Rheumatoid Arthritis: Extraarticular Manifestations and Treatment Overview

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Disclosures

- Relevant Financial Interests to Report
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Objectives

- List the characteristic features of the arthritis of Rheumatoid Arthritis
- List the extraarticular features of Rheumatoid Arthritis & their risk factors
- Know when to refer to consultants
- List the key components in the treatment of Rheumatoid Arthritis
Outline

- Review definition and articular features of Rheumatoid Arthritis
- Describe extraarticular manifestations of Rheumatoid Arthritis
- Review goals and strategies for Rheumatoid Arthritis treatment

Review definition and articular features of Rheumatoid Arthritis

Rheumatoid Arthritis: Definition

Severe, common inflammatory disorder characterized by chronic polyarthritis and systemic manifestations

Prevalence of ~ 1% in Caucasians of northern European ancestry. Affects all age groups, females > males. 2010 ACR/EULAR criteria for diagnosis included in Supplement.
What are the articular features of RA?
- Chronic polyarthritis
  - Inflammatory
  - Symmetric
  - Small and large joint involvement
  - Upper cervical spine involvement; not lower back
  - Potentially any synovial joint
  - May develop into destructive arthritis

Chronic arthritis – complaints > 6 weeks of duration (insidious onset) with warm/swollen/tender joints; not erythematous/hot/excruciatingly tender joints of acute arthritis.

Reminder: inflammatory arthritis is defined by history - pain that is worse after immobility, typically in AM; improves with gentle activity, worsens with rest; associated significant AM stiffness (≥ 1 hr).

Distribution in hands: MCPs/PIPs; in feet: MTPs/PIPs; wrists.

Destructive arthritis = joint subluxation & erosive disease on x-rays (see Supplement)

What joints are involved?
Early disease is < 6 months duration.

See Supplement for additional information on polyarthritis of RA (photo of advanced disease, pathophysiology, x-rays of erosive disease)

What are the atypical presentations of RA? *
- Intermittent or migratory (pallindromic rheumatism)
- Acute fulminant polyarthritis – especially in the elderly
- Monoarthritis
- PMR-like
- Extraarticular manifestation - rare

* Arrow indicates decreasing prevalence.

Pallindromic rheumatism = mono- or oligoarthritis arises abruptly, lasts for hours – days, recurs often at a different location; 30-60% will progress to RA, especially if rheumatoid factor and anti-CCP – positive; response to anti-malarials suggests will develop into RA

Monoarticular = may develop after trauma to that joint, usually develops polyarthritis within weeks to months

PMR- like = early on "myalgic" in same distribution as PMR, then develops typical RA distribution; slower response to steroids than PMR

Extraarticular manifestations eg nodules & episcleritis, others less likely
KEY POINTS
Articular Features of RA
- Common
- Chronic inflammatory POLYarthritis
- Predilection for PROXIMAL SMALL JOINTS HANDS/FEET, WRISTS, upper neck
- Atypical presentations occur - uncommon
- May develop into destructive arthritis if not managed early & aggressively

Describe extraarticular manifestations of Rheumatoid Arthritis

What are the most common extraarticular manifestations of RA?
- Constitutional symptoms
- Osteopenia
- Muscle weakness
- Cardiovascular disease (non-vasculitic)
- Rheumatoid nodules
- Pulmonary disease
- Secondary Sjögren's syndrome
- Vasculitis
- Neutropenia
- Nervous system involvement

All of these may be involved as will be discussed on the next set of slides.

May occur in up to 40% of patients (top 3 may occur more often). Associated with increased overall morbidity & premature mortality, & therefore, extraarticular manifestations are a marker of severe disease.

Generally, these extraarticular manifestations occur in individuals who are older, with poorly controlled, long-standing disease who smoke & have high levels of RF and anti-CCP.
Constitutional Symptoms

- Fatigue
- Low grade temperature
- Weight loss
- AM stiffness

Constitutional symptoms are exception – these can occur at disease presentation & with flares.

Temperature elevation is low grade; if > 101° consider Still's disease, infection or another diagnosis, ie SLE/vasculitis.

Osteopenia localized to joint is typically due to periarticular demineralization, which is a characteristic feature of RA.

Osteoporosis is common. Those with erosive disease, may have earlier bone loss.

Increased risk of osteoporotic fracture: major osteoporotic fracture increased 30% & hip fracture increased 40%. Higher risk of stress fractures, esp fibular – not related to trauma. **Need to evaluate any new acute & severe bone pain.**

**Need to diagnose osteoporosis early, and treat aggressively:** use DEXA & FRAX tool.

Muscle Weakness

- Atrophy resulting from synovitis
- Myositis
- Neuropathy
  - Vasculitis
  - Nerve entrapment
- Drug-induced myopathy
  - Steroids (uncommon < 10 mg qd)
  - Anti-malarials
  - Lipid-lowering drugs

Myositis usually low grade with biopsy evidence of sporadic lymphocytic infiltrates – rarely develops into full blown polymyositis.
Non-vasculitic Cardiovascular Disease

- Independent risk factor
  - Cardiac diseases
    - Coronary artery disease
    - Heart failure
    - Atrial fibrillation
  - Peripheral vascular disease
  - Cerebral vascular disease
- Increased risk of sudden death & MI
- Increased prevalence in those with more systemic disease, greater disease activity & longer duration of disease


Important to control other risk factors for these diseases!

Rheumatoid Nodules

Most common cutaneous manifestation of RA (20-35% of pts). These are firm, flesh colored, usually mobile. Can be affixed to bone, but usually subcutaneous at pressure points & on extensor surfaces. Typically, not as hard as tophi, which may be white-cream colored but may occur at same locations. Treatment not indicated unless painful; can then use steroid injection.

Presence is predictor of more severe articular disease & other extraarticular manifestations, eg Felty’s & vasculitis.

Rheumatoid Nodule Pathology

H & E stains of an early (< 6 months, left panel) vs late (right panel) rheumatoid nodule. Small vessel vasculitis with necrosis seen early. Palisading histiocytes & central necrosis seen late.
Pulmonary Manifestations*

- Interstitial lung disease / Organizing pneumonia (BOOP)
- Pleural effusions / pleurisy
- Rheumatoid nodules

* Arrow signifies decreasing prevalence. Prevalence difficulty to estimate. Much more common than cardiac manifestations.

ILD most common esp in smokers; looks like idiopathic interstitial pneumonias; usually insidious onset, basilar fibrosis. Organizing pneumonia symptomatic – cough, fever, dyspnea, weight loss, fever. Need to consider infection/drug toxicity/malignancy in the differential for both.

Pleural effusions next most common; typically asymptomatic & identified on exam or CXR (different than those seen in SLE, which tend to be symptomatic). Thoracentesis required. Characteristics: exudative - very low glucose, high LDH, pH<7.3, WBC<5000

Rh nodules in all sizes – need to consider infection/malignancy

NEED TO GET PULMONARY INVOLVED to eliminate other causes.

Secondary Sjögren’s Syndrome

- Keratoconjunctivitis sicca
- Xerostomia

Occurs in 10-20% of patients. RA is most common cause of secondary SS. Usually mild & with sicca complaints only. Rare to have extraglandular disease typical of primary SS.

Vasculitis

- Skin
  - Rheumatoid nodules
  - Digital infarcts
  - Leg ulceration
- Eye
  - Scleromalacia perforans
- Nervous system
  - Neuropathies

POTENTIALLY SERIOUS COMPLICATION! Vasculitis may affect small vessels (rh nodules) to medium sized arteries (PAN-like).

Has predilection for these organ systems. May affect other organ systems but much less likely (pericardium, bowel, lungs).

Often occurs when arthritis is “burned out” (inactive).

Suspect when worsening constitutional symptoms in absence of infection – patient with failure to thrive, weight loss, unexplained increased inflammatory markers or fever.
Cutaneous Vasculitis

What do you see in each panel?

Top: Digital infarcts (nailfold infarcts are common & benign)
Bottom: Digital gangrene (rare); more indicative of larger vessel vasculitis.

Skin vasculitis most common manifestation of rheumatoid vasculitis (< 90%). Can also see lower extremity deep cutaneous ulcers at malleoli from medium vessel vasculitis.

Need to consider other causes, eg thromboembolic disease, vasculopathy (systemic sclerosis, buerger's disease), & other forms of vasculitis.

Episcleritis

25 yo man presents to your clinic with active synovitis from RA & this ocular finding. He has slight eye discomfort but no real pain. What do you see? What is diagnosis?

Episcleritis is benign cause of red eye & occurs in < 1% RA pts. Must be distinguished from more severe causes. Need ophthalmology evaluation to eliminate more serious conditions.

Scleritis & Scleromalacia

70 yo woman with h/o RA presents with severely painful red eyes. What do you see? What is diagnosis?

Scleritis is a serious eye disease, which may result in vision loss; may be painless so requires thorough eye examination for scleral thinning. EYE EMERGENCY – contact ophthalmology immediately. These 2 conditions occur in < 5% patients with RA but can be very serious.
75 yo man with inactive RA & tobacco use complains of 1 week of right foot dragging & 3 days of left hand numbness. What is his diagnosis?

Left panel: low power HE showing nerve fiber with vasa nervorum. Right panel: high power HE of artery supplying the nerve.

Mononeuritis multiplex: characterized by asymmetry, asynchrony & predilection for distal nerves. NEUROLOGY EVALUATION KEY: diagnose by EMG/NCV & nerve biopsy.

Neutropenia may occur by 2 mechanisms.

Declining prevalence of Felty’s syndrome over time with more effective treatment (<1%).

Seen in setting of long-standing disease, 1/3 pts “burned out”.

Clue: high ESR, associated with other extraarticular manifestations.

Predisposes to recurrent infections of skin / respiratory tract, esp if PMNs <1000, skin ulcers, steroid therapy.
LGLs are a subclass of circulating lymphocytes with characteristic granules. May proliferate in RA, causes neutropenia +/- splenomegaly. May develop into large granular lymphocytic leukemia. Uncommon.

**WBCs need to be monitored yearly**; if low, repeat with differential; refer to hematology for further evaluation – will do flow subset analysis, cytogenetics, T cell receptor gene studies & bone marrow.

**Nervous System Involvement**
- Entrapment neuropathies
  - Carpal tunnel syndrome
  - Tarsal tunnel syndrome
- Myelopathy from cord compression
- Vasculitic neuropathies
  - Distal sensory neuropathy
  - Mononeuritis multiplex

Increased risk of myelopathy in patients with C1/C2 subluxation.

Vasculitic peripheral neuropathy has rapid onset; characterized by anesthesia > pain; muscle weakness may follow.

**Always ask about neurologic symptoms & neck pain**!
Do focal neurologic exam, expand as needed.

**KEY POINTS**

**Extraarticular Manifestations**
- Typically occur in individuals with longstanding disease, high titers of RF/anti-CCP, smokers & h/o poorly controlled / aggressive disease
- Spectrum of severity
  - Benign: nodules, sicca, constitutional, nerve entrapments
  - Serious: organizing pneumonia, LGL leukemia, myelopathy, vasculitis
- Usually a diagnosis of exclusion
  - May need specialty referral
- Need to monitor for Osteoporosis, ASVD & muscle weakness
Review goals and strategies for Rheumatoid Arthritis treatment

Goals of Therapy
- Prevent disease progression in early disease
  - Limit functional impairment
  - Control symptoms
  - Prevent erosive disease
- Preserve and maximize function in end-stage disease

Choice of therapy depends on severity of disease activity when therapy is initiated & response of patient to prior therapeutic interventions.

Strategy to achieve remission or low disease activity
- Control inflammation
  - Full strength NSAIDs
  - Low dose prednisone (10-15 mg qd)
- Initiate disease-modifying antirheumatic drug (DMARD) therapy early
- Modify therapy frequently
- Prevent joint pain from injury
  - OT/PT referral for splints/ROM

Refer patients to Rheumatologist if symptoms present for ~ 6 weeks (acute arthritis may be viral or reactive & resolve spontaneously). Use agents to control inflammation but would not initiate DMARD therapy until evaluated by rheumatology. Prednisone used as bridge therapy & prescribed as burst & taper. NO NEED TO USE PREDNISONE 40-60 MG QD!

If synovitis is intermittent (ie pallindromic rheumatism), may start hydroxychloroquine (<6.5 mg/kg lean body weight).

Earliest treatment has best outcomes (damage may occur as early as 6 months). Aim for remission/low disease activity by frequent adjustments of medications as described in American College of Rheumatology guidelines for treatment of RA (Arthritis Care & Research: Vol. 64, No. 5, May 2012, pp 625–639). Efficacy & toxicity of treatment assessed clinically ~ q3 months.
First Line Drugs for RA (traditional/non-biologic DMARDs)

- Methotrexate (MTX)
- Leflunomide [Lef (Arava)]
- Sulfasalazine [SSZ (Azulfidine), usually enteric-coated]
- Hydroxychloroquine [HCQ (Plaquenil)]
- May be used singly (for mild, early RA) or in combination (for moderate-severe or late-onset RA)

Methotrexate / leflunomide usually starting drug for all but those with mildest RA or contraindications to use (liver disease or propensity for liver disease, pregnancy or planned, recurrent infections, non-adherence with lab testing, renal disease for MTX). Use SSZ or HCQ when can’t use 1st two; often in combination. Monitoring guidelines included in Supplementary information.

Second line drugs for Early RA (biologic DMARDs)

- Anti-cytokine therapies
  - Tumor necrosis factor inhibitors (TNFI)*
    - IL-6 receptor antagonist [tocilizumab (Actrem)]
  - T cell costimulation blocker
    - Abatacept [CTLA4-Ig (Orencia)]*
  - B-cell depleting therapies
    - Rituximab* (Rituxan)
  - Janus Kinase inhibitor – inhibits cytokine & growth factor signaling
    - Tofacitinib (Xeljanz)

* most commonly used biologics

All FDA-approved, expensive (most produced by recombinant DNA technology) & parenterally – administered except for Tofacitinib.

Common TNFI: Enbrel, Humira, Remicade. See Supplementary info for more details on composition & route of administration

TNF Inhibitors: Adverse Effects*

- Relatively unique to infusible forms
  - Infusion reactions: BP changes, chest pain, myalgias, arthralgias, anaphylaxis
- Unique to injectable forms
  - Injection site reactions
- Common to all
  - Allergic reactions: pruritus, hives
  - URI sx, sinusitis
  - SERIOUS INFECTIONS
  - TB REACTIVATION esp high risk individuals
  - DEMYELINATING Disease
  - Drug-induced autoimmunity
  - Decompensation of CHF

* many of these are common to all biologics

Watch for these toxicities: especially those capitalized. Patients will often present to you with these complaints.

SLE-like syndrome/ANCA-associated vasculitis/psoriasis can develop. Tendency to form autoantibodies is more common than actual autoimmune disease. These features not seen with other biologics (so far).

Cytopenias & hyperlipidemia more common with Tocilizumab – so may be asked to monitor lipids more closely with this agent.
Management of RA – this rheumatologist’s approach

- Confirmation of diagnosis clinically
  - Based on patient’s clinical features
  - Exclude mimickers
- Staging as to whether early or advanced disease
- Determine likely prognostic category
  - Lab evaluation
    - Acute phase reactants
    - Rheumatoid factor / anti-CCP
  - Radiographs of hands/feet

Other causes of chronic, inflammatory polyarthritis need to be excluded (SLE & related conditions, hepatitis C, crystal or paraneoplastic arthritis).

Staging as to whether early (< 6 months) or late disease is obtained by history.

Prognostic evaluation determines course of treatment.

Management of Early RA

- If RF- or min + and no erosions
  - Escalate Methotrexate rapidly to 25 mg qwk
  - If control isn’t achieved within 3 mos, add TNF inhibitor or Sulfasalazine / Hydroxychloroquine
  - NSAIDs or low dose prednisone for symptom control
  - OT/PT

Management of Early RA Continued

- If significantly RF+ and erosions
  - Triple therapy at onset
  - TNF inhibitors with Methotrexate or Leflunomide
  - Low to medium dose prednisone
  - OT/PT

Triple therapy = methotrexate or leflunomide & hydroxychloroquine & sulfasalazine
These are the patients that you are more likely to see. You need to decide if they have active disease by history and exam. If they do, then refer to Rheumatology. If they do not, then follow algorithm for inactive disease.

Management of Advanced RA
- If active disease, same as for RF+/erosion+
- If inactive “burned-out” disease
  - Aggressive OT/PT for deconditioning/loss of function
  - Surgery for painful and dysfunctional joints
  - Monitoring for sequelae
    - Secondary OA
    - Fibromyalgia
    - Extraarticular manifestations
  - Analgesia for pain control

KEY POINTS
Overview of Treatment
- Treatment is most effective when initiated early
- Single or combination DMARDs are mainstay of treatment
- Treatment to target of remission or low disease activity is goal
- Monitoring for drug toxicities is crucial

Take Home Points
- RA is a systemic autoimmune disease
- Arthritis of RA is chronic, polyarticular, inflammatory & has a characteristic joint distribution; atypical presentations occur but are less common
- Extraarticular manifestations are common & vary from relatively benign to life-threatening
- Treatment is multidisciplinary & aimed at reducing inflammation, preventing joint damage, & monitoring for complications of disease & drug toxicity
2010 ACR/Eular\(^1\) classification criteria for RA

- Number & site of joints involved with synovitis\(^2\):
  - 1 point = 2-10 large joints\(^3\)
  - 2 points = 1-3 small joints\(^4\)
  - 3 points = 4-10 small joints
  - 5 points = > 10 joints (including > 1 small joint)
- Serological abnormality (RF or anti-CCP)\(^5\):
  - 2 points = low positive (> ULN\(^6\))
  - 3 points = high positive (> 3 times ULN)
- Elevated ESR or CRP above the ULN = 1 point
- Symptom duration > 6 weeks = 1 point
- Need 6/10 and exclusion of other causes for synovitis for definite diagnosis of RA

\(^1\) Accepted criteria from American College of Rheumatology and European League Against Rheumatism for individuals with newly presenting arthritis (early RA < 6 months).

\(^2\) Synovitis = joint swelling associated with tenderness

\(^3\) "Large joints" = shoulders, elbows, hips, knees, and ankles.

\(^4\) "Small joints" = MCPs, PIPs, 2\(^{nd}\) – 5\(^{th}\) MTPs, thumb interphalangeal joints, and wrists

\(^5\) RF = rheumatoid factor; anti-CCP = antibodies to citrullinated proteins

\(^6\) ULN = upper limits of normal

What joints are involved?

How do you know that this is of longer duration? – atrophy of muscles in dorsum of hands and subluxation
RA: Pathologic Features

- Inflammatory proliferation of synovium
- Periarticular osteopenia
- Destruction of cartilage and bone
- Resultant uniform joint space narrowing and marginal erosions
- Stretching of periarticular structures
- Resultant subluxation

Autoimmune process occurs in synovium; stimulates ingress of inflammatory cells & activates synoviocytes to produce mediators of inflammation (cytokines, chemokines, etc). These inflammatory molecules are responsible for clinical & radiologic features.

Progression of an Erosion

Development of an erosion at a PIP joint of a patient with RA. Panel A: fairly normal except for mild soft tissue swelling around the joint. Panel B with uniform joint space narrowing (solid arrow) and more swelling. Panel C with marked joint space narrowing (solid arrow) and marginal erosion (dashed arrow).

TNF Inhibitors (partial list)

- Etanercept (Enbrel)
  - Recombinant fusion protein TNF receptor and Fc portion of Ig
  - Injectable
- Infliximab (Remicade)
  - Humanized monoclonal antibody to TNF
  - IV infusion
- Adalimumab (Humira)
  - Recombinant human antibody to TNF
  - Injectable

There are other forms too not as commonly used at uihc – Certolizumab: human anti-TNF Fab’ linked to polyethylene glycol & Golimumab: human anti-TNF
**Rituximab**
- Humanized monoclonal antibody to CD20
  - Deletes B cells
  - Minimal effect on humoral immunity
- FDA-approved for RA in TNFI failures
- Given by IV infusion in 2 doses - 2 weeks apart
- Infusion reactions major adverse reaction

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* Package insert for diclofenac (Voltaren) recommends that AST and ALT be monitored within the first 8 weeks of treatment and periodically thereafter. Monitoring of serum creatinine should be performed weekly for at least 3 weeks in patients receiving concomitant angiotensin-converting enzyme inhibitors or diuretics.

- Refer to the UpToDate topic on antimalarial drugs in the treatment of rheumatic disease.
- Symptoms of myelosuppression include fever, symptoms of infection, easily bruised skin, and bleeding.
- Monitoring for osteoporosis is discussed in the UpToDate topics on the pathogenesis, clinical features, and evaluation of glucocorticoid-induced osteoporosis and on the prevention and treatment of glucocorticoid-induced osteoporosis.