

Navigating the Maze of Connective Tissue Diseases

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Connective Tissue Disease=Collagen Vascular Disease

- 1942 Dr Klemperer introduced “diffuse collagen disease” based upon tissue studies of SLE and SScI patients
- 1946 Dr Rich introduced “collagen-vascular disease” based upon vasculitis
- 1952 Dr Ehrlich suggested term “connective tissue diseases”

Connective Tissue Diseases

- Systemic Lupus Erythematosus (SLE)
- Sjogrens Syndrome (SS)
- Systemic Sclerosis (SScl)
- Rheumatoid Arthritis
- Dermatomyositis / Polymyositis (DM/PM)
- Mixed Connective Tissue Disease (MCTD)

Suggestive History

- Female 20-50 years old with
 - Polyarthritis / polyarthralgias
 - Photosensitivity
 - Raynaud's / hand puffiness
 - Muscle weakness
 - Dry eyes / dry mouth
 - Unexplained fevers
 - Serositis
 - Family history of CTD

Laboratory Testing

- Positive Antinuclear antibody (ANA)
 - >98% sensitive for SLE
 - Non-specific

Antinuclear Antibody (ANA)

- Not specific for any rheumatic disease
- False + increase with age
- These diseases are based upon **CLINICAL** parameters and supported by suggestive laboratory findings

Non Rheumatic Conditions with +ANA

- Autoimmune Hepatitis
- Autoimmune Thyroid Disease
- Hepatitis C
- Lymphoma
- Idiopathic Pulmonary Fibrosis
- Aging

Systemic Lupus Erythematosus

SLE - Epidemiology

- F:M 6-10:1
- Peak incidence – 15-40 years old
- Affects 1 in 2000 individuals but prevalence varies with race, ethnicity, and socioeconomic status
- Incidence 2-4 times greater in African Americans and Hispanics than Caucasians in the U.S.

SLE Antibodies and Clinical Associations

- dsDNA (40-60%)
- Sm (smith)
- ssA (Ro) (30-45%)
- ssB (La) (10-15%)
- Phospholipids, B2-glycoprotein (30%)
- High specificity SLE can correlate with disease activity
- High specificity SLE
- Neonatal lupus, SS, SCLE, Photosensitivity
- Neonatal lupus, SS
- LAC, thrombosis, recurrent fetal loss, thrombocytopenia

SLE – Organ Involvement

- Skin – photosensitivity, malar rash, discoid rash, SCLE, panniculitis, vasculitis
- Mucosal – oral, nasopharyngeal ulcers
- Arthritis – non-erosive
- Serositis – pleuritis, pericarditis
- Renal – proteinuria ($>.5\text{gm}/24\text{ hr}$ or $>+3$), cellular casts
- Neurologic – seizures, psychosis
- Hematologic – hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia

SLE – diagnostic criteria (4/11)

- Malar rash -Hematologic disorder
- Discoid rash -Immunologic disorder
- Photosensitivity -ANA
- Oral ulcers
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder

Treatment - SLE

- Symptomatic for non life- / non organ-threatening disorders
 - Education
 - Avoid UV exposure
 - Avoid cigarette exposure
 - NSAIDS
 - Plaquenil
 - Balance rest/activity
 - (Low dose steroids)

Treatment – SLE

- Aggressive treatment for life or organ threatening disorders
 - High dose corticosteroids
 - Azothioprim
 - Methotrexate
 - Cyclophosphomide
 - Mycophenylate Mofetil
 - Rituxamab

Sjogren's Syndrome

Sjogren's Syndrome (SS)

- Keratoconjunctivitis sicca (KCS) – systemic disease associated with dry eyes, dry mouth and arthritis

Sjogren's Syndrome

- Epidemiology
 - 1-2 million in US
 - Primary disease 1/1000 – equivalent to SLE
 - Secondary disease (50%) – associated with another connective tissue disorder (SLE, RA)
 - F:M 9:1
 - Mean age of diagnosis = 50years

Sjogren's Syndrome - pathology

- Lymphocytic infiltration of glandular and nonglandular organs
- Lymphocytes predominantly CD4+ helper cells
- B cells account for 20% of the lymphocytes and are responsible for increased immunoglobulin production

Sjogren's Syndrome

- Initial manifestations of primary disease
 - Xerophthalmia 47%
 - Xerostomia 42%
 - Arthralgia/arthritis 28%
 - Parotid enlargement 24%
 - Raynaud's 21%
 - Fever/fatigue 10%
 - Dyspareunia 5%

Clinical Manifestations of Dry Mouth

- Difficulty swallowing food
- Inability to speak continuously
- Change in taste
- Burning
- Increased dental caries
- GERD
- Oral candidiasis
- Difficulty wearing dentures

Clinical Manifestations of Dry Eyes

- Foreign body sensation
- Burning
- Itching
- Blurred vision
- Redness
- Photophobia
- Blepharitis
- Corneal ulceration

Testing for Sjogren's Syndrome

- Eyes
 - Schirmer's
 - Schirmer's II
 - Rose bengal
- Mouth
 - Salivary gland scan
 - Salivary gland biopsy-lymphocytic infiltration

SS – Extraglandular Manifestations

- Arthralgias/arthritis 60-70%
- Raynaud's 35-40%
- Esophageal dysfunction 30-35%
- Lymphadenopathy 15-20%
- Vasculitis 5-10%
- Lung involvement 10-20%
- Kidney involvement 10-15%
- Liver involvement 5-10%
- Peripheral neuropathy 2-5 %
- Myositis 1-2%
- Lymphoma (44X) 5-8%

SS – Laboratory Findings

- Rheumatoid factor 85-90%
- ANA 90%
- ssA 50-90%
- ssB 50-90%

SS – Laboratory Findings

- Nonspecific
 - Elevated ESR
 - Hypergammaglobulinemia
 - Anemia
 - Leukopenia
 - Thrombocytopenia

Sjogren's Syndrome - Treatment

- Artificial tears
- Humidifiers
- Punctual occlusion
- Topical cyclosporine
- Dental care
- Avoid alcohol
- Avoid concentrated sweets
- Salivary substitutes
- Sugarless gum/candy
- Cholinergic drugs (pilocarpine/cevimeline)

Sjogren's Syndrome - Treatment

- NSAIDS
- Antimalarials
- Treat secondary fibromyalgia
- Corticosteroids
- Immunosuppressives

Sjogren's Mimics

- Diffuse infiltrative lymphocytosis syndrome (DILS)
- Seen in HIV positive individuals
- Fever, lymphadenopathy, weight loss, bilateral parotid gland enlargement
- Infiltrating lymphocytes are CD8+
- Lack antibodies for SS-A/SS-B

Scleroderma

Scleroderma

- An uncommon connective tissue disease characterized by thickening/fibrosis of the skin

Scleroderma - Epidemiology

- F:M – 3:1
- Peak incidence 35-64 years
- Slightly more common in African American women during child bearing years
- Over all ages, there is no significant predominance among racial groups

Classification of Scleroderma

- Localized
 - Morphea
 - Linear Scleroderma
- Systemic Sclerosis
 - Diffuse systemic sclerosis
 - Localized systemic sclerosis (CREST)
- Overlap

Scleroderma

Cutaneous Disease

- Thickened Skin – abnormal fibroblast activity
→ normal type I collagen, glycosaminoglycan & fibronectin
 - Loss of sweat glands/hair
 - Skin thickening **always** begins in fingers & progresses proximally
- Calcinosis – cutaneous deposits of basic calcium phosphate
- Telangectasias – dilated venules, capillaries, arterioles on hands, face, lips, oral mucosa

Raynaud's Phenomenon

- Reversible vasomotor disturbance
- Color changes b/l fingers, toes, ears, nose, lips
- Pallor, cyanosis, erythema
- Response to cold/emotional stress

Raynaud's Phenomenon

Clinical Factors Suggesting SScI

- +ANA, anticentromere ab, Scl 70
- Nailfold capillary abnormalities
- Tendon friction rubs
- Puffy swollen fingers
- GERD

Raynaud's Phenomenon Treatment

- Warmth – hands & body
- Smoking cessation
- Vasodilators
 - Calcium channel blockers
 - Antiadrenergics
 - ACE inhibitors
 - ASA
 - Niacin

Scleroderma

Organ System Involvement

Clinical	Diffuse SScI	Limited
Skin thickening	100%	95%
Telangiectasias	30%	80%
Calcinosis	5%	45%
Raynaud's	85%	95%
Arthralgias/ Arthritis	80%	60%

Scleroderma

Organ System Involvement

Clinical	Diffuse SScI	Limited
Tendon friction rub	65%	5%
Myopathy	20%	10%
Esophageal	75%	75%
Pulm fibrosis	35-59%	35%
Pulm HTN	<1%	12%
CHF	10%	1%
Renal crisis	15%	1%

Scleroderma

Gastrointestinal Involvement

- Esophageal dysmotility
- Bowel dilatation
- Bacterial overgrowth
- Malabsorption
- Large bowel diverticuli
- Watermelon stomach –gastric antral venous ectasia

Scleroderma Lung Disease

	Interstitial Lung Disease	Pulmonary Hypertension
Localized Disease	None	None
Limited Disease (CREST)	Bibasilar Nonprogressive	8-28% Poor prognosis
Diffuse SScI	31-59% can progress and lead to death	Rare

Scleroderma Lung Disease

- Interstitial Lung Disease
 - Limited basilar involvement
 - Progression to middle and upper lobes
 - Inflammatory findings suggest better response to immunosuppressive therapies – prednisone, cytoxan, MTX

Scleroderma Lung Disease

- Pulmonary artery hypertension
 - Associated with significant morbidity and mortality
 - Progressive increase in pulmonary vascular resistance, right heart failure, and death
 - Eight current FDA approved therapies for PAH
 - Early recognition and aggressive treatment by an experienced physician is key

Systemic Sclerosis Cardiac Involvement

- 50% at autopsy
- Clinical symptoms uncommon
 - Pericardial effusion
 - Myocardial fibrosis
 - CAD/vasculopathy (steroids)
 - Conduction defects
 - CHF

Systemic Sclerosis Renal Involvement

- Hypertension
- Acute renal crisis
 - ACE inhibitors (diastolic BP < 90mm Hg)

Systemic Sclerosis

Bone/Articular Involvement

- Bone resorption
 - Ribs, mandible, acromion, radius, ulna
- Arthralgias
- Hand deformities / skin tightening
- Tendon friction rubs (wrist, ankles, knees)
- Myopathy/myositis

Systemic Sclerosis

Traditional Drug Therapies

- Colchicine
- P-Aminobenzoic Acid
- D-Penicillamine
- Chlorambucil
- Corticosteroids (not favored due to potential complications)

Systemic Sclerosis

Experimental Therapies

- Relaxin
- Methotrexate
- Photophoresis
- 5-Fluorouracil
- Cyclosporine
- Gamma interferon
- Plasmapheresis
- Immunosuppression – cytoxan, mycophenolate mofetil, autologous hematopoietic stem cell trans.
- Biologics in development to neutralize TGF-B
- Recent reports of encouraging results with rituxamab / imatinab





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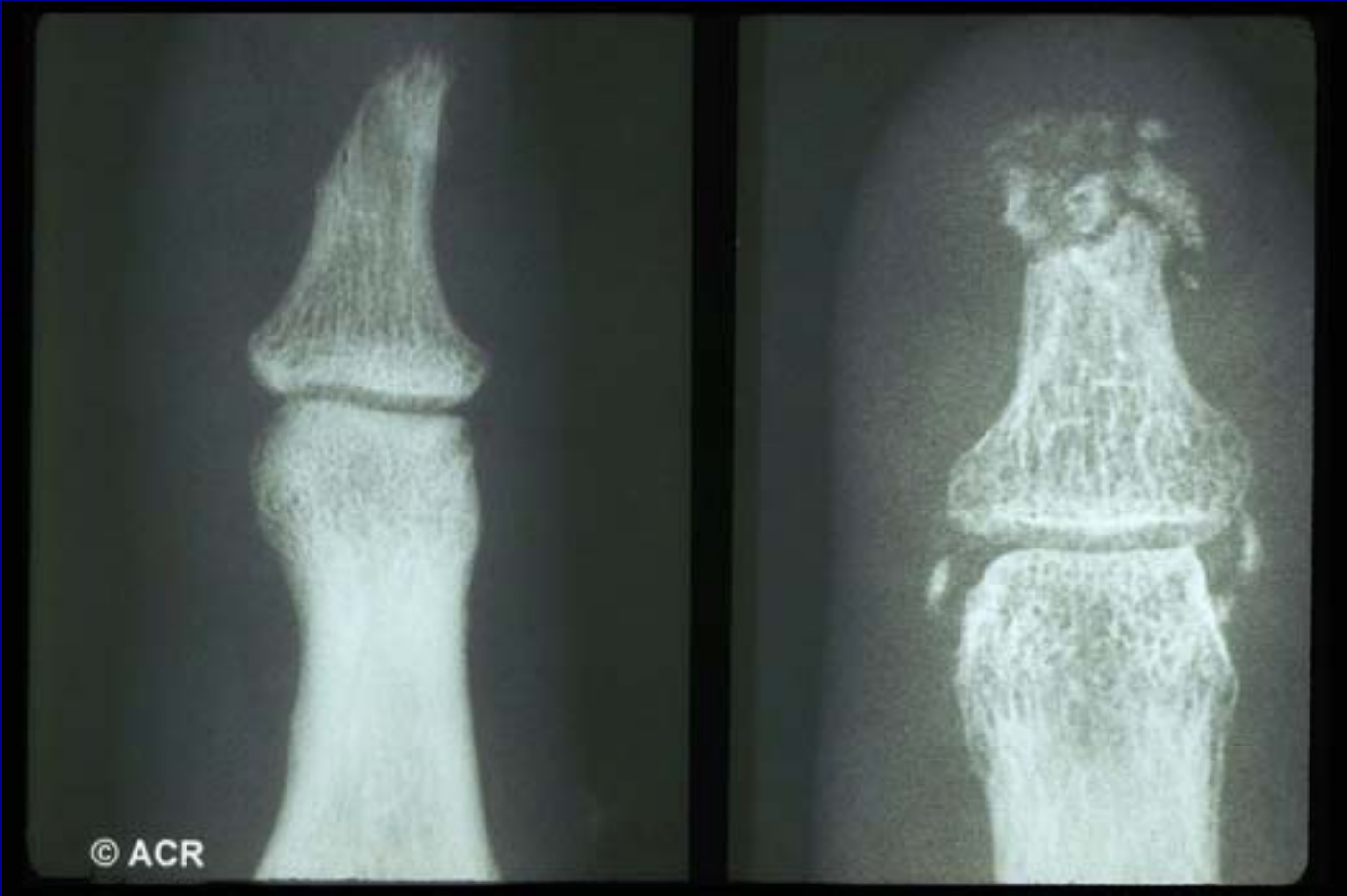


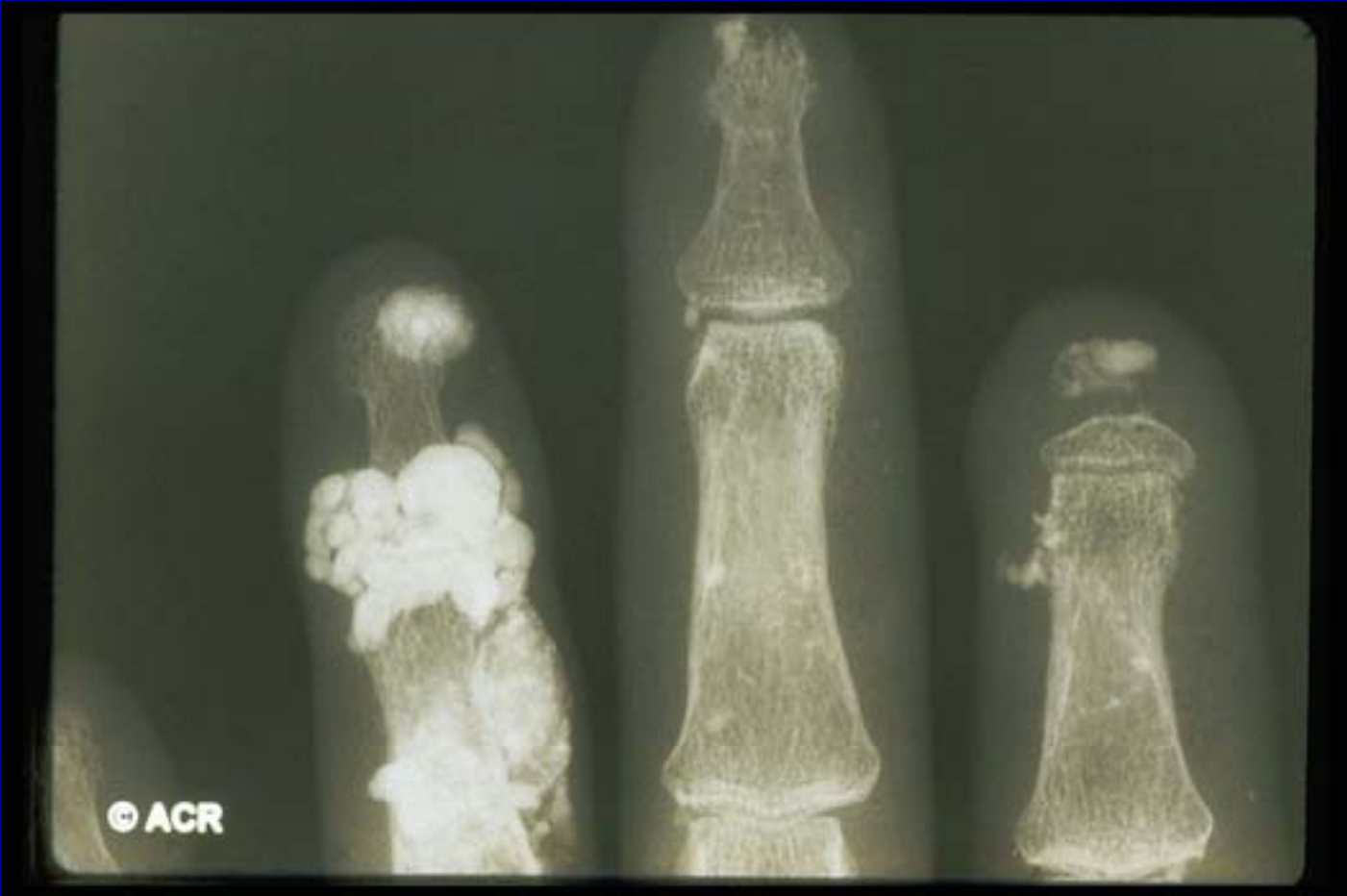
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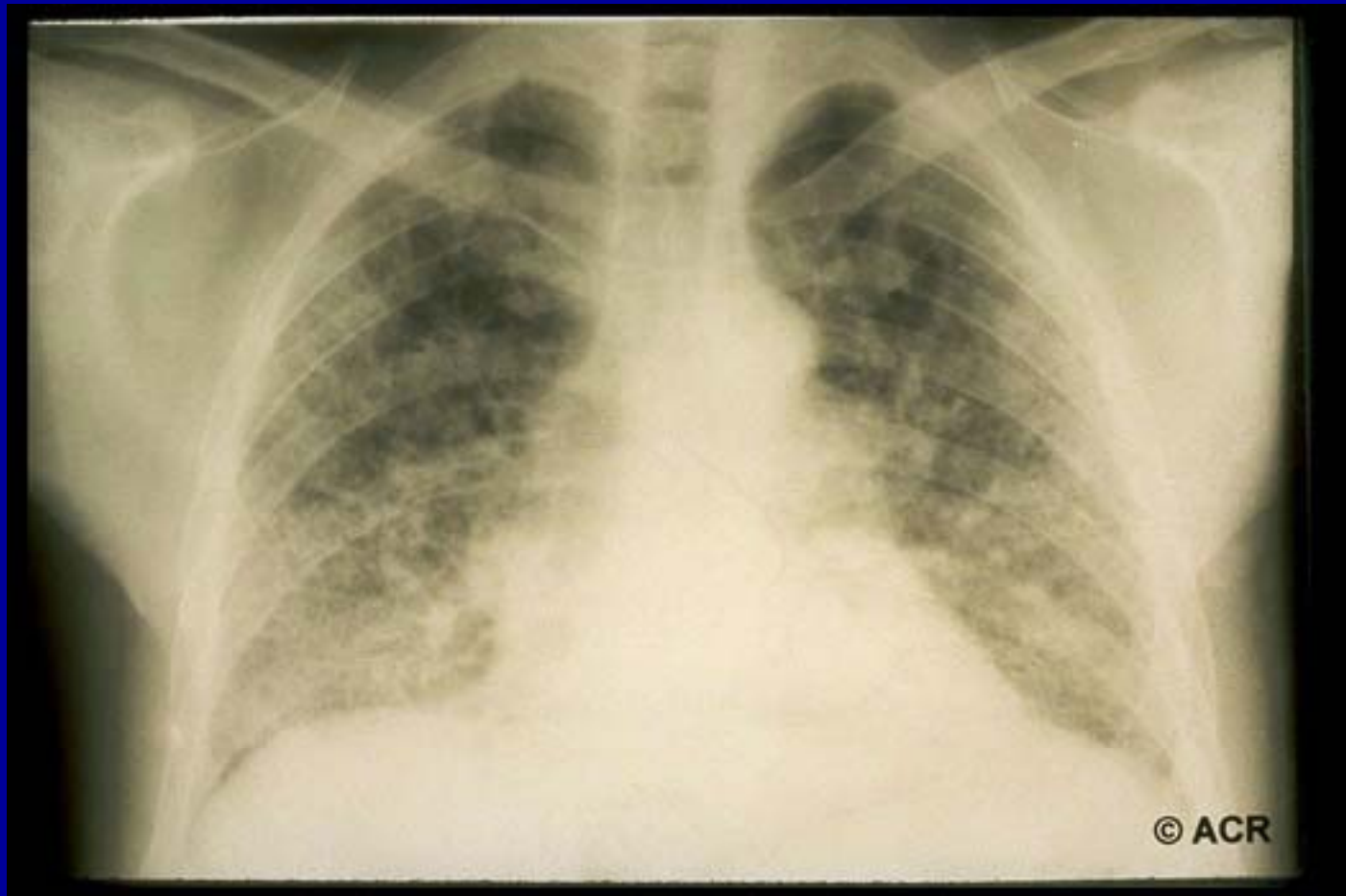
























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