Rheumatological Diseases

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Rheumatological Diseases

<u>Disease</u>

Systemic Lupus Erythematosus Rheumatoid Arthritis Sjogrens Syndrome Systemic Sclerosis Polymyositis/Dermatomyositis Mixed Connective Tissue Disease Wegener's Granulomatosus Autoantibody
Anti-dsDNA, Anti-SM
RF, Anti-RA33
Anti-Ro(SS-A),Anti-La(SS-B)
Anti-Scl-70, Anti-centromere
Anti-Jo-1
Anti-U1-RNP

c-ANCA

Systemic Lupus Erythematosus

- General
 - autoimmune multisystem disease
 - prevalence 1 in 2,000
 - 9 to 1; female to male (1 in 700)
 - peak age 15-25
 - immune complex deposition

Systemic Lupus Erythematosus

- Common complaints and presentations
 - Fever
 - Malaise
 - Joint pains
 - Myalgias
 - Fatigue
 - Loss of cognitive abilities

Systemic Lupus Erythematosus

- Dermatological Manifestations
 - 40-60 % present with some derm symptom
 - 30 60 % of them as a malar rash
 - Photodermatitis
 - Discoid lupus -
 - Alopecia
 - Mucosal ulcers

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus

- Discoid Lupus: Cutaneous manifestations
- Scar upon healing



Systemic Lupus Erythematosus



Systemic Lupus Erythematosus

- Musculoskeletal Manifestations
 - Joint pains
 - Often small joints wrist and fingers
 - Not as disabling as RA of hand and wrist
 - Doesn't cause severe destruction of joints

Systemic Lupus Erythematosus



Systemic Lupus Erythematosus

- Most common cause of death is end organ damage
- 80% of end organ damage is caused by Prednisone

Systemic Lupus Erythematosus

End Organ Damage

- Musculoskeletal 25.2%
- Neuropsychiatric 15%
- Ocular 12.6%
- Renal 11.7%
- Pulmonary 10.4%
- Cardiovascular 10.1%
- Gastrointestinal 7.3%
- Skin 7.4%
- Peripheral Vascular 5.5%
- Diabetes Mellitus

Systemic Lupus Erythematosus

Exogenous Estorogens

- Estrogen increases autoantibody production
- 2 alpha vs 16 alpha hydroxylation
- Reversing hydroxylation pathway
- Broccoli helps reverse hydroxylation (clinically relevant?)

Systemic Lupus Erythematosus

Exogenous Estrogens SELENA Study

- Hormone Replacement Therapy
 - No increase in severe flares
 - 20%increse in overall flares (Lahita 1981)
- Oral Contraceptive Therapy
 - No increase in flares

But 50% of women have aPL

Systemic Lupus Erythematosus

Environmental Triggers

- UVA and UVB
- Drugs: Bactrim and Neupogen
- Smoking
- Infections
 - Pets Dogs
 - Lab workers
- Silica
- Mercury

Prognosis and Survival 100% 1953-1978 1978 1960 60% 1953 1953

Anti-Phospholipid Syndrome

 APS occurs either as a primary condition or as a secondary condition in the setting of an underlying disease, particularly disorders in the spectrum of systemic lupus erythematosus (SLE).

Anti-Phospholipid Syndrome

Definition:

- Presence in the serum of at least one type of autoantibody known as an antiphospholipid antibody (aPL)
- The occurrence of at least one clinical feature from a diverse list of potential disease manifestations, the most common:
 - venous or arterial thromboses
 - recurrent fetal loss
 - thrombocytopenia

Anti-Phospholipid Syndrome

Although the clinical manifestations of APS occur in other disease populations, in the APS they occur by definition in the context of aPL. .APL may be detected by:

- Lupus anticoagulant tests
- Anticardiolipin antibody ELISA
- Anti-ß2 glycoprotein-I ELISA

Anti-Phospholipid Syndrome

Clinical suspicion for APS should be raised in the following scenarios:

- Occurrence of one or more otherwise unexplained thrombotic or thromboembolic events.
- One or more specific adverse outcomes related to pregnancy, as defined in the preceding section
- Otherwise unexplained thrombocytopenia or prolongation of a test of blood coagulation (eg, PT or aPTT).

Clinical Manifestations of the Antiphospholipid Syndrome | Test & Clinical Manifestations of the Antiphospholipid Syndrome | Test & Clinical Manifestation | Test | Test

Anti-Phospholipid Syndrome

False positive tests -

- Transient aCL have been reported in up to 10 percent of healthy blood donors on initial testing, but persist on repeat testing in only about 1.5 percent of individuals
- Transiently increased aCL may occur in the setting of viral or other infections
- Before making the diagnosis of APS aCL, anti-B2-GP-I, or LA should be repeated in 12 weeks

Anti-Phospholipid Syndrome

Differential Diagnosis of Venous Thrombosis

- Inherited and acquired coagulation and anticoagulation factor disorders (eg, protein C and protein S deficiency, factor V Leiden deficiency)
- Defective clot lysis
- Cancer and myeloproliferative disorders
- Nephrotic syndrome

Anti-Phospholipid Syndrome

Differential diagnosis of Arterial Thrombosis

- Atherosclerosis
- Embolic disease
 - Atrial fibrillation or, much less common, atrial myxoma
 - Marked left ventricular dysfunction
 - Endocarditis
 - Cholesterol emboliParadoxical embolism
- Paradoxical embolism
- Decompression sickness (Caisson's disease)
 Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome
- Polyarteritis nodosa and other forms of systemic vasculitis

Rheumatoid Arthritis

- 1% of the population
- Women affected 2-3 X more than men
- Age of onset is 40-50
- Juvenile form

Rheumatoid Arthritis

- Clinical features
 - Immunological
 - Lymphadenopathy
 - Amyloidosis
 - Haematological
 - Anaemia
 - Skin
 - Rheumatoid nodules
 - Vasculitis

Rheumatoid Arthritis

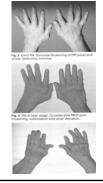
- Clinical features
 - Bones and muscles

 - □ Osteoporosis
 - Eyes
 - Sjogren's syndrome
 - Scleritis
 - Nervous system
 - $\ensuremath{\,\boxtimes\,}$ Peripheral nerve and cord compression

Rheumatoid Arthritis

Rheumatoid Arthritis

Rheumatoid Arthritis







Clinical features

- Heart

 - Myocarditis
 - Myocardial infarction
- Lungs
 - □ Pleuritis
 - **□** Obliterative bronchiolitis
 - □ Pulmonary nodules

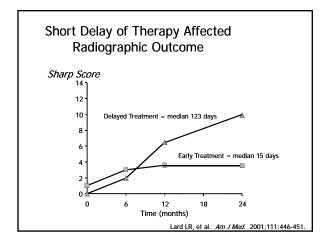
Rheumatoid Arthritis: Diagnostic Criteria

- 1. Morning stiffness (>1h)
- 2. Swelling of three or more joints
- 3. Swelling of hand joints (prox interphalangeal, metacarpophalyngeal, or wrist)
- 4. Symmetric joint swelling
- 5. Subcutaneous nodules
- 6. Serum Rheumatoid Factor
- 7. Radiographic evidence of erosions or periarticular osteopenia in hand or wrists

Criteria 1-4 must have been present continuously for 6 weeks or longer and must be observed by a physician. A diagnosis of rheumatoid arthritis requires that 4 of the 7 criteria are fulfilled.

Rheumatoid Arthritis: Diagnostic Criteria

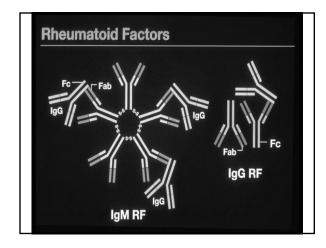
Diagnostic Criteria may be less clinically useful in the face of newer treatment strategies

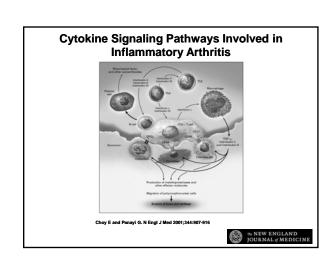


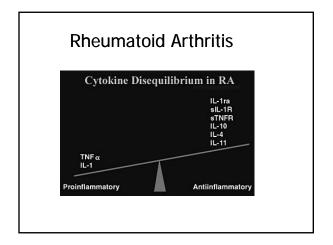
Consequences of RA

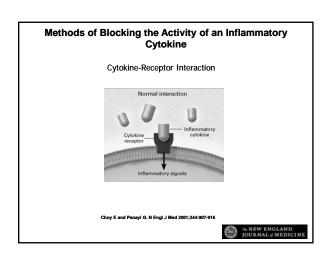
- Premature mortality
- Increased morbidity
- Significant impact on quality of life
 - Pain with associated functional disability
 - Fatigue, 81% of patients; 41% with severe fatigue
 - Depression
- Work disability
 - 25% within 7 years of onset, 50% within 21 years
 - 33% reduction in income vs non work-disabled

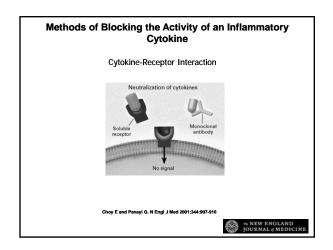
Wolfe F, Hawley D J, J Rheum. 1998;25:2108-2117. Wolfe F et al. Arthritis Rheum. 1994;37:481-494.

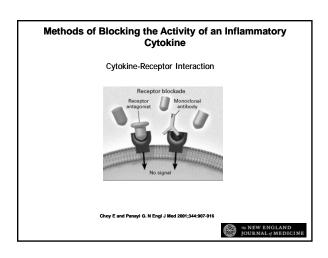


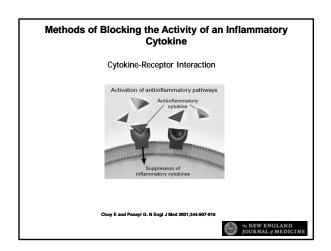


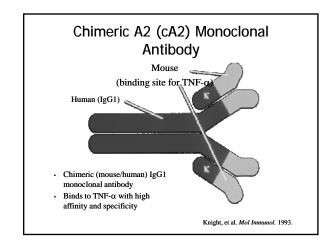




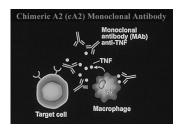




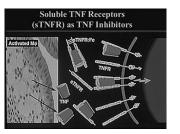




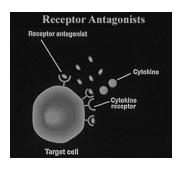
Rheumatoid Arthritis



Rheumatoid Arthritis



Rheumatoid Arthritis



Sjogren Syndrome

- Chronic disorder characterized by immunemediated destruction of exocrine glands
- Primary vs Secondary:
- Primary is diagnosis of exclusion
- Secondary refers to the sicca complex accompanying any of the connective tissue diseases (xerophthalmia, keratoconjuntivitis, xerostomia with/without salivary gland enlargement)

Sjogren Syndrome

- 1% of the population and in 10-15% of RA patients
- 9:1 female:male preponderance
- Age of onset 40-60 years
- Associated with a 33-44 times increased risk of lymphoma.

Sjogren Syndrome

- May affect the skin, external genitalia, GI tract, kidneys, and lungs
- Minor salivary gland biopsy demonstrates lymphocytic infiltration.
- Parotid biopsy more sensitive and specific
- Associated with Sjogren Syndrome A (RO-SS-A) in 60% and Sjogren Syndrome B (LA-SS-B) in 30%

Sjogren Syndrome Diagnostic Criteria

- Dry eyes (>3mos), sensation of sand or gravel in eyes, or use of tear substitutes>3x per day
- Dry mouth (>3mos), recurrent or persistent swollen salivary glands, or frequent drinking of liquids to aid in swallowing dry foods.
- 3. Schirmer-I test (<5mm in 5 min) or Rose Bengal score
- 4. >50 mononuclear cells/4mm2 glandular tissue
- 5. Abnormal salivary scintigraphy or parotid sialography or unstimulated salivary flow <1.5ml in 15 min
- Presence of anti-Ro/SS-A, anti-La/SS-b, antinuclear antibodies, or rheumatoid factor.

Sjogren Syndrome

- 80% experience xerostomia
- Difficulty chewing, dysphagia, taste changes, fissures of tongue and lips, increased dental caries and oral candidiasis
- Salivary gland enlargement
- Sicca syndrome

Sjogren Syndrome









Sjogren Syndrome: Treatment

- Symptomatic: saliva substitutes, artificial tears, increased oral fluid intake
- Avoid decongestants, antihistamines, anticholinergics, diuretics
- Pilocarpine, antifungals, close dental follow-up, surveillance for malignancy

Scleroderma

- Also known as systemic sclerosis
- Sclerotic skin changes often accompanied by multisystem disease.
- Progressive fibrosis from increased collagen deposition in intersitium and intima of small arteries and connective tissues
- May be benign cutaneous involvement or aggressive systemic disease.

Scleroderma

- 4-12 new cases per million per year
- 3-4:1 female preponderance
- Average age of onset between 3rd and 5th decade

Scleroderma Diagnostic Criteria

- One major criterion: scleromatous skin changes proximal to the metacarpalphalangeal joints
- Two of three minor criteria: sclerodactyly, digital pitting scars, bi-basilar pulmonary fibrosis on CXR

Scleroderma

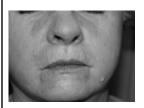
presentation

- Raynaud's phenomenon
- edema fingers and hands
- skin thickening

visceral manifestations

■ GI tract, lung, heart, kidneys, thyroid arthralgias and muscle weakness often

Scleroderma





Scleroderma





Polymyositis and Dermatomyositis

- Proximal muscle weakness and nonsuppurative inflammation of skeletal muscle
- 5 cases per million per year
- 2:1 female:male
- Age 40-60, but a pediatric variant of 5-15 year old

Polymyositis/Dermatomyositis Diagnosis

- Proximal muscle weakness
- Elevated serum creatinine kinase
- Myopathic changes on electromyography
- Muscle biopsy with evidence of lymphocytic inflammation

Dx is definitive with all four, probable with three, and possible with two.

Rash accompanies these in dermatomyositis

Dermatomyositis



Polymyositis: Head and Neck Manifestations

- Difficulty phonating and deglutition 2nd to affected tongue musculature
- Nasal regurg 2nd to affected pharyngeal and palatal musculature
- 30% with dysphagia 2nd to involvement of upper esophagus, cricopharyngeus, pharynx, and superior constrictors
- Aspiration pneumonia

Polymyositis and Dermatomyositis:Treatment

- Steroids for symptomatic patients
- Methotrexate and immunosuppressants for non-responders

Mixed Connective Tissue Disease

- Coexisting features of SLE, scleroderma, and polymyositis
- High titers of Anti-U1RNP
- 80% female, 30-60 years
- Head and neck: combination of manifestations of the above.
- Treat with steroids

Vasculitides

The vasculitides are a group of diseases characterized by non infectious necrotizing vasculitis and resultant ischemia.

The associated phrase is "palpable purpura"

Henoch-Schoenlein Purpura

- The most common dermatological dilemma presented to me
- Hypersensitivity vasculitis was a common synonym

Henoch-Schoenlein Purpura

- Most common presentation: purple splotches on leas
- 90% of cases are kids under 10 years old
- Usually follows and upper respiratory infection
- Can follow infections with strep, hepB, HSV, parvovirusB-19, MMR, mycoplasma and more
- Can be idiosyncratic to AtBx, ACE's,
- Only 35% of cases can be traced to an etiology
- The most common vasculitis in childhood 20 per 100,000 children per year

Henoch-Schoenlein Purpura

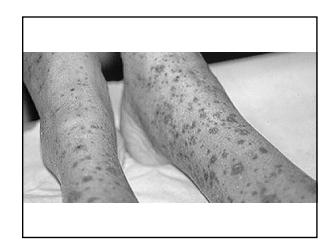
- Most common presentation: purple splotches on legs
- Triad of purpura, arthritis and abdominal pain
- 40% have findings on UA
- Can include gastrointestinal hemmorhage
- Can include intussusception
- Most of the time just purple splotches

Henoch-Schoenlein Purpura

- Needs observation, not treatment unless secondary findings are present
- NSAIDS make joint pain better but GI symptoms worse
- Steroids are avoided
- Very high recovery rate 90%
- Other Rx: Dapsone, I















Hypersensitivity Vasculitis

- General
 - collective term group of diseases
 - inflammation of small vessels
 - arterioles, capillaries, venules
 - circulating and deposited immune complexes
 - skin always involved
 - hemorrhage or classic purpura
 - major organ system involvement less common

Polyarteritis Nodosa

- Prototype of vasculitis
- Less than 1/100000 per year
- Males = Females
- 50-60 years of age
- Involves small and medium arteries
- May result from Hep B infection (30%)
- GI, hepatobiliary, renal, pancreas and skeletal muscles

Polyarteritis Nodosa

Head and neck symptoms primarily involve the ear and include SNHL and vestibular disturbance.

Proposed mechanism is thromboembolic occlusion of inner ear arteries

May also see CN palsies

Wegener's Granulomatosis

- General
 - necrotizing granulomas of upper airway, lower airway, kidney
 - bilateral pneumonitis 95%
 - chronic sinusitis 90%
 - mucosal ulceration of nasopharynx 75%
 - renal disease 80%
 - hallmark pathologic lesion
 - necrotizing granulomatous vasculitis

Wegener's Granulomatosis

- antineutrophil cytoplasmic antibody (c-ANCA)
 - sensitivity 65-90%
 - high specificity
- need to confirm diagnosis
 - often 3-4 biopsies necessary
 - nasopharynx commonly involved good site
 - open pulmonary biopsy occasionally needed
 - untreated mortality of 90% at two years

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Wegener's Granulomatosis

- Head and Neck Manifestations
 - nasal symptoms
 - crusting, epistaxis, rhinnorrhea, erosion of septal cartilage, saddle deformity, recurrent sinusitis
 - oral cavity
 - hyperplasia of gingiva, gingivitis

Wegerner's Granulomatosis

- Treatment
 - meticulous dental and nasal care
 - middle ear drainage
 - cyclophosphamide 2 mg/kg plus prednisone 1 mg/kg
 - remission 93%
 - azathioprine or methotrexate alternative to cyclophosphamide

Wegener's Granulomatosis

- Treatment
 - isolated sinonasal disease
 - low dose steroids, saline irrigation, antibiotics as needed
 - subglottic stenosis
 - may warrant tracheotomy

Wegener's Granulomatosis





Giant Cell Arteritis (Temporal Arteritis)

- Only extracranial vessels involved
- Focal granulomatous inflammation of medium and small arteries
- Most common vasculitis
- Prevalence:850/100000
- Age 80+

Giant Cell Arteritis

- Most common initial complaint: Headache-boring and constant (47%), up to 90% will develop headache
- ESR >50mm/hr
- Confirmed by temporal artery biopsy of affected side: 5-7cm in length. If negative, biopsy contra lateral side.
 False negative rate of 5-40%
- Tender and erythematous temporal artery 50%
- Tender scalp
- Jaw ischemia 50%
- Lingual ischemia 25%

Giant Cell Arteritis

- Otologic: vertigo and hearing loss
- Dysphagia: ascending pharyngeal involvement
- CN deficits, vertebrobasilar insufficiency, psychosis=intracranial disease
- Blindness: 1/3 untreated patients
- Treatment with prednisone and normalization of ESR

Giant Cell Arteritis (Temporal Arteritis)



Polymyalgia Rheumatica

- Seen in 50% of patients with giant cell arteritis
- Muscular pain, morning stiffness of proximal muscles, elevated ESR without inflammatory joint or muscle disease
- Low grade fever, wt loss, malaise
- Low dose prednisone

Behcet's Disease

- Vasculitis with triad of oral and genital ulcers and uveitis or iritis
- Aphthous like ulcers, covered in pale pseudomembrane
- Painful, on lips, gingiva, buccal mucosa, tongue, palate and oropharynx
- Genital ulcers similar in appearance
- Heal in days to weeks with scarring

Behcet's Disease





Kawasaki Disease

- Mucocutaneous lymph node syndrome
- Disease of children
- Fever, conjuctivitis, red dry lips, erythema of oral mucosa, polymorphous truncal rash, desquamation of the fingers and toes, cervical lymphadenopathy
- Oral cavity erythema and cervical adenopathy are presenting symptoms
- Cardiac abnormalities cause 1-2% mortality rate

Kawasaki Disease



Kawasaki Disease Lab Features

- ↑ WBC
- ↑ ESR, positive CRP
- Anemia
- Mild ↑ transaminases
- ↓ albumin
- Sterile pyuria, aseptic meningitis
- ↑ platelets by day 10-14

Kawasaki Disease Differential Diagnosis

- Measles
- Scarlet fever
- Drug reactions
- Viral exanthems
- Toxic Shock Syndrome
- Stevens-Johnson Syndrome
- Systemic Onset Juvenile Rheumatoid Arthritis
- Staph scalded skin syndrome

Kawasaki Disease Difficulties with Diagnosis

- Clinical diagnosis
- No single test
- Diagnosis of exclusion
- Atypical KD
 - Do not fulfill all criteria
 - More common in < 1 year and > 8 years

Kawasaki Disease Treatment

- Admit to monitor cardiac function
- Complete cardiac evaluation
 - CXR, EKG, echo
- IV Ig
- ASA

Kawasaki Disease Treatment

- IV lg 2 g/kg as single dose
 - Expect rapid resolution of fever
 - Decrease coronary artery aneurysms from 20% to < 5%
- ASA low dose vs high dose
 - 80-100 mg/kg/day until day 14
 - 3-5 mg/kg/day for 6 weeks
- Repeat echocardiogram at 6 weeks









Spondyloarthtitis (Ankylosing Spondylitis)

- Characteristics
 - Axial skeletal involvement
 - Absence of serum rheumatoid factors

Psoriatic Arthritis

- Epidemiology
 - Prevalence: affects approximately 10% of patients with psoriasis
 - 0.1-0.2% of the population
 - Age: Usually 30-40 years old
 - Affects women and men equally
 - Genetics:
 - 50% with psoriatic spondylitis HLA B27 gene positive

Psoriatic Arthritis

- Clinical features
 - Mild and intermittent
 - 15% arthritis precedes rash
 - No correlation
 - Skin involvement and severity of arthritis
 - Eye conjunctivitis, iridocyclitis, episcleritis

Psoriatic Arthritis

- Clinical features
 - Arthritis
 - Mono/Oligo:70%
 - Axial:25%
 - poly:10%
 - DIP joint:10%
 - Arthritis mutilans:5%

Psoriatic Arthritis

- Prognosis
 - 5% develop severe disabling and deforming arthritis

Sexually Acquired Reactive Arthritis (SARA)

- Characteristics
 - Oligoarticular asymmetrical arthritis
 - Urethritis/cervicitis
 - Conjunctivitis
 - Eponym
 - Reiter's syndrome

Sexually Acquired Reactive Arthritis (SARA)

- Epidemiology
 - Incidence: Uncommon. About 1% of people with urethritis develop SARA
 - Age: Usually 16-35 years of ageSex: About 95% of patients are male
 - Race: No association

Sexually Acquired Reactive Arthritis (SARA)

- Epidemiology
 - Genetics: HLA-B27 gene present 60-90% of patients
 - Geography: worldwide

Sexually Acquired Reactive Arthritis (SARA)

- Aetiology and Pathogenesis
 - Triggered by infectious agent
 - Chlamydia trachomatis
 - Ureaplasma urealyticum
 - Arthritis is reactive
 - Not caused by direct infection of the joint

Sexually Acquired Reactive Arthritis (SARA)

- Clinical features
 - Early
 - Mild systemic
 - Intermittent mucopurulent penile discharge
 - Dysuria
 - Eye
 - Conjunctivitis, uveitis, keratitis, optic neuritis

Sexually Acquired Reactive Arthritis (SARA)

- Clinical features
 - Musculoskeletal
 - Arthritis
 - sausage shaped digits dactylitis
 - acute asymmetrical oligoarticular
 - knees, ankles, MTPJs, IPJs
 - Sacroiliitis
 - Achilles tenosynovitis
 - Enthesitis
 - Plantar fasciitis

Sexually Acquired Reactive Arthritis (SARA)

- Clinical features
 - Skin
 - Keratoderma blenorrhagica
 - Circinate balanitis
 - Papules: palms, soles and glans penis

Sexually Acquired Reactive Arthritis (SARA)

- Prognosis
 - Recovery from initial symptoms several months
 - 33% chronic disease
 - 15-25% permanent disability

Sexually Acquired Reactive Arthritis (SARA)

Sexually Acquired Reactive Arthritis (SARA)

 Preceding infection — Two types of bacteria can cause reactive arthritis: those causing enteric infections and those causing urethritis. The enteric bacteria associated with reactive arthritis include:

Reactive Arthritis

CLINICAL FEATURES

 Two types of bacteria can cause reactive arthritis: those causing enteric infections and those causing urethritis.

Reactive Arthritis

- Salmonella of various serovars
- Shigella especially Shigella flexneri but also Shigella dysenteriae and sonnei
- Yersinia including Yersinia enterocolitica 0:3 and 0:9 and Yersinia pseudotuberculosis
- Campylobacter especially Campylobacter ieiuni
- Clostridium difficile

Arthritis Associated with Gastrointestinal Disease

- Diseases include:
 - Post-dysenteric reactive arthritis
 - Inflammatory bowel disease
 - Crohn's disease
 - Ulcerative colitis

Arthritis Associated with Gastrointestinal Disease

- Epidemiology
 - Prevalence (post-dysenteric) 27/100,000
 - IBD-associated arthritis:
 - Peripheral arthritis 12% UC
 - 20% of CD
 - Axial arthritis 6% UC and CD

Arthritis Associated with Gastrointestinal Disease

- Epidemiology
 - Age: IBD-associated peripheral arthritis 25-45 years
 - Sex/Race: No association
 - Genetics: 50% IBD-associated axial arthritis and HLA-B27 50%
 - Geography: Post-dysenteric reactive arthritis more common mainland Europe

Arthritis Associated with Gastrointestinal Disease

- Etiology and pathogenesis
 - Post-dysenteric reactive arthritis
 - Shigella dysenteria
 - Shigella flexneri
 - Salmonella typhimurium
 - Yersinia enterocolitica
 - Campylobacter jejuni

Arthritis Associated with Gastrointestinal Disease

- Clinical features
 - Arthritis usually follows IBD by 6 months to several years
 - Exacerbations related to severity of arthritis
 - Clinical features of postdysenteric reactive arthritis similar to SARA

Arthritis Associated with Gastrointestinal Disease

- Prognosis
 - IBD-associated arthritis
 - Peripheral arthritis mild
 - Axial arthritis usually progressive

Sarcoidosis

- Characteristics
 - Multi-system granulomatous disease
 - Systemic
 - Skin
 - Eyes
 - Lungs
 - Joints

Sarcoidosis

- Epidemiology
 - Prevalence: 5/100,000 population
 - Age: Peak early adult life
 - Sex: More common in women
 - Race: Severe 16 x Afro-Caribbeans. Least common Asian and Chinese
 - Geography: Most common large black populations

Sarcoidosis

- Clinical features
 - Acute illness
 - Pyrexia, malaise, lymphadenopathy
 - Erythema nodosum, skin sarcoid
 - Polyarthralgia
 - Uveitis and keratoconjunctivitis
 - Shortness of breath

Sarcoidosis

- Additional investigations
 - Serum angiotensin converting enzyme
 - Raised calcium
 - Chest radiography
 - Bilateral hilar lymphadenopathy
 - Parenchymal infiltration

Sarcoidosis



