Overview
Pathogenesis
Clinical features
Red flags — Atlanto axial subluxation
Pericarditis
Monoarticular flare
Eye involvement
Other manifestations
Dg — History
PE
Labs
Imagings
Synovial fluid analysis
Differential Dg

Overview

Chronic systemic inflammatory disease
Wide spectrum manifestations → articular
→ extra-articular
Joint destruction → deformities → disability
Mortality Morbidity
Early Dg
Early DMARDs → ↓progression

Pathogenesis

Genetic predisposition : HLA DR 1 and 4
Environmental triggers : smoking → ↑citrulination
Auto immune synovitis → hypertrophy → destruction of bone cartilage → progressive joint damage → disability
↑
dysregulated inflammatory process
↓
extra articular tissues

Cells T and B
Cytokines TNFα and IL6

Dysregulated inflammation
Dysequilibrium of cytokines

Clinical features

- Dg
- Activity
- Severity
- Extra articular manifestations

Sex ration: 3:1 ♀ > ♂

♀: increase from mid 20s To peak between 45–75 y
♂ rare before 30 y

Onset

Insidious

Small joints of hands and feet
- PIP
- MCP
- Wrist
- MTP
- Forfoot

Symmetrical pattern

Acute (less common)

mono articular palindromic rheumatism
asymmetrical large joint arthritis

Manifestations

Articular

Theoretically any synovial joint can be affected
But spine joints other than cervical are rarely involved

Spared joints

DIP
Low back
Sacroiliac

Extra articular

Almost any organ system can be affected.
Various inflammatory mechanisms:

Inflamm
- Cytokines production
- Immune complexes deposition
- direct endoth injury

Mechanics
Mechanical insults:
- synovial hypertrophy
- joints subluxation → neurovascular entrapment
- abnormal mechanics / disuse
  - degenerative changes and osteoporosis

Red flags

Atlanto-axial subluxation	Atlanto axial joint involvement may be asymptomatic **suspect subluxation:** Pain around the occiput Radiating arm pain Numbness, Weakness of the limbs Vertigo on neck mvts	Presurgical evaluation: lat. views of cervical spine in flexion and extension
Pericarditis	Chest pain worsened by lying flat Accompanied by pericardial rub	Echocardiogram Steroids Rule out infective causes (TB) • aspiration
Monoarticular flare	Single joint worsening septic arthritis or a flare predisposed: damaged joint immunosuppressed (RB trt)	•Aspiration → rule out septic arthritis •Prudent Int initiation for septic arthritis until it is ruled out
Episcleritis	Sudden onset of eye pain Risk of perforation: scleromalacia perforans	Look for it

Other manifestations

Neurological → Entrapment neuropathies Carpal Tunnel sd
Ocular → sclerits episcleritis keratoconjunctivitis
Pulmonary → pleural effusion interstitial LD bronchiolitis obliterans
Cardiac → pericarditis Coronary vasculitis (rare)
Hematological → Anemia Thrombocytosis Felty's sd
Cutaneous → Skin nodules Cutaneous vasculitis Leg ulcers
Other → Xerostomia Osteoporosis

Diagnosis

History

Time: onset and progression with time
Distribution:
- progressive pattern of joint involvement
- stiffness
- ↑ pain after period of inactivity
- joint swelling

⇨ inflammation

Family hx of autoimmune disease → ↑ suspicion

PE

Distribution Chronicity Inflammatory Extra articular

Distribution: symmetrical involvement of hands (MCP, PIP, wrists) with relative sparing of axial skeleton.

Chronicity

Inflammatory: swelling
tenderness
restriction of mvt of the joint

Extra articular
Support → rheumatoid nodules
refute → psoriatic patches

Labs

Blood:
↑ESR, ↑CRP } Acute phase response may not be present in early
↑ platelets
↑ ferritin
Anaemia of chronic disease
if ↑↑ Leucocytes → infection

Antibodies:
RF
Anti CCP → more specific

Synovial fluid analysis
Monoarticular presentation
to rule out: infective
crystal } etiology

↑ protein
↑ leukocytes
ϕ crystals
ϕ organisms Gram stain/culture.

Imagings

Plain x Rays
Periarticular erosions within first 3 years
Juxta articular osteopenia } earlier less specific
Joint space narrowing

MRI: Soft tissue changes
- synovitis
- bone edema
- early erosive changes

U/S of small joints
synovitis
joint erosions

High resolution CT
interstitial lung disease

Differential

Joint involvement pattern → distinguishable RA

Atypical presentation → challenging Dg

psoriatic arth. → nail pitting or skin lesions

Crystal " → aspiration

Other connective tissue disease → SLE..

Hep B and C } in mind
HIV

2010 ACR/EULAR classification criteria of RA

Patients with:

I) ≥ 1 joint synovitis clinically

II) no better explanation by another disease (after exclusion)

A	B	C	D
Articular	anti Body	CRP/ESR	Duration
/5	/3	/1	/1

A. Articular Joints involvement /5

- Large: 1 → 0; 2-10 → 1
- Small: 1-3 → 2; 4-10 → 3
- > 10 (with ≥ 1 small) → 5

B. anti Bodies : Serology /3

- ⊖ RF and anti CCP → 0
- low " or " → 2
- high " or " → 3

C. CRP/ESR Acute phase reactant

- normal → 0
- abnormal → 1

D. Duration

- < 6 weeks → 0
- ≥ 6 weeks → 1

RA

Systemic condition with predominant manifestations on periph. joints
Major cause of disability.

Synovial Joint inflammation → Cartilage destruction
→ Bone erosion
→ Tendon, lig. stretching → deformities → disabilities
→ Synovial thickening
→ effusion

Pathogenesis

1) Cellular pathology

Chronic inflammation in Synovial joint

Leukocytes infiltration ⟺ (interaction) Indigenous synovial cells
- T cells
- B cells
- Macrophages
- synoviocytes

Infiltration ✗✗ Proliferation ✗✗ hyperplasy locally invasive

Angiogenesis

Nutrient, Oxygen } supply to ↑ cells
synovio → ✗
inflamm → coming

Perpetuation

Cytokines → (+) Enzymes - MMP → (+) { Bone, Cartilage destruction

Chronic inflammation Synovial joints

T cells ↑
B cells ✗
MΦ

Infiltration ↑ ⟺ (Interaction) Synoviocytes, fibroblast like cell

Angiogenesis → Nutrients, Oxygen

Proliferation ↑
- hyperplasy
- local invasion

Cytokines → Enzymes MMP → destruction → Bone, Cartilage

2) Genetic factors

Identical twins concordance rate ≈ 30%
→ Genetic contribution ~~polygenic~~
→ Non inherited factors are important too } Poly factorial

4) PTP N22 polymorphism

Protein Tyrosine Phosphatase Nav 22 receptor. lymphocyte specific
↳ suppressing activation of → T cells

1858T allele → ↑ susceptibility to RA
Diabetics I
Auto immune

5) Antibodies

RF: Ab anti Fc portion of Ig G
IgM +++
Ig A
Ig G

Anti CCP

Citrulination - loss of amino group from Tyr residus
occurs in healthy people
at sites of inflammation

RA: dvpt of Ab against citrulinated auto-antigen collagen type II
vimentin

6) Cytokines

Mϕ
Fibroblast like cells } → cytokines: TNFα, IL 1, IL 6, ~~IL 8~~, GM-CSF
→ Chemokines
} → inflammatory cells - migration, activation

Cytokines → T cells costimulation → IFNγ, IL 2, IL 4 ← sparsely expressed
IL 7, 12, 15, 18
↳ Th 17 → ↑ IL 17 ++ ↑

Abundant expression of anti-inflammatory cytokines IL 10, IL 13, TGF β and IL 1 ra, TNF soluble receptors
up-regulated
insufficient to suppress synovitis

Concept of cytokine desequilibrium

TNFα Dominant position in the apex of pro-inflam cytokines network
(block TNFα → no IL 1 and others
IL 1 → still be TNFα)

TNFα Pleiotropic ↑ → ↑ synovial proliferation
↑ → prostaglandins production
↑ → Metalloproteinases production

anti TNF: ameliorate symptoms, prevent joint destruction

Twins [identical → concordance rate 30% → genetic + environmental
non identical → 5%] → polygenetic and not a single gene

3) HLA polymorphism

Genes → class II HLA → Predisposition / Severity of RA

HLA DR
- ④ → Predisposition More severe
- ① → Predisposition Less severe

Subtypes
Dw 4, 14, 15 → Similarities AA. 70–74 ← HLA DR 1

HLA DR
- ① → Predisposition
  Similarities with Dw 4, 14, 15
- ④
  - Dw 4, 14, 15 → Predisposition
    Similarities -with each other -with DR①
  - Dw 10 → Negative association
    different from previous

70 – 71
Glutamine – Arginine
Basic
↑ affinity for peptide Ag

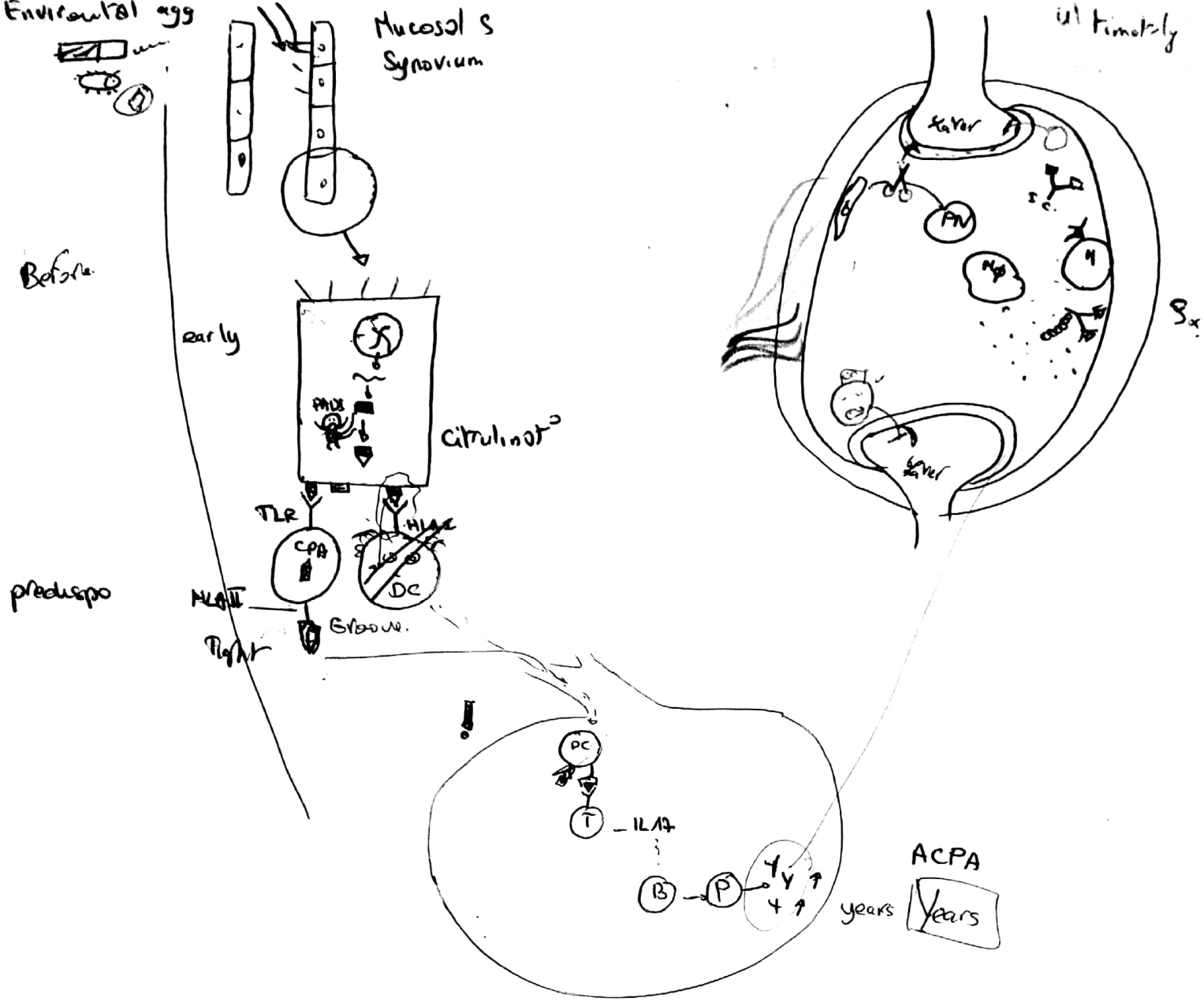
≠

70 – 71
aspartic – glutamic
Acidic
↓ affinity for peptide Ag

70–74 AA → wall of peptide binding groove → Ag binding

1 → predisposition + ↓ severe
4 → predisposition + ↑ severe → subtypes Dw 4 = 14 = 15 → shared epitope 70–74 with conservative Arg / Lys substit
4 → negative association → subtype Dw 10 ≠ 70 – 71
Asp – Glutamic Acid → ↓ affinity
≠ Glutamine – Arg Basic → ↑ affinity

HLA II on CPAs



: modify auto Ag

: DC : CPA

: T cells

: B. cells → plasmac → Y Ab

Immune complexes

Mast cells → vasoactive mediators

Ag Ab Complement Cytokines chim

Cells

DC
T, B, Plasma
Mastocytes
FLS
Macrophages

Cells

- Immune
  - DC Mφ
  - T, B, Plasma
  - Mast
  - Neutro
- → Research
  - FLS
  - Osteoclasts

Humoral

Enzymes
- PADI
- Proteolytic

Im...
- Ag modif...
- Ab
- Immune complexes
- Vasoactive products
- Complement
- Cyto. chemo kines

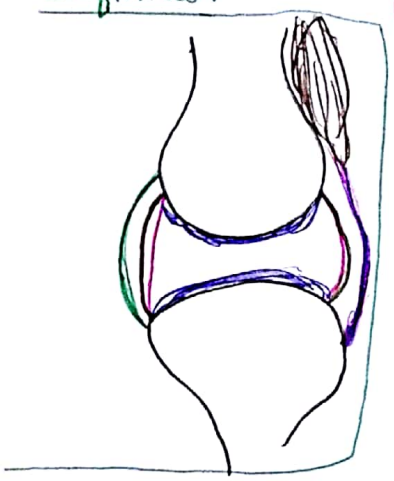
RA: Color handbook

Def
Epidemio and etiology
Pathogenesis
Clinical Hx and PE
- Systemic
- Articular
- Extra articular

Diff
Investigations: Labs, Imaging
Managment

Rheumatoid Arthritis

Definition



Systemic

Predominance in synovial joints

Synovial mb → synovitis proliferative
Art cartilage → destruction
Bone → erosion
Tendon → stretching
Ligaments → stretching

→ deformities → disability

Epidemio / Etiology

1 % of adults
♀ > ♂ 3 : 1
♀: ↑ incidence → 50 y → plateau
♂: rare before 40 y → ↑
New onset ♀ and ♂ at 20 - 30 not uncommon
Childbearing years +++

1. 1% of adults
2. Twins concordance
3. 3:1 sex ratio ♀ : ♂
4. rare before 40 y in ♂ then ↑
5. ↗ → 50 y in ♀ then —

HLA DR 4 ++++ (Shared epitope) in hypervariable region
Concordance rate in monozygote twins: 15%
- strong genetic component
- other factors must be implicated

Smoking associated with a subset of patients with anti CCP ab.
1/3 RA patients → no smoking hx → other factors implicated

Pathogenesis

Ab anti-CCP → specific
RF → non specific

Complex interaction { APC: MΦ, DC; T cells; B cells } → auto Ab

Lymph. gg

RA joint: cells above
synoviocytes
Neutrophils

Pro inflammatory cytokines:
TNFα, IL 1, IL 6
IL 23 (by Th 17) → erosion

Clinical

Onset symmetrical polyarthritis primarily MCP, PIP and MTP with morning stiffness

Systemic:
Fatigue
Weight loss
Anemia
Systemic inflam. → blood vessels damage → atherosclerosis

Articular:
Order of joint involvement:
Early: MCP, PIP, MTP
Interm.: wrist, ankle, elbow, knee
Late: Shoulders, hips, C1-C2

Starts in small art of hands and feet
effusion → soft tissue swelling
→ stretching of Tendons / Lig → deformities

C1-C2 subluxation to take significant flexion → xRay surgery under anesthesia

Extra art:
Skin: s/c nodules also in lung heart
pyoderma gangrenosum

Cardiopulmonary:
- CAD and atherosclerosis
- Pleural/Pericardial effusions
  Constrictive pericarditis → rare
- Interstitial lung disease
  bronchiectasis, nodules

Sjogren Sd
Eyes: scleritis and episcleritis
Hematologic:
Anemia → chronic disease
Thrombocytosis
Felty sd: Leucopenia
Large Granular Lymphocyte

Vasculitis
Systemic: mimic polyarteritis nodosa
Localized: s/c nodules and digital infarct°
Bones: osteoporosis → f#

Diff Dg

Viral associated
OA
other forms of inflammatory arthritis lupus, psoriatic, crystalline

Investigations

Labs: ↑anemia Thrombocytosis
↑CRP → ↓ ESR
Ab: RF
anti-CCP
ANA: 1/3 → severe disease

Histology: Synovial biopsy
Synovial layer hypertrophy → folds
hyperplasia, angiogenesis → infiltration of predominantly CD4+ T cells, B and MΦ

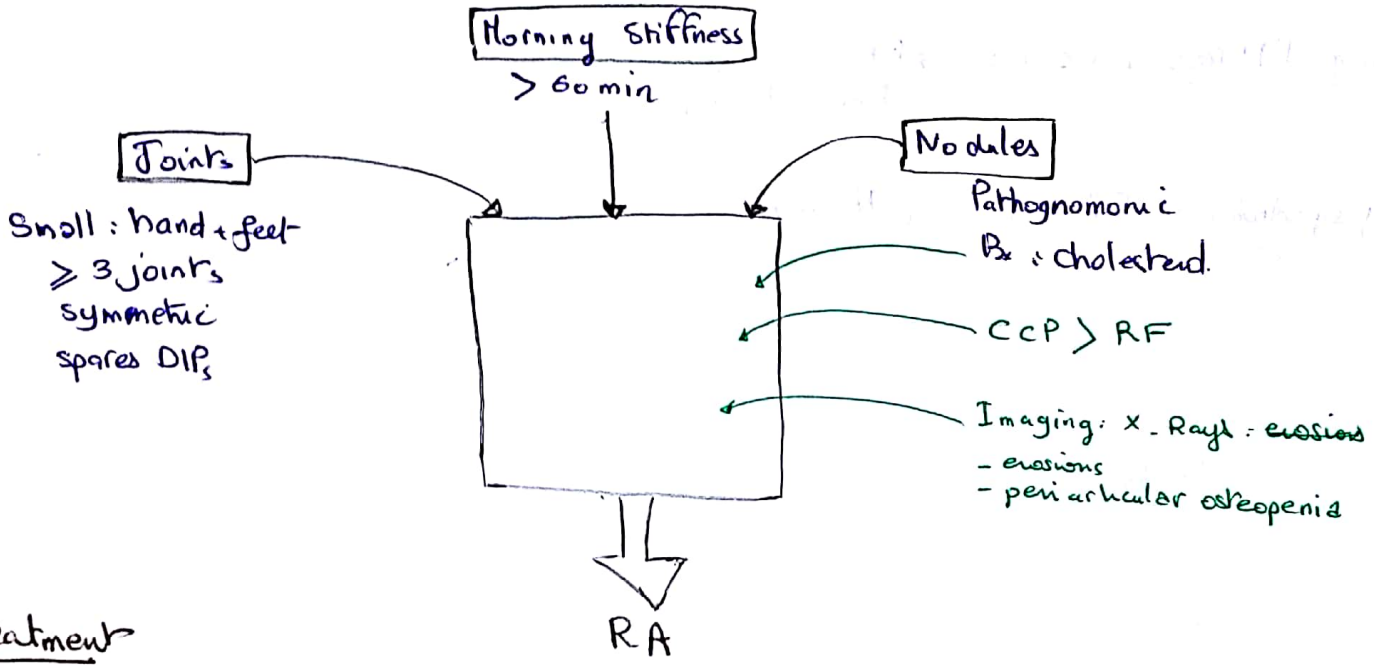
Imaging
Plain xRay of hands and feet
periart osteopenia
marginal erosions
Radio. of C spine → C1-C2 subluxat°
Chest xRay and CT → pulmonary involvement

Rhumatoid Arthritis

Path: Auto-immune
- ♀ > ♂
- ≥ 45 years

Problem: Pannus formation → joint destruction (erosions)

Dg → Combination of clinical clues



Treatment

NSAID (cx) → Ibuprofen, Meloxicam — NEVER monotherapy

\+ DMARD (every one) → Methotrexate
- Leflunamide
- Hydroxychloroquine
- Sulfasalazine

± Biologic (severe) → TNFα inhib
- infliximab
- rituximab
- entarcept

Before:
- Vaccination
- TB
- Fungi

... steroids: plaques → Prednisone (short term)

Combine DMARDs before going to Biologics

CCP → more expensive → more specific
RF → cheaper → more sensitive

DMARDs

MTX → 1st line

Leflunomide → 2nd line

Hydroxy → if we can't use ↑ Pregnancy
non erosive disease

Sulfa → additive

MTX 1st
Leflunomide 2nd
Hydroxy + 3rd
Sulfasalazine + 4th ⊕ → add

Pregnant } → Start hydroxychloroquine
Non erosive }

Morning stiffness + C1-C2 → RA
*Ray : Pre-Op

Felty syndrome: RA + SPMG + Neutropenia