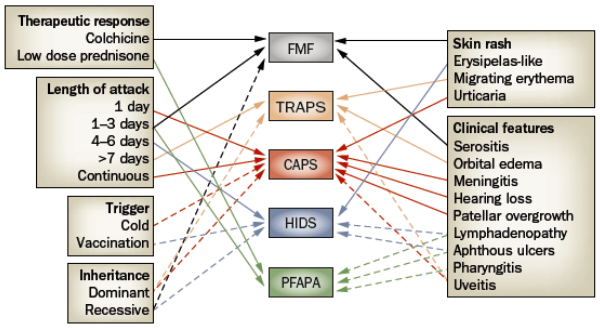
Differentiation of Periodic Fever Syndromes



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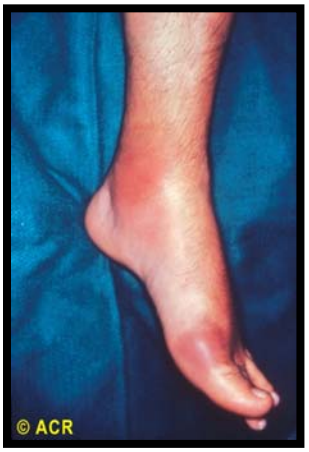
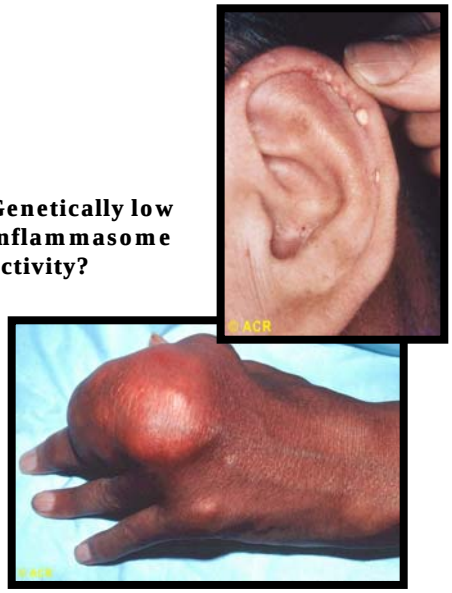
Hoffman, H. M. & Simon, A. *Nat. Rev. Rheumatol.* 5, 249–256 (2009); doi:10.1038/nrrheum.2009.40

Gout: An Autoinflammatory Disorder?

Genetically high inflammasome activity?



Genetically low inflammasome activity?



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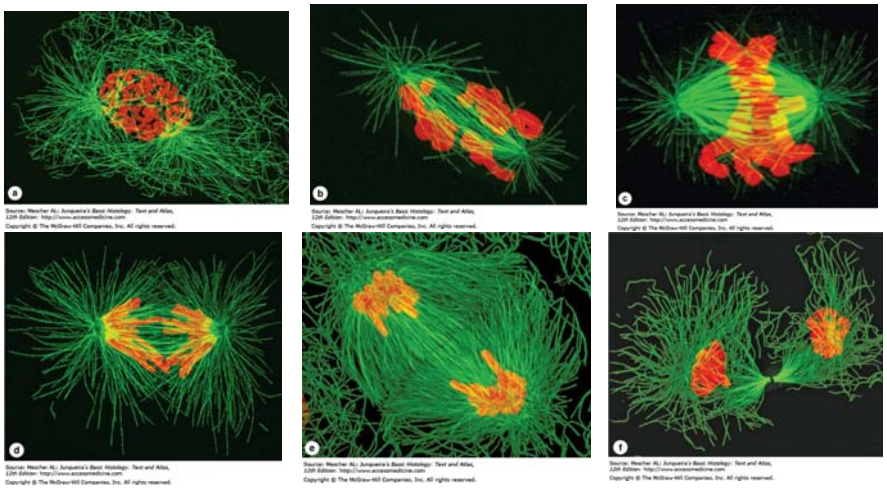
Microtubule Structure and Function: Mitosis



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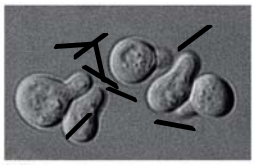
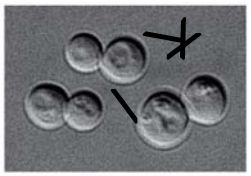
Microtubule Structure and Function: Gout

Normal Microtubule Function



(B)

+ Colchicine



(A)

Colchicine: Anti inflammatory Mechanisms

Table 1. Mechanisms of action of colchicine in crystal-induced inflammation

Study	Biologic effect	Biochemical basis
Caner [60]	↓ Neutrophil chemotaxis	↓ Tubulin polymerization
Wright and Malawista [61]	Stabilization lysosomes	↓ Tubulin polymerization
Phelps [62], Spilberg et al. [63], McCarty [64•]	↓ Release CCF	↓ Tubulin polymerization
Roberge et al. [66]	↓ Neutrophil activation ↓ Leukotriene B4	↓ Tyrosine phosphorylation
Martinon et al. [22••]	↓ NALP3 inflammasome driven caspase-1, IL-1β processing and release	↓ Tubulin polymerization
Cronstein et al. [70]	↓ Neutrophil L-selectin	↓ Tubulin polymerization
Cronstein et al. [70]	Block IL-1–induced ↑ neutrophil adhesion by change distribution E-selectin on endothelial cells	↓ Tubulin polymerization
Abramson et al. [48], Roberge et al. [66], Minta and Williams [71], Chia et al. [72••]	↓ Neutrophil superoxide anion	↓ Tubulin polymerization

CCF—crystal-derived chemotactic factor; IL—interleukin; NALP3—NACHT-LRR-PYD-containing protein-3.

Current Rheumatology Reports 2008, 10:218–227

Treatment of Gout with Anakinra

A pilot study of IL-1 inhibition by anakinra in acute gout
Alexander So1, Thibaut De Smedt2, Sylvie Revaz1 and Jürg Tschopp3

Arthritis Research & Therapy 2007, **9**:R28 (doi:10.1186/ar2143)

Anakinra 100 mg daily for three days

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Treatment of Gout with Anakinra

Table 1

Clinical summary of the 10 patients studied and their response to treatment

Patient	Clinical presentation	Affected joints	Serum uric acid (normal range, 160–390 µmol/l)	Serum creatinine (normal range, 44–80 µmol/l)	Hypouricemic treatment	Effect of anakinra (hours)	Patient assessment of improvement in pain (%)
Case 1 (female, 72 years old)	Chronic tophaceous gout, renal stones	Fingers, toes	637	79	Uricase	36	70
Case 2 (male, 70 years old)	Chronic tophaceous gout	Ankle, toes	564	202	Allopurinol	24	90
Case 3 (male, 72 years old)	Acute gout	Knee, ankle, foot	482	121	Allopurinol	24	90
Case 4 (male, 51 years old)	Acute gout	Ankle, toe	396	84	Allopurinol	24	100
Case 5 (male, 40 years old)	Acute gout	Ankle, toe	322	113	Allopurinol	36	100
Case 6 (female, 72 years old)	Acute gout	Feet, toe	572	72	None	36	80
Case 7 (male, 76 years old)	Acute gout	Ankle, foot	338	79	None	36	100
Case 8 (male, 70 years old)	Acute gout	Wrist, elbow, hand	779	406	None	48	50
Case 9 (male, 53 years old)	Chronic tophaceous gout	Elbow, finger, foot, ankle	660	84	Allopurinol	48	50
Case 10 (male, 38 years old)	Acute gout	Wrist, finger	540	84	None	24	60

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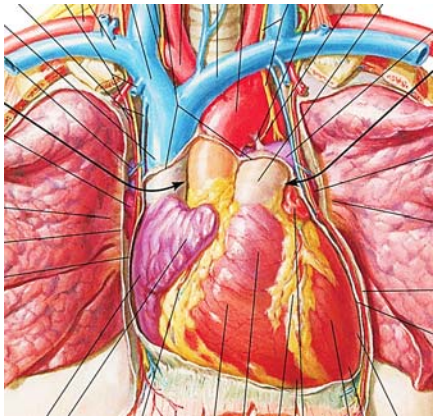
Idiopathic Recurrent Acute Pericarditis



Pericardium

IRAP Treatment with Colchicine

Prevention of Recurrent Pericarditis With Colchicine in 2012

Gal Markel, MD, PhD; Massimo Imazio, MD; Antonio Brucato, MD; Yehuda Adler, MD

Clin. Cardiol. 36, 3, 125–128 (2013)

- Colchicine + aspirin compared to aspirin alone
  - 50% reduction in recurrent pericarditis compared to aspirin alone.
  - Previous or concurrent corticosteroids reduced efficacy of colchicine.

IRAP: An Autoinflammatory Disorder?

Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis

Luca Cantarini [a,*,1], Giuseppe Lopalco [b,1], Carlo Selmi [c,d], Salvatore Napodano [e], Gabriella De Rosa [e], Francesco Caso [a,f], Luisa Costa [g], Florenzo Iannone [b], Donato Rigante [e]

Autoimmunity Reviews 14 (2015) 90–97

- Turkish patients with FMF
  - 1.4% develop pericarditis
- Italian patients with IRAP
  - 0% with FMF gene mutation
  - 6% with TRAPS gene mutation.

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IRAP Secondary to TRAPS

Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study

Luca Cantarini • Orso Maria Lucherini • Antonio Brucato • Luca Barone • Davide Cumetti •

Clin Res Cardiol (2012) 101:525–531

- TNFRSF1A gene mutations can be detected in about 6% with recurrent pericarditis.
- positive family history for pericarditis and/or recurrent fever syndrome.
- recurrences/year after the first year from the index attack of acute pericarditis
- colchicine failure
- need of immunosuppressive agents

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IRAP Treatment with Anakinra

Successful treatment of adult patients with idiopathic recurrent pericarditis with an interleukin-1 receptor antagonist (anakinra)

Dimitrios Vassilopoulos [a], George Lazaros [b,*], Costas Tsioufis [b], Panagiotis Vasileiou [b], Christodoulos Stefanadis [b], Dimitrios Pectasides [a]

International Journal of Cardiology 160 (2012) 66–77

- Three patients with treatment resistant IRAP
- All three responded to anakinra given over several months.
  - One relapsed off QD anakinra and responded to QOD reinstitution.
  - One relapsed off QD anakinra but responded to NSAIDs and colchicine.
  - One did not relapse 15 months after discontinuing anakinra

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Genetic Disorders Reference

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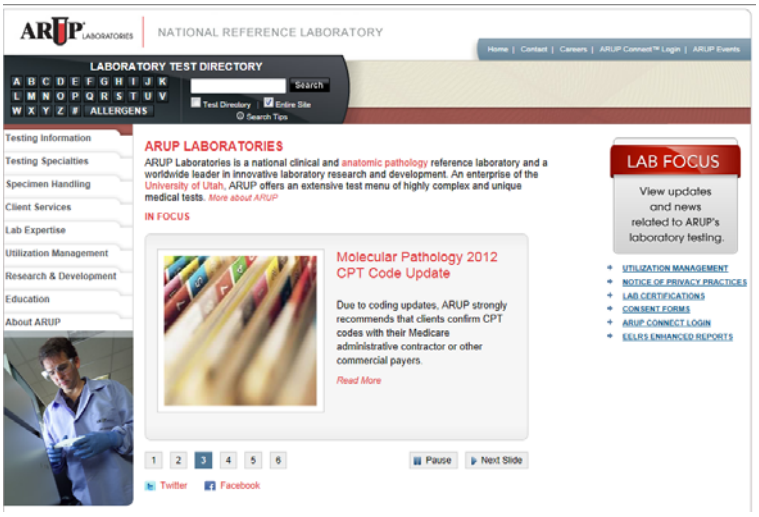
Genetic Testing



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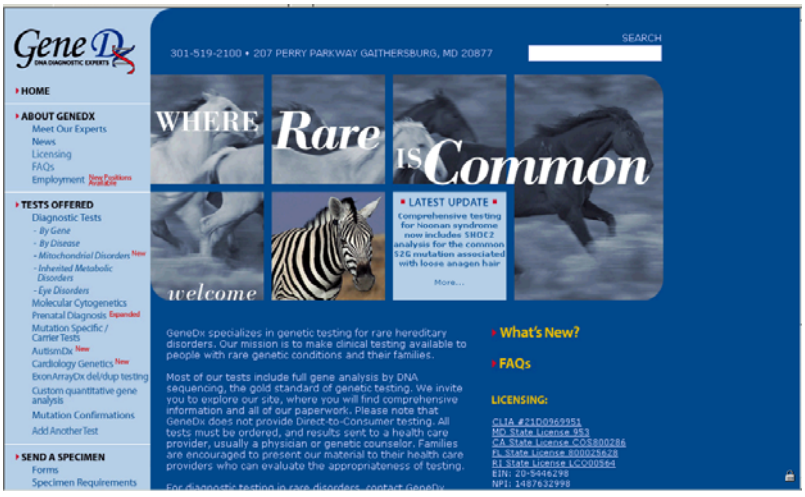
Genetic Testing



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Periodic Fever Disorders

Summary

- Elevated IL-1 is a common cause of fever.
- Elevated circulating IL-1 largely explains the fever and other inflammatory manifestations of gout, IRAP and periodic fever disorders such as FMF and TRAPS.
- Spontaneous excess production of IL-1 by the NLRP3/Cryopyrin inflammasome explains the fevers in periodic fever disorders.
- Effective IL-1 antagonists are available.
- Genetic testing may be helpful in identifying patients with periodic fever disorders.

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2. Masters S, et. al. Horror Autoinflammaticus: The Molecular Pathophysiology of Autoinflammatory Disease. Annu. Rev. Immunol 2009;27:621-668.
3. Hoffman H, Simon A. Recurrent Febrile Syndromes-What a Rheumatologist Needs to Know. Nature Reviews Rheumatology 2009;5:249-256.
4. Ben-Chetrit E, Touitou I. Familial Mediterranean Fever in the World. Arthritis & Rheumatism 2009;61:1447-1453.
5. Ozturk M, et. al. Therapeutic Approach to Familial Mediterranean Fever: A Review Update. Clin Exper Rheum 2011;29(Suppl.):S77-S86.

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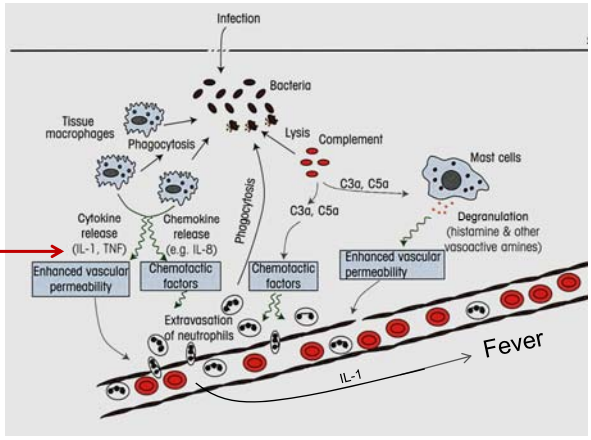
Acute inflammatory response



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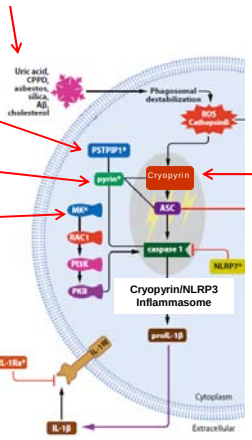
Gout: The Inflammasome

PAPA(Pyogenic Arthritis, Pyoderma gangrenosum, Acne

Familial Mediterranean Fever

Mevalonate Kinase Deficiency (Hyperimmunoglobulin D Syndrome)

DIRA(Deficiency of Interleukin-1 Receptor Antagonist



CAPS(Cryopyrin Associated Periodic Syndromes)

1. FCAS(Familial Cold Autoinflammatory Syndrome.
2. MWS(Muckle-Wells Syndrome)
3. NOMID(Neonatal Onset Multisystem Inflammatory Syndrome)

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Annu. Rev. Immunol. 2009. 27:621–68

Periodic Fever Disorders

	Viral URI
Stimulus	H1N1
Fever	✓
Fatigue	✓
Myalgia	✓
Arthralgia/itis	✓
Rash	✓
Conjunctival inj.	✓
Abd pain	
IL-1 ⇧	✓
ESR/CRP⇧	✓ episodic
Treatment	NSAIDs
Gene defect	None

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Periodic Fever Disorders

	Viral URI	Gout
Stimulus	H1N1	Urate crystals Joint trauma
Fever	✓	✓
Fatigue	✓	
Myalgia	✓	
Arthralgia/itis	✓	✓
Erythroderma	✓	✓
Conjunctival inj.	✓	
Abd pain		
IL-1 ⇧	✓	✓
ESR/CRP⇧	✓ episodic	✓episodic
Treatment	NSAIDs	Colchicine NSAIDs Corticosteroids Anakinra
Gene defect	None	None

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Periodic Fever Disorders

	Viral URI	Gout	FMF
Stimulus	H1N1	Urate crystals Joint trauma	?Stress physical, emotional
Fever	✓	✓	✓
Fatigue	✓		✓
Myalgia	✓		
Arthralgia/itis	✓	✓	✓
Erythroderma	✓	✓	✓
Conjunctival inj.	✓		
Abd pain			✓
IL-1 ⇧	✓	✓	✓
ESR/CRP⇧	✓ episodic	✓episodic	✓episodic
Treatment	NSAIDs	Colchicine NSAIDs Corticosteroids Anakinra	Colchicine NSAIDs Corticosteroids ?Anakinra ?TNF inhibitors
Gene defect	None	None	MEFV (pyrin) AR

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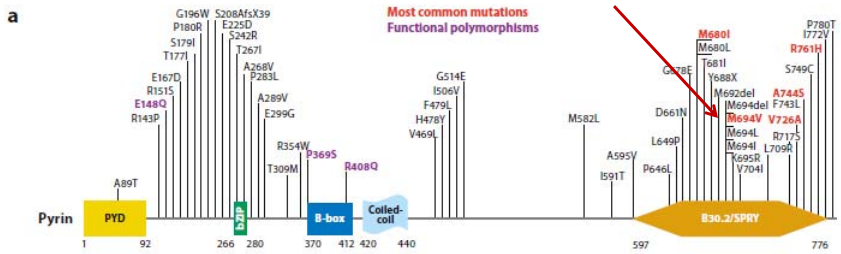
MEFV gene(Pyrin) Mutations



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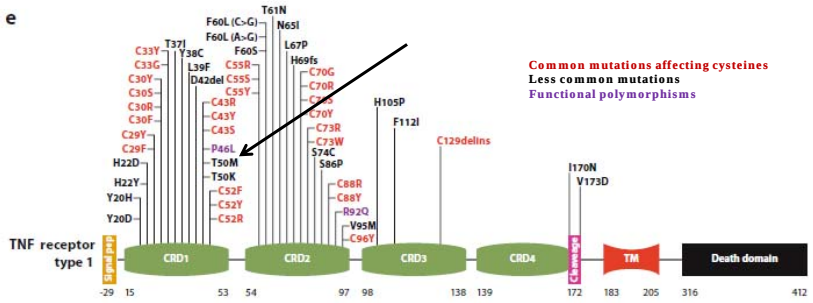
Annu. Rev. Immunol. 2009. 27:621–68

TRAPS Gene Mutations



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Annu. Rev. Immunol. 2009. 27:621–68

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