Categories of Rheumatic Diseases with their Immune and Laboratory Correlates

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Conflict of Interest Disclosure

I have no conflicts and nothing to disclose

Learning Objectives

- 1) To grasp the General CATEGORIES of Connective Tissue Diseases
- 2) To understand the Step Approach to their diagnosis (History, Exam, Lab, Imaging, Taps, Bx…)
- 3) Utilize CLASSIFICATION CRITERIA for definitive diagnosis

Lecture Outline
Categories of Degenerative & Immune Disease

- I) Regional Musculoskeletal Abnormalities
  - Osteoarthritis & degenerative spinal disease
- II) Inflammatory Diseases (Sero-Negative)
  - SpondyloArthritis Group
  - Polymyalgia Rheumatica
- III) AutoImmune Diseases: (Sero-Positive)
  - Systemic Lupus
  - Rheumatoid Arthritis
- IV) Vasculitic Syndromes
  - Large, Medium & Small vessel Dz

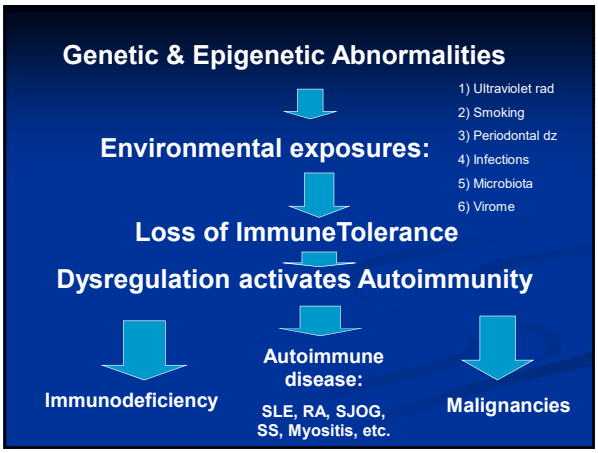
General Principals in the Diagnosis of Inflammatory & Autoimmune Diseases

- 1) Carefully perform History & Physical
  (Is there a Suspicion of an Immune Disease?)
- 2) Order screening lab tests: CRP, ANA, RF, CCP, etc…
  Aspirate, biopsy and analyze your data
- 3) Next order specific auto-antibody titers: Sm, DNA…
- 4) Utilize the Categories & Diagnostic Criteria
- 5) Evaluate Dz activity; DZ activity scores & labs
  CRP, ESR, C4, C3, gamma globulin levels
- 6) Evaluate major organ systems

Statements on Rheumatic Labs

- Requires an elevated suspicion of Immune Dz
- Your Initial Clinical Impression is your guide to the diagnosis
- Sensitive, but sometimes non-specific
- Immune labs serve as confirmatory data
- Many patients with a pos RF & ANA do not have RA & SLE
- In acute presentations rule out infections as an etiology for positive rheum labs

Shmerling RH. South Med J. Diag tests in rheum dz. 2010 Jul;98(7):704-11.



*Categories of Connective Tissue Diseases

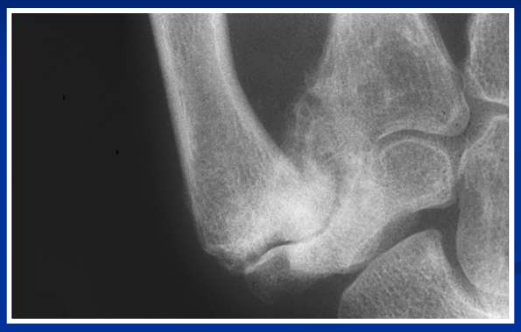
- 0) ***I) Regional Musculoskeletal Abnormalities***
  - *Osteoarthritis and associated degenerative disorders*
  - **II) Inflammatory Diseases (Sero-Negative)**
  - Arthritis 2' to legitimate immune response:
    - Infections: Active Vs Reactive, Crystallopathies, Metabolic disease….
  - Primary inflammatory conditions: Spondyloarthritis, PMR …
  - Auto-Inflammatory Diseases: Hereditary Periodic Fever
  - Malignancies: MGUS, Plasmacytoma, MM, Lymphomas...
- **III) Auto-Immune Diseases: RA, SLE, SS, Sjog etc.**
- **IV) Vasculitic Syndromes**

Regional Musculoskeletal Diseases Characterized:

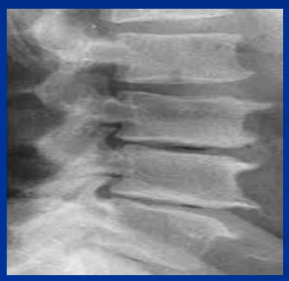
- History:
  - ***Pain exacerbated by activity and relieved by rest***
  - ***Localized Pain*** within weight bearing joints
- Physical Examination:
  - Localized joint hypertrophy with crepitus, tendonitis and bursitis
- Laboratory Studies:
  - All normal: ESR, CRP, ANA, RF, CCP, ANCA
- X-Rays:
  - Asymmetrical narrowing, sclerosis and hypertrophy

Degenerative Joint Disease

Osteoarthritis: First Carpometacarpal Joint

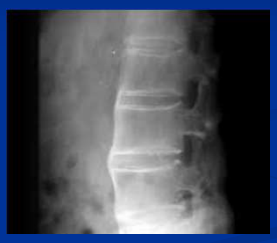


Lumbar Degenerative Disc Disease (Spondylosis)

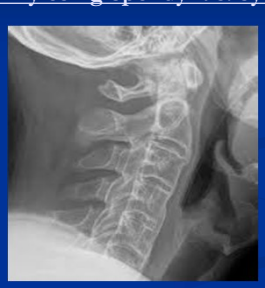


Cervical Spine Degenerative Disc Disease

Lumbar Ankylosing Spondylitis: Syndesmophytes



Cervical Ankylosing Spondylitis: Syndesmophytes



Bone Abnormalities

Degenerative Joint Diseases

- Asymmetrical cartilage deterioration
- Subchondral sclerosis
- Eburnation, osteophytes
- Osseous hypertrophy
- Weight bearing joints

Inflammatory Diseases

- Symmetrical narrowing of joint spaces
- Periarticular osteopenia
- Syndesmophytes (bone formation)
- Osteoporosis
- Enthesitis

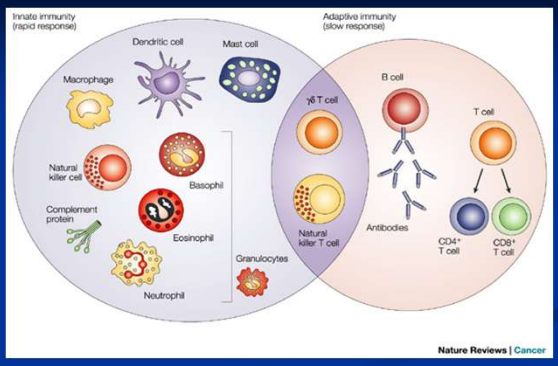
Categories of Connective Tissue Diseases

- I) Regional Musculoskeletal Abnormalities
  - Osteoarthritis and associated disorders
- ***II) Inflammatory Diseases (Sero-Negative)***
  - Arthritis 2' to legitimate immune response:
    - Infections, Infections, Reactive arthritis & Crystalline Dz
  - Primary inflammatory Dz: Spondyloarthritis, PMR …
  - Auto-Inflammatory Diseases: Hereditary Periodic Fever Syndromes
  - Malignancies: MGUS, Plasmacytoma, MM, Lymphomas...
- III) Auto-Immune Diseases (Sero-Positive)
  - RA, SLE, Sjogren's Synd, Scleroderma, Myositis etc…
- IV) Vasculitic Syndromes

Innate Immune Features
(Inflammatory Diseases)

- First Line of Defense
- Early Rapid Inflammatory Response
- Selective Receptors: Structures common to Microbes
- Cells: Neutrophils, Macrophages, DCs & NK cells
- Soluble portion:
  - Inflammatory mediators (cytokines): CRP, TNF, IFNs...
  - Complement System C3, C4, CH50 …
- No Immunological Memory, No Autoimmunity

Innate Immune Cells



Univ of Mass Medical School, Program in Innate Immunity: 2016

Cytokines and the Inflammatory Response

Origene Co. 2019

Complement System

Features Inflammatory Diseases (Sero-Negative)

- History:
  - ***Nocturnal and early morning Stiffness/Swelling***
  - Stiffness is relieved with activity and exacerbated with rest (Gelling)
- Physical Examination:
  - Inflammatory joint features; synovitis, erythema, swelling, effusions and enthesitis
- Labs: Elevated inflammatory mediators; increased CRP, ESR & alpha-1 or 2 fraction on SPEP
  - ANA, CCP & RF are Negative (Sero-Negative Dz)
- X-Rays: Symmetrical narrowing, periarticular osteopenia and osteoporosis

* Secondary Inflammatory Diseases

- **Infections:** Hepatitis-C, Endocarditis…
- **Post-Infectious reactive arthritis**
- **Crystalline arthropathies:** Gout, CPPD & Basic calcium phosphate disease etc…
- **Tic born infections:** Lyme, Ehrlichiosis, Babesiosis, RMSF etc…
- **Malignancies**: Multiple myeloma, plasmacytomas, lymphomas, leukemias etc.

* Primary Inflammatory Conditions

(Sero-Negative)(Cytokine mediated)

- **SpondyloArthritis Group**
- **Polymyalgia Rheumatica**
- **Adult-Onset Stills Disease**
- **Hereditary Periodic Fever Syndromes**
  (systemic auto-inflammatory disorders)

Makysmowych W et al. 2012;64:6,1713-19.

*SpondyloArthritis Group

(Axial & Peripheral distribution)
(Pre & Post-radiographic)

- Ankylosing Spondylitis
- Psoriatic Spondyloarthritis
- Inflammatory Bowel Dz assoc Arthritis
- Reactive Arthritis (post-infectious)
- Undifferentiated Spondyloarthritis

Ritchenlin C,et al. NEJM 2017; 376: 957-70

General Features of Spondyloarthritis (SpA)

- **Inflammatory back pain & SI joint symptoms**
- **Prolonged nocturnal & AM stiffness**
- **Peripheral Inflammatory arthritis**
- **Stiffness improved with exercise**
- **Reduced spinal & chest mobility over time**
- **Enthesitis & syndesmophytes (bone formation)**
- **Extra-skeletal manifestations**
- **Elevated ESR/CRP & associated HLA-B27**

Taurog J et al. NEJM 2016, 374(26): 2563-74.
Rudwaleit M et al. Inflammatory back pain in AS. Arth & Rheum 2006, 54(2):569-78.
Firestein G et al. Text Rheumatology 8th Ed. 2009

Axial Spondyloarthritis

Early Dz

- Pre-Radiographic Stage
- Inflammatory back pain
- STIR MRI-sacroiliitis

Late Dz

- Radiographic Stage
- Inflammatory back pain
- X-Ray sacroiliitis/erosions
- Syndesmophytes

---------- Time (years) ---------->

1984 NY Criteria

2011 ASAS axial SpA classification criteria

ASAS classification criteria for axial spondyloarthritis (SpA).6 CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

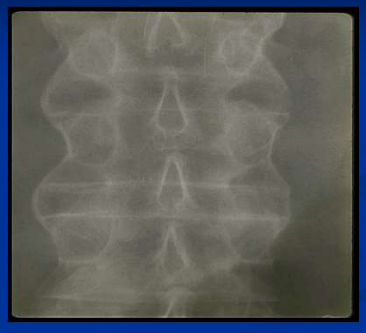
Désirée van der Heijde et al. Ann Rheum Dis 2011;70:905-908

Pathways of Bone Resorption and New Bone Formation in Patients with Ankylosing Spondylitis.

Fisher MC et al. N Engl J Med 2014;371:1447-1455

Ankylosing Spondylitis

(syndesmophytes formation "bambooing")



Advanced Ankylosing Spondylitis
Syndesmophytes, apophyseal ankylosis & SI Fusion

Yoong JK. N Engl J Med 2008;359:404-404.

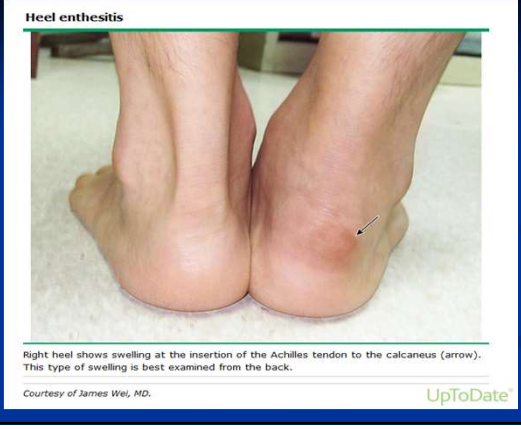
Ankylosing Spondylitis
(Sacroiliitis on Ferguson view)

Sacroiliac Erosions STIR MRI

Webber U et al. Arthritis Res Ther 2012

Psoriatic Spondylitis

(Sausage digits: pitting, swelling, erythema & onycholysis)



Psoriatic Mutilans

"telescoping fingers"

Features of Polymyalgia Rheumatica

- **Age greater than 50 years**
- **Weight loss, fatigue & fevers**
- **Significant bilateral AM stiffness**
- **Hip & Shoulder girdle symptoms**
- **Elevated ESR/CRP, Negative RF, CCP, ANA**
- **Dramatic response to steroids (polymyalgia dramatica)**
- **PMR is associated with Giant Cell Arteritis**

Kermani TA, et al. PMR. Lancet 2013; 381:63.
Weyand C, et al. GCA & PMR. NEJM 2014; 371: 50-7.
Salvarani C, et al. PMR & GCA. Lancet 2008; 372: 234.

Immune Laboratory Testing

** Innate Immunity (Inflammatory Dz) (Spondyloarthritis, PMR etc.)

- ESR: Pos
- CRP: Pos
- ANA: Negative
- RF: Negative
- Anti-CCP: Negative
- Uric Acid: Pos/Neg
- ANCA: Negative

Adaptive Immunity (Auto-Immune Dz) (RA, SLE, Sjog, MCTD etc.)

- ESR: Pos/Neg
- CRP: Pos/Neg
- ANA: Pos → ENA
- RF: Pos
- Anti-CCP: Pos
- ANCA: Pos → PR3 → MPO

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- ***III) Auto-Immune Diseases: RA, SLE, Sjogren's synd, scleroderma, myositis, etc…***

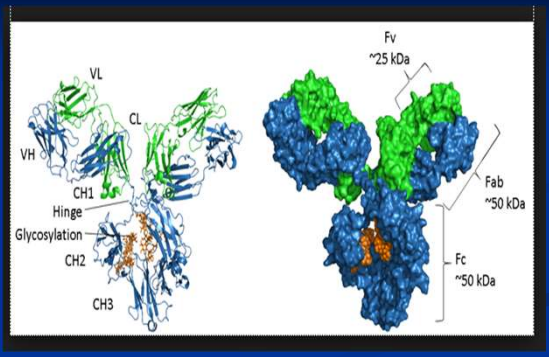
Adaptive Immunity (Antibodies)

- Delayed Onset antibody activity
- Highly specific antibodies
- Antibodies generated to a diversity of targets
- Cellular system: T-cells, B-Cells and Plasma cells
- Soluble effectors: Gamma globulins
- Immunological Memory
- Autoimmunity: SLE, RA, Sjog, Scleroderma…

Adaptive Immunity

Immunoglobulins

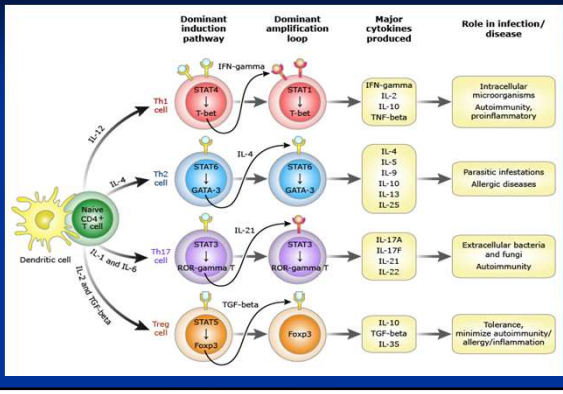
IgG Antibody



Targeted Therapeutic Approaches in Systemic Lupus Erythematosus

Rahman A, Isenberg D. N Engl J Med 2008;358:929-939

Adaptive Immunity: T-cell Biology



Rheumatoid Arthritis Defined:

- Chronic autoimmune disease with inflammatory features
- Characterized by polyarthritis with progressive joint damage, erosions, deformities, nodules and osteoporosis
- Organ involvement includes; ILD, pleuropericarditis, neuropathy, scleritis, splenomegaly, vasculitis etc.
- Multiple innate & adaptive immune abnormalities with augmented systemic inflammation
- The ideology is multifactorial

McInnes IB et al. NEJM 2011; 365: 2205
Aletaha D et al. Ann Rheum Dis 2010; 69(9): 1580.

2010 Amer Coll Rheum / European League Classification of Rheumatoid Arthritis

- 1) At least 1 joint with Synovitis (swelling)*
- 2) Synovitis not explained by another disease!**
- A) Joint Involvement score (0-10 pts)
- B) Serology: RF & CCP antibody (0-5 pts)
- C) Acute phase reactants : ESR & CRP (0-1 pt)
- D) Duration of symptoms (0-1 pt)

A score of > 6 needed for DX of RA

Aletaha D et al. RA classification criteria. Arthritis Rheum 2010 ;62(9):2569-81.

Non-Rheumatic Conditions with a Positive Rheumatoid Factor

- **Aging: (age greater than 70): 10 - 25%**
- **Infections: Bacterial endocarditis 25-50%, TB 8%, Syphilis 0-13%, Parasitic infections 20-90%, Viral Infections 15-65%, especially Hep-C**
- **Pulmonary Diseases: Sarcoidosis, Pulmonary Fibrosis 10-50%, Asbestosis…**
- **Primary biliary cirrhosis**

Newkirk et al. J Rheumatol 2002; 29: 2034
Sansonno D, J Immunol 1998; 160: 3594

Rheumatic Diseases Associated with a Positive Rheumatoid Factor

- Rheumatoid arthritis (80-85%)
- Sjogren's syndrome (75-95%)
- MCTD (50-60%)
- Primary Scleroderma (20-30%)
- Systemic Lupus (15-35%)
- Sarcoid (15%)
- Polymyositis/Dermatomyositis (5-10%)

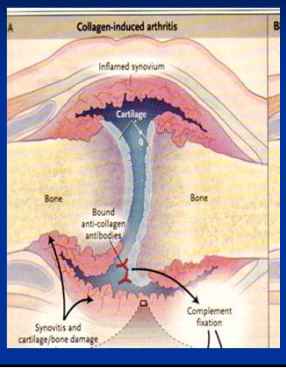
Klippel JH et al. Primer on Rheum Dz. Arthritis Found, 13 Ed, 2008, 329-427.

CCP antibody Summary

- CCP ab is more specific for RA than RF
- Is present during the Early stages of RA
- Associated with higher disease activity, erosive disease, and worse long term outcome
- Associated with the development of extra-articular disease and organ involvement
- Assists in identifying early aggressive disease so that early aggressive treatment may be initiated

Whiting PF et al. Ann Intern Med 2010; 152(7): 456.
Nishimura K et al. Ann Intern Med 2007; 146(11): 797.

Synovial Pathology in Rheumatoid Arthritis



- Synovial lining hyperplasia
- Mononuclear cellular infiltrate with lymphocytes and macrophage
- Augmented angiogenesis
- Multinucleate osteoclasts form pannus destroying bone & cartilage
- Augmented cytokine production with release of collagenases, stromelysins and metalloproteinase

Schett G et al. Arthritis Rheum 2000;43:2501

RA Pannus Formation
(Inflamed synovium)

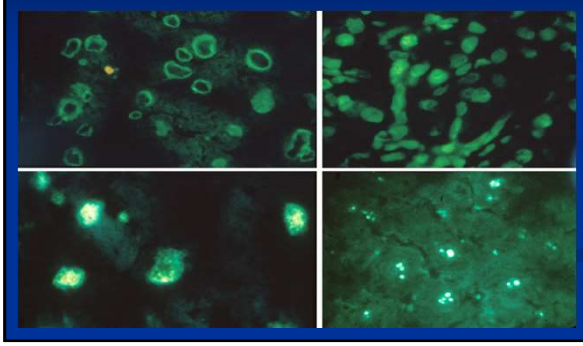
Early Rheumatoid Arthritis
(Symmetrical fusiform swelling)

Chronic Rheumatoid Arthritis

Rheumatoid Arthritis

RA Atlantoaxial Subluxation

ANA: peripheral, diffuse, speckled & nucleolar



Antinuclear Antibodies

- ANA is highly sensitivity but of low specificity
- ANA (+) 30% of normal persons
- ANA (+) may pre date Autoimmune Disease*
- Other conditions with a positive ANA titer:
  - Infections, Drugs, Malignancy ….
- Organ Specific Autoimmune Dz: Thyroiditis …
- Undifferentiated Connective Tissue Disease
- Systemic Autoimmune Diseases
- Of all positive ANA's only 5% will be Lupus

To CH, Petri M. 2005;52:4003-10. Harvard Medical School 2012

Development of Autoantibodies before the Clinical Onset of SLE: Dept of Defense Repository study

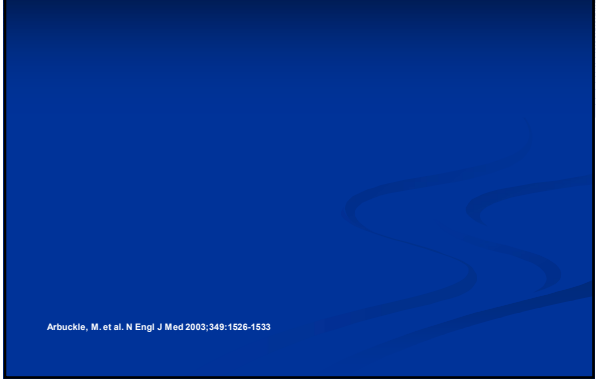
- **30 mil specimens were prospectively collected from 5 million US Armed Forces personnel**
- **The serum of 130 persons diagnosed with SLE were examined**
- **115 of 130 (88%) patients with SLE had at least 1 SLE-Ab up to 9 years before diagnosis**
- **A predictable course of accumulating auto abs occurred**
- **Conclusion: Autoantibodies are typically present many years before the Dx of SLE**

Arbuckle M et al. N Eng J Med 2003;349:1526-33

Kaplan-Meier Curves for the Proportion of Patients with Positive Antibody Tests Relative to the Time of Diagnosis or Appearance of the First Clinical Manifestation of (SLE)

Arbuckle, M. et al. N Engl J Med 2003;349:1526-1533

Accumulation of Systemic Lupus Autoantibodies



Arbuckle, M. et al. N Engl J Med 2003;349:1526-1533

Features of Autoimmune disease

- Morning stiffness, synovitis, tenosynovitis effusions etc.
- Raynaud's phenomena
- Photosensitivity, skin rashes, patchy alopecia …
- Ophthalmologic: episcleritis, uveitis, retinitis…
- Pleuritis, pericarditis

Harvard Medical School 2015

Classic Autoimmune Syndromes

Undifferentiated CT Disease (UCTD)
Rheumatoid Arthritis
Systemic Lupus Erythematosus
Sjogren's Syndrome
Systemic Sclerosis / CREST Syndrome
Mixed Connective Tissue Disease (MCTD)
Inflammatory Muscle Disease
Antiphospholipid Syndrome
OverLap Syndromes (ex Rupus …)

Bodolay et al. 5 yr F/U 665 Hung pts. Clin Exp Rheumatol. 2003;21 (3):313-20.
Mosca M et al. UCTD. Autoimmun Rev.2006 Nov;6(1):1-4.

Clinical Features of Systemic Lupus

- Multisystem autoimmune Dz with relapsing course
- Variable features; joint/skin dz to multiorgan involvement
- Array of Autoantibodies and Complement activation
- Ds-DNA and Smith abs have greatest specificity
- African-American, Asian & Hispanic women have the highest prevalence of disease
- Lupus nephritis is the most common live-threatening manifestation
- Accelerated atherosclerosis requires aggressive risk factor modification

Pons-Estel GJ et al. Semin Arth Rheum 2010;39:257-68

Overview of the Pathogenesis of Systemic Lupus Erythematosus.

Tsokos GC. N Engl J Med 2011;365:2110-2121

SLE Criteria (4 of 11 required)

- 1) Malar rash: fixed erythema over malar eminence
- 2) Discoid rash: raised, keratotic & atrophic scaring
- 3) Photosensitivity: Rash from sunlight reaction
- 4) Oral, nasopharyngeal & tongue ulcers: Painless
- 5) Inflammatory arthritis: Synovitis
- 6) Serositis: a) Pleuritis b) Pericarditis

Flynn A et al. Clin Rheum 2018; 37(3): 817.
Tiao J et al. J Am Derm 2016;74(5) :862.
Petri M et al. Arthritis Rheum 2012; 64: 2677.

SLE Criteria (cont)

- 7) Renal disease: a) persistent proteinuria >0.5 g/d
  b) cellular casts: Red blood cells, granular or mixed
- 8) Neurologic: a) Seizures b) Psychoses & Mono neuritis multiplex.
- 9) Hematologic: a) hemolytic anemia
  b) leukopenia; < 4000/mm
  c) lymphopenia; < 1500/mm
  d) thrombocytopenia; < 100,000/mm

SLE Criteria (cont)

- 10) Immunologic: 1) ds-DNA ab 2) Smith ab
  3) phospholipid antibodies

11) ANA positive

Primer on Rheumatic Diseases. 13th Ed., 2008. Arthritis Foundation.
Firestein G et al. Text Rheumatology 8th Ed, 2009

Extractable Nuclear Antigens (ANA-profile)

- **anti-dsDNA Ab*: SLE & Nephritis**
- **anti-Smith Ab: SLE**
- **anti-U1-RNP Ab: SLE & MCTD**
- **anti-SSA & SSB: SLE, Sjogrens & fetal heart dz**
- **SCL-70 ab: Diffuse scleroderma**
- **anti-Histone Ab: SLE & Drug-SLE**
- **anti-Centromere Ab: Limited scleroderma**
- **Phospholipids: Thrombosis & Pregnancy loss**

Rahman A, Isenberg D. SLE. N Engl J Med 2008;358:929-39.

Renal Involvement-1

- Renal disease is common in SLE
- Up to 90% of SLE Pts have pathological evidence of renal Dz on biopsy
- Only 50% develop clinically significant nephritis
- Clinical presentation is highly variable from hematuria to rapidly progressive glomerulonephritis

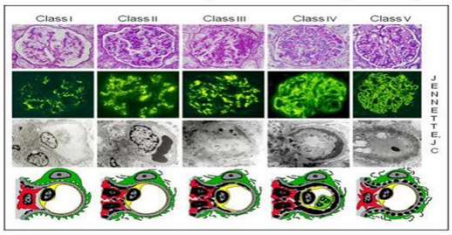
Danila MI et al. Rheumatology 2009;48:542.

Lupus Nephritis

Table 1: The 2003 International Society of Nephrology and International Pathology Society Classification of lupus nephritis

- Class I: Minimal mesangial lupus glomerulonephritis (LGN)
- Class II: Mesangial proliferative LGN
- Class III: Focal LGN (< 50% glomeruli)
- Class IV: Diffuse LGN (≥ 50% glomeruli)
  - Class IV-S: Predominantly segmental
  - Class IV-G: Predominantly global
- Class V: Membranous LGN

Class VI: Advanced sclerotic LGN (> 90% sclerotic glomeruli)



Immune Laboratory Testing

Innate Immunity (Inflammatory Dz) (Spondyloarthritis, PMR etc.)	** Adaptive Immunity (Auto-Immune Dz) (RA, SLE, Sjog, MCTD etc.)
ESR: Pos	ESR: Pos/Neg
CRP: Pos	CRP: Pos/Neg
ANA: Negative	ANA: Pos → ENA
RF: Negative	RF: Pos
Anti-CCP: Negative	Anti-CCP: Pos
ANCA: Negative	ANCA: Pos → PR3 → MPO

Systemic Lupus

Discoid SLE

SLE: Photosensitivity

Selected Scleroderma Spectrum Diseases

- Mixed Connective Tissue Disease
- Limited Scleroderma
- Diffuse Scleroderma

Patients with Raynaud's Phenomenon.

Wigley FM, Flavahan NA. N Engl J Med 2016;375:556-565

Raynauds Assoc Diseases

- Primary Raynauds (benign)
- Systemic Lupus: Sm ab, RNP ab, dsDNA ab, etc
- Sjogrens Syndrome: SSA & SSB ab

Scleroderma Spectrum Diseases

- MCTD: RNP (high titer abs)
- Limited Scleroderma (CREST): Centromere ab
- Diffuse Scleroderma: SCL-70, RNA Pol-III ab

Wigley F et al. Raynauds. NEJM 2016; 375: 556-65.
Mariette X et al. Prim Sjog Synd. NEJM 2018; 378: 931-9.

Mixed Connective Tissue Disease

- Raynauds Phenomenon
- Overlap: SLE, Scleroderma, Polmyositis
- Scleroedema, Sclerodactaly
- Esophageal dysmotility disorders
- *Interstitial Lung Disease: CXR, PFTs, HRCT
- *Pulmonary Arterial Hypertension: ECHO
- Lab Order: high titer RNP abs

Ungprasert P et al. Arth Care Res. 2016; 68(12): 1843.
Tani C et al. J Autoimmune. 2014; Feb;48:46.
Hoffman RW et al. Clin Immunol. 2008;128(1):8.

Limited Scleroderma

- Slow onset of disease
- Raynauds for years, long latency period
- Skin fibrosis limited: hands, feet, face (peripheral)
- Nailfold capillary abnormalities typical for SS
- Pulmonary hypertension (10-15%)
- Renal disease rare
- Centromere abs (50-60%)

Gabrielli A et al. NEJM 2009; 360: 1989-2003.

Diffuse Scleroderma

- Rapid onset of disease c aggressive damage
- Raynauds followed, within 1 year, puffy and hidebound skin
- Accelerated Nailfold capillary abnormalities
- Early and significant incidence: interstitial lung dz, diffuse GI dz, renal dz and cardiac dz
- ANA: Nuceolar, SCL-70 ab (30%) or RNA polymerase III ab.

Gabrielli A et al. NEJM 2009; 360: 1989-2003

Clinical Findings in Patients with Scleroderma in Four Countries

Gabrielli A et al. N Engl J Med 2009;360:1989-2003

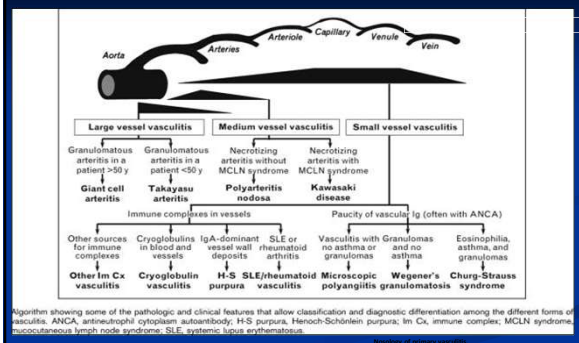
Lesions in Different Stages of Scleroderma

Gabrielli A et al. N Engl J Med 2009;360:1989-2003

Necrosis of the Fingers and Toes

Y Taniguchi, S Inotani. N Engl J Med 2018;379:2557-2557.

Vasculitis Types



Algorithm showing some of the pathologic and clinical features that allow classification and diagnostic differentiation among the different forms of vasculitis. ANCA, antineutrophil cytoplasm autoantibody; H-S purpura, Henoch-Schönlein purpura; Im Cx, immune complex; MCLN syndrome, mucocutaneous lymph node syndrome; SLE, systemic lupus erythematosus.

Nosology of primary vasculitis.
Jennette, J; Falk, Ronald
Current Opinion in Rheumatology. 19(1):10-16, January 2007.
DOI: 10.1097/BOR.0b013e3280159f77

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Thank You