

Rheumatoid Arthritis

Autoimmune synovitis • pannus • joint destruction

Immune mechanisms

Morphologic changes

Clinical correlation

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Learning objectives: Mechanistic and diagnostic reasoning

- Explain how autoimmunity produces chronic synovial inflammation.
- Connect CD4⁺ T-cell cytokines and autoantibodies to tissue injury.
- Recognize pannus, erosions, nodules, and possible ankylosis.
- Use distribution, serology, and imaging to distinguish RA from OA.

LECTURE FRAMEWORK

Autoimmune initiation



Synovial inflammation



Tissue destruction



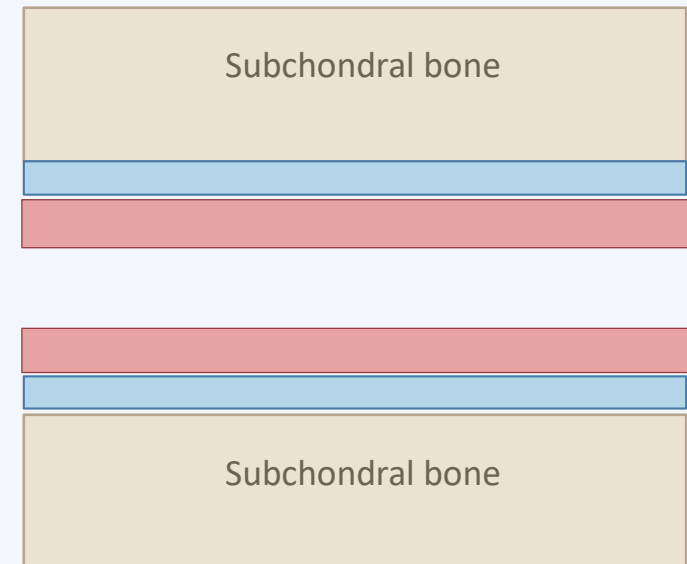
Clinicopathologic interpretation

RA is a chronic autoimmune synovitis

- RA principally targets synovial joints, rather than beginning as primary cartilage degeneration.
- The synovitis is nonsuppurative, proliferative, and inflammatory.
- Persistent inflammation can destroy articular cartilage and adjacent bone.
- Disease may culminate in fibrous and subsequently bony ankylosis.

DEFINITION

Joint section — schematic



Synovial expansion

The central injury model links immunity to erosions

- Loss of immune tolerance permits reactions to self-antigens associated with joints.
- Activated lymphocytes and macrophages establish an inflammatory synovial milieu.
- Synovial proliferation and protease release damage cartilage.
- Osteoclast activity produces periarticular bone erosion.

CAUSAL SEQUENCE

Loss of tolerance



Inflammatory synovitis



Pannus + proteases



Cartilage and bone erosion

Epidemiologic features

- Reported US prevalence: Approximately 0.25%–1%.
- Incidence peaks in the third to fourth decades.
- Females are affected approximately three times as often as males.
- These are broad textbook population descriptors, not clinical diagnostic criteria.

SOURCE-REPORTED EPIDEMIOLOGY

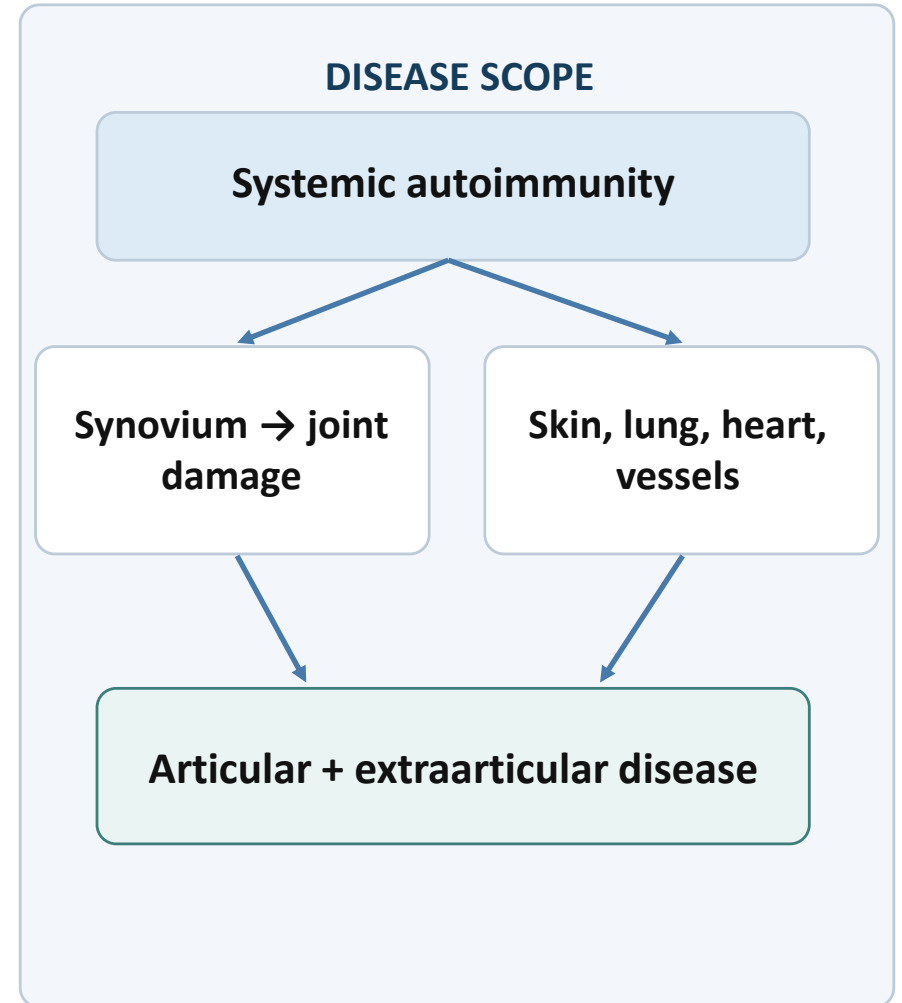
US prevalence: ~0.25%–1%

Peak incidence: 3rd–4th decades

Female:male $\approx$ 3:1

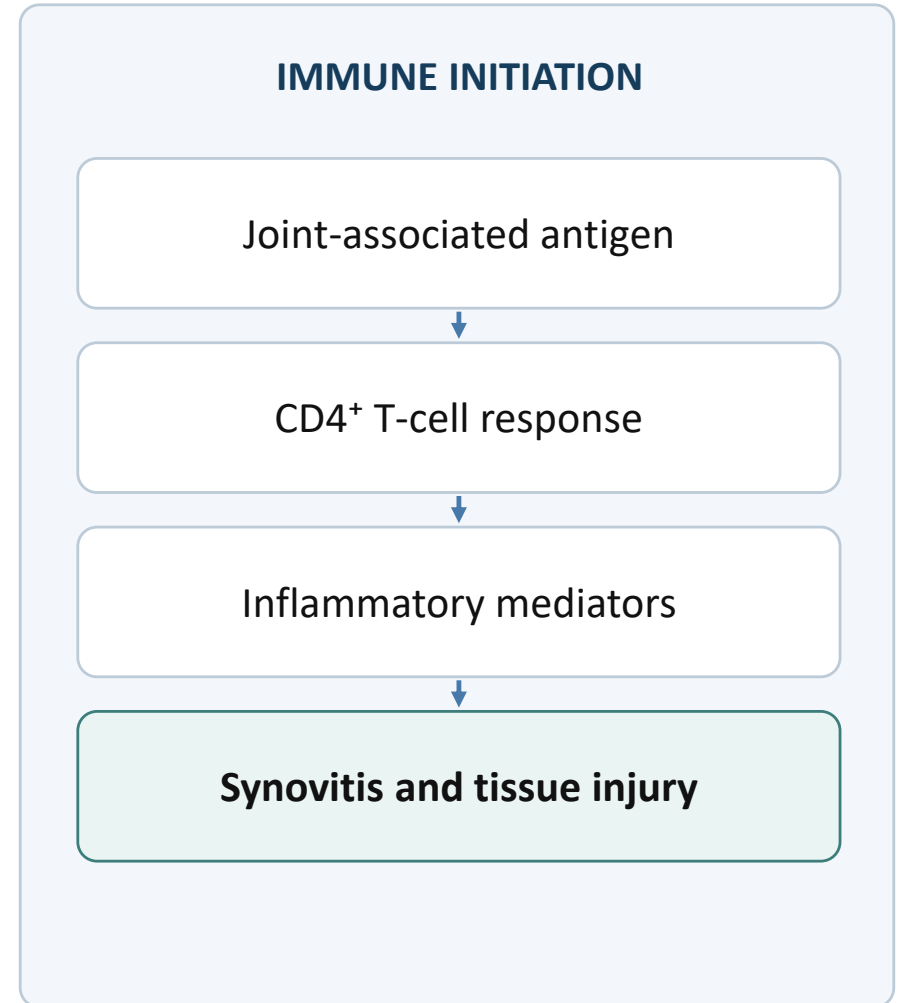
RA has articular and extraarticular expression

- The small joints of hands and feet are common initial sites.
- Inflammation may also involve skin, heart, vessels, and lungs.
- These systemic manifestations reflect RA as an autoimmune disorder.
- Extraarticular findings can overlap with those of other systemic autoimmune diseases.



RA is primarily an immune-mediated joint disease

- CD4⁺ helper T cells reacting to joint-associated antigens initiate the proposed response.
- A number of candidate antigens have been suggested; No single trigger is established here.
- Both cellular immunity and humoral autoimmunity contribute to the pathogenic model.
- The damaged target tissue is inflamed synovium with adjacent cartilage and bone.



Candidate antigens include modified self-proteins

- Collagen and chemically modified peptides have been proposed as joint antigenic targets.
- Citrullination modifies arginine residues within proteins.
- Modified epitopes may become targets of autoantibody and T-cell responses.
- The initiating antigen(s) remain incompletely defined.

ANTIGEN MODIFICATION

Native self-protein



Arginine → citrulline



Modified epitope



Potential autoreactivity

Citrullination creates antigenic epitopes

- Citrullinated proteins contain post-translationally modified arginine residues.
- Examples of targets described include fibrinogen, type II collagen, α -enolase, and vimentin.
- Antibodies to citrullinated peptides are termed ACPAs.
- Epitope modification is implicated in immune recognition; It is not proof of one universal initiating site.

SOURCE-LISTED AUTOANTIGENS

Fibrinogen

Type II collagen

α -Enolase

Vimentin

ACPA bridges autoimmunity and diagnosis

- Anti-citrullinated peptide antibody (ACPA) detects humoral autoreactivity.
- Serum ACPA detection in up to 70% of RA patients.
- ACPA is a useful diagnostic marker, not a standalone test that confirms or excludes RA.
- Some evidence links ACPA, with citrulline-reactive T cells, to persistence and severity.

AUTOANTIBODY INTERPRETATION

Citrullinated self-proteins



ACPA production



Serum antibody detection



Support for RA diagnosis

Rheumatoid factor is directed against IgG

- Rheumatoid factors include IgM and IgA autoantibodies binding the Fc region of IgG.
- RF in approximately 80% of people with RA.
- RF may form or deposit as immune complexes within joints.
- RF is neither universally present in RA nor specific to RA alone.

RF TARGET AND CONSEQUENCE

IgG Fc region



Binding by RF (IgM/IgA)



Immune complexes



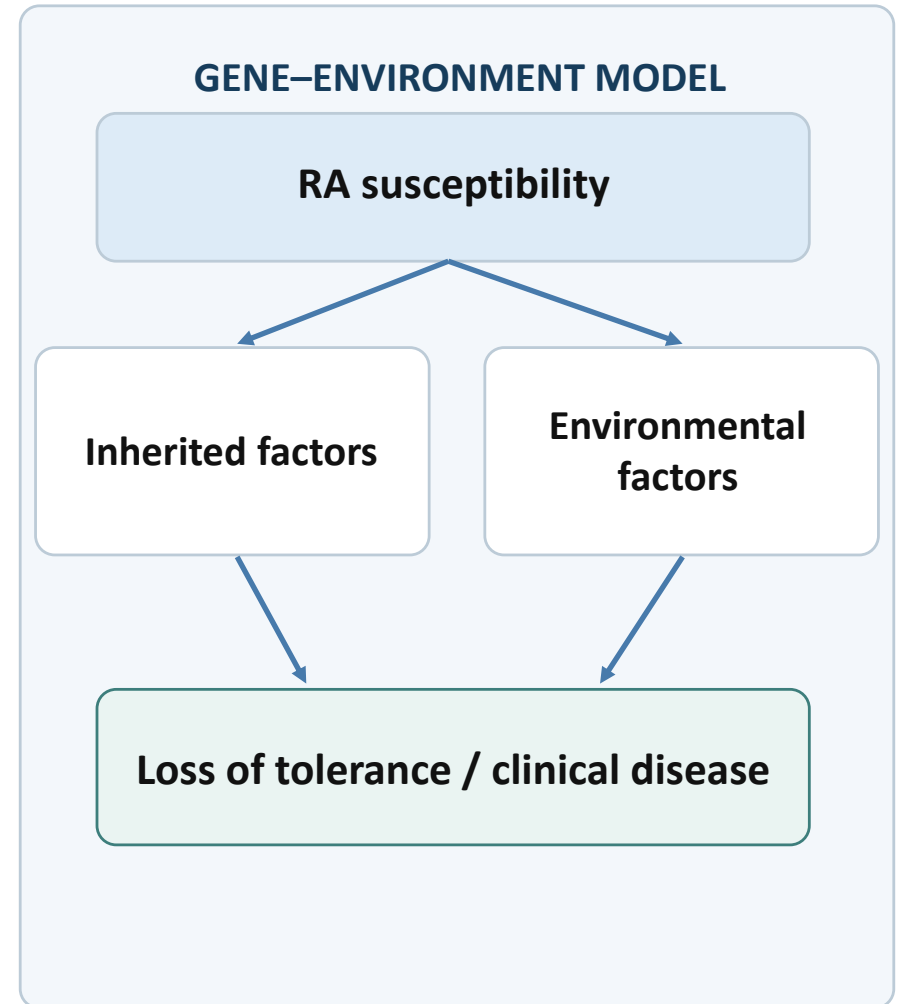
Potential inflammatory contribution

ACPA and RF are complementary—not interchangeable

Feature	ACPA	Rheumatoid factor
Antigen	Citrullinated peptides	Fc region of IgG
Textbook frequency	Up to 70% of RA	About 80% of RA
Clinical role	Diagnostic support	Diagnostic support
Specificity caveat	Cannot stand alone	May occur without RA
Proposed damage	May influence persistence	Immune complexes possible

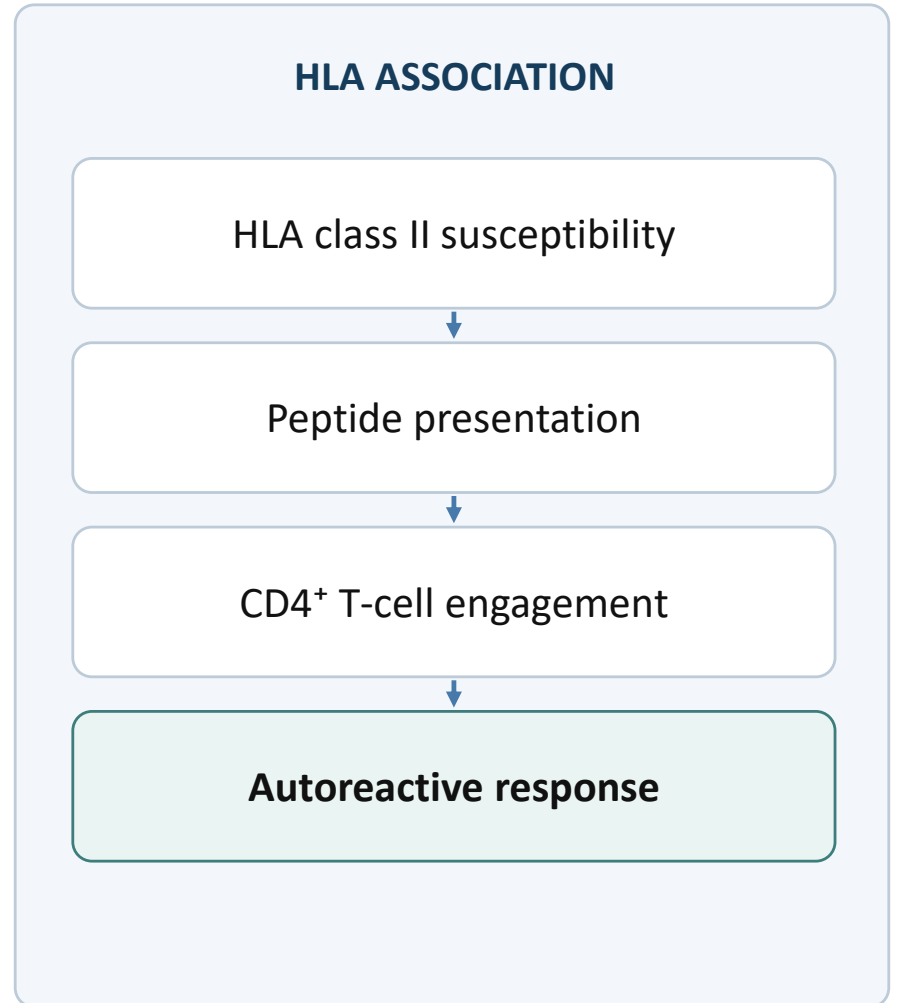
Genetic susceptibility is substantial

- Inherited variation contributes to developing and sustaining RA.
- The textbook estimates that about half of susceptibility is inherited.
- Susceptibility is polygenic and interacts with environmental exposures.
- Genetic predisposition does not by itself establish the disease.



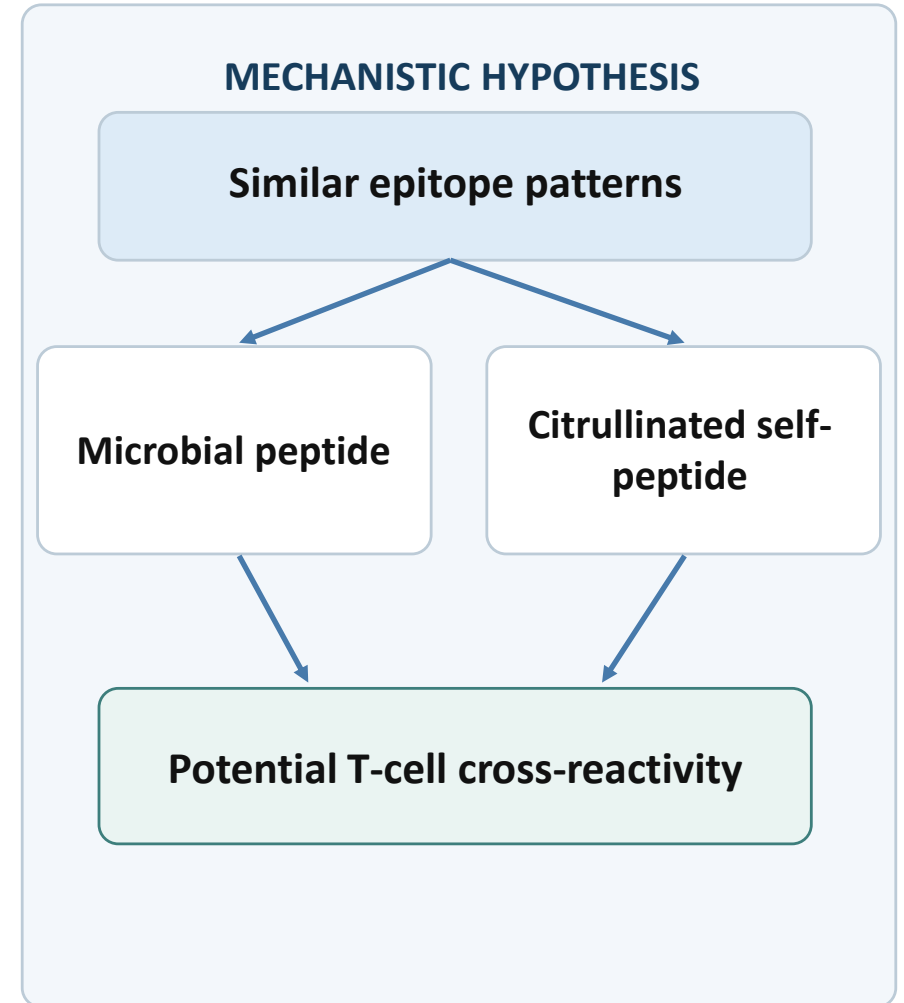
HLA-DR4 is linked to ACPA-positive disease

- The HLA-DR4 allele is associated particularly with ACPA-positive RA.
- Class II HLA molecules participate in antigen presentation to CD4⁺ T cells.
- Presentation of citrullinated peptides offers a plausible link to autoreactive responses.
- HLA association is not sufficient for a clinical diagnosis.



Molecular mimicry remains a proposed mechanism

- A peptide epitope on citrullinated proteins may resemble microbial epitopes.
- Certain epitopes may be presented by HLA-DR4.
- Such cross-reactivity could promote activation of autoreactive lymphocytes.
- The source presents this as a hypothesis, not an established universal trigger.



Environment may promote autoimmune priming

- Environmental contributors are suspected but remain incompletely defined.
- Smoking and infection, including periodontitis, are proposed influences.
- A suggested connection is increased citrullination of self-proteins.
- Do not interpret an association as proof that one exposure causes every case.

PROPOSED TRIGGERS

Smoking / infection / periodontitis



Possible citrullination



Novel antigenic epitopes



Autoimmune activation?

Failure of tolerance precedes inflammatory injury

- Self-reactive lymphocytes persist or become inappropriately activated.
- Recognition of modified or other joint antigens sustains the response.
- Leukocytes enter the synovial tissue, amplifying inflammation.
- Synovial and bone-resorbing cells then mediate structural damage.

IMMUNOLOGIC SEQUENCE

Immune tolerance failure



T-/B-cell activation



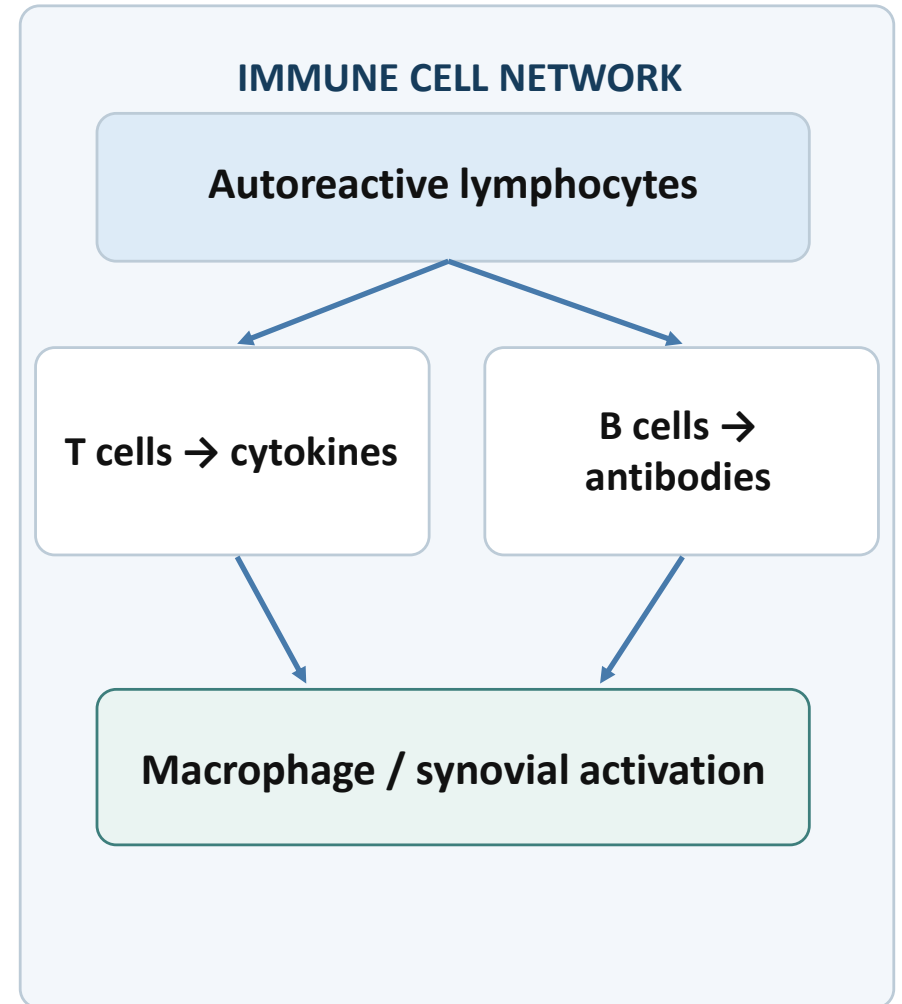
Cell recruitment to synovium



Pannus and erosions

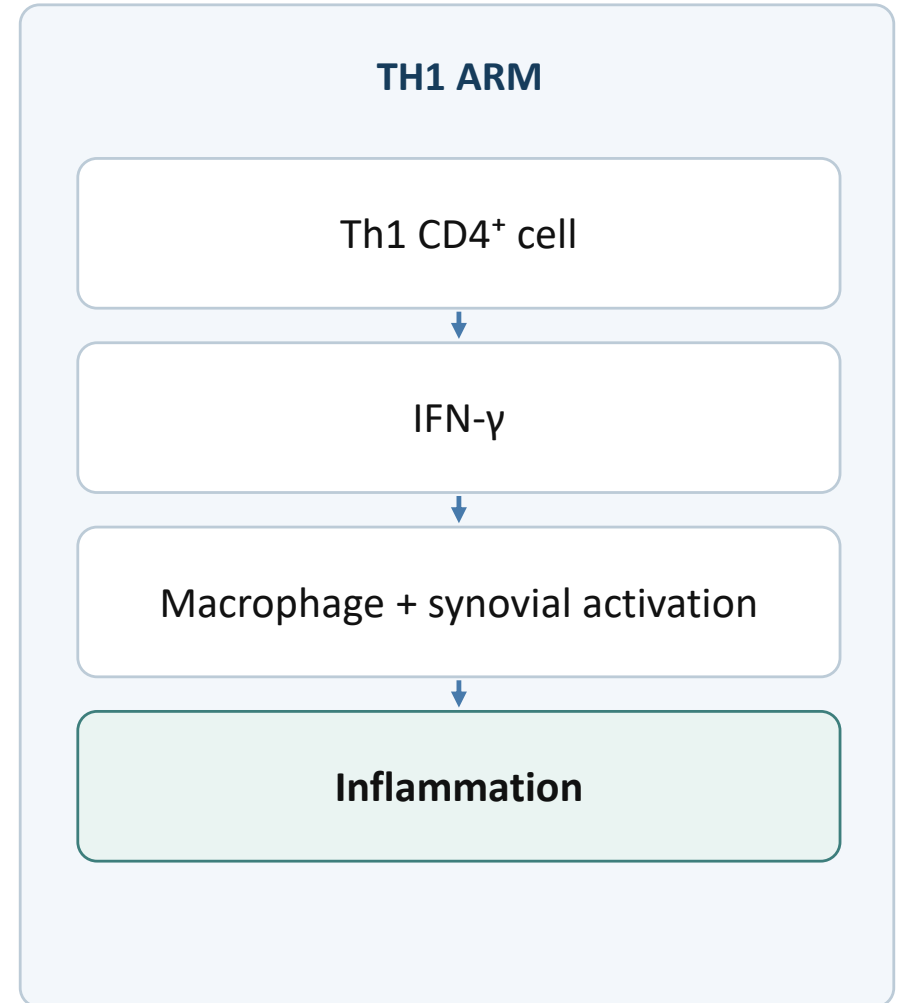
T cells and B cells form an interacting network

- CD4⁺ helper T cells can orchestrate local inflammatory responses.
- B cells and plasma cells provide autoantibodies and lymphoid infiltrates.
- Macrophages release cytokines important in synovitis.
- Inflamed synovial cells, chondrocytes, and osteoclasts execute tissue injury.



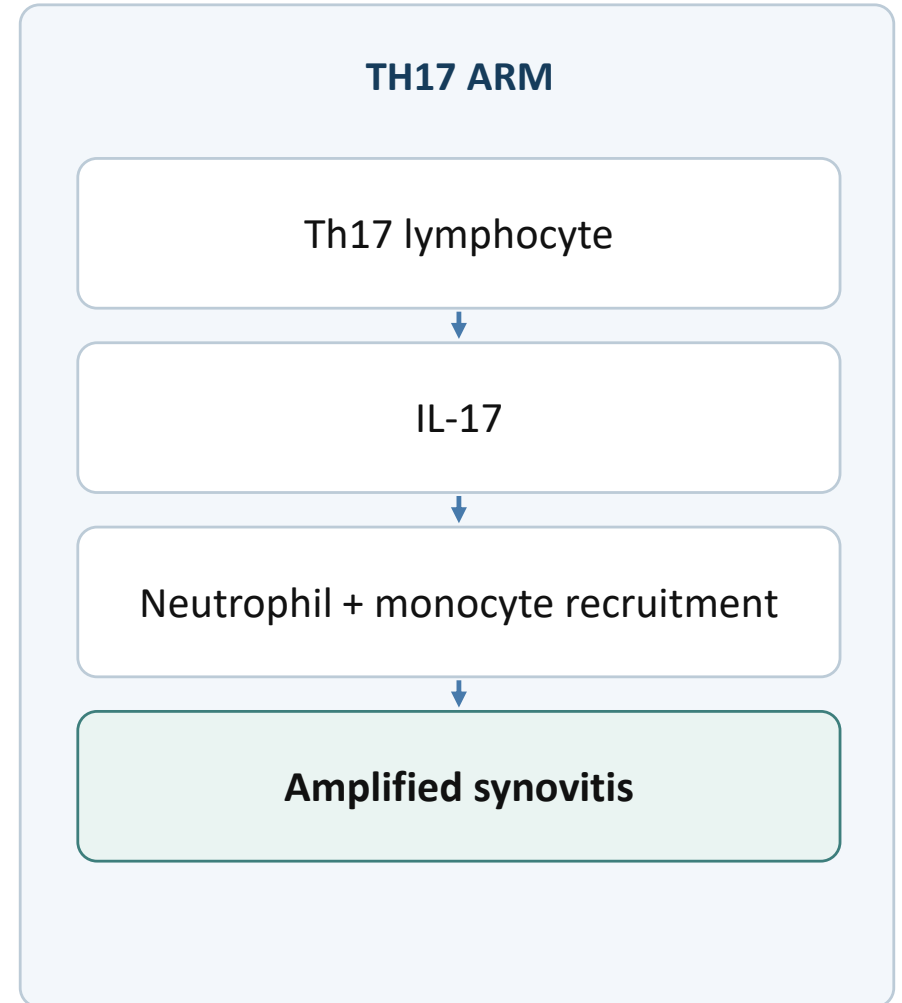
Th1 cells activate inflammatory effector cells

- Th1 is a CD4⁺ T-helper subset implicated in RA.
- Th1-derived interferon- γ (IFN- γ) activates macrophages.
- IFN- γ can stimulate resident synovial cells.
- Macrophage and stromal responses support persistent tissue inflammation.



Th17-derived IL-17 recruits leukocytes

- Th17 cells are another implicated CD4⁺ helper population.
- IL-17 promotes recruitment of neutrophils and monocytes.
- Recruited inflammatory cells reinforce synovitis.
- This differs from the predominantly macrophage-activating action of Th1-derived IFN- γ .



Macrophage cytokines drive synovial destruction

- Macrophages secrete TNF, IL-1, and IL-6 within the inflammatory network.
- These mediators recruit and activate leukocytes.
- They induce synovial cells to release matrix-degrading proteases.
- Enzymatic damage erodes hyaline articular cartilage.

CYTOKINE–MATRIX AXIS

Activated macrophage



TNF / IL-1 / IL-6



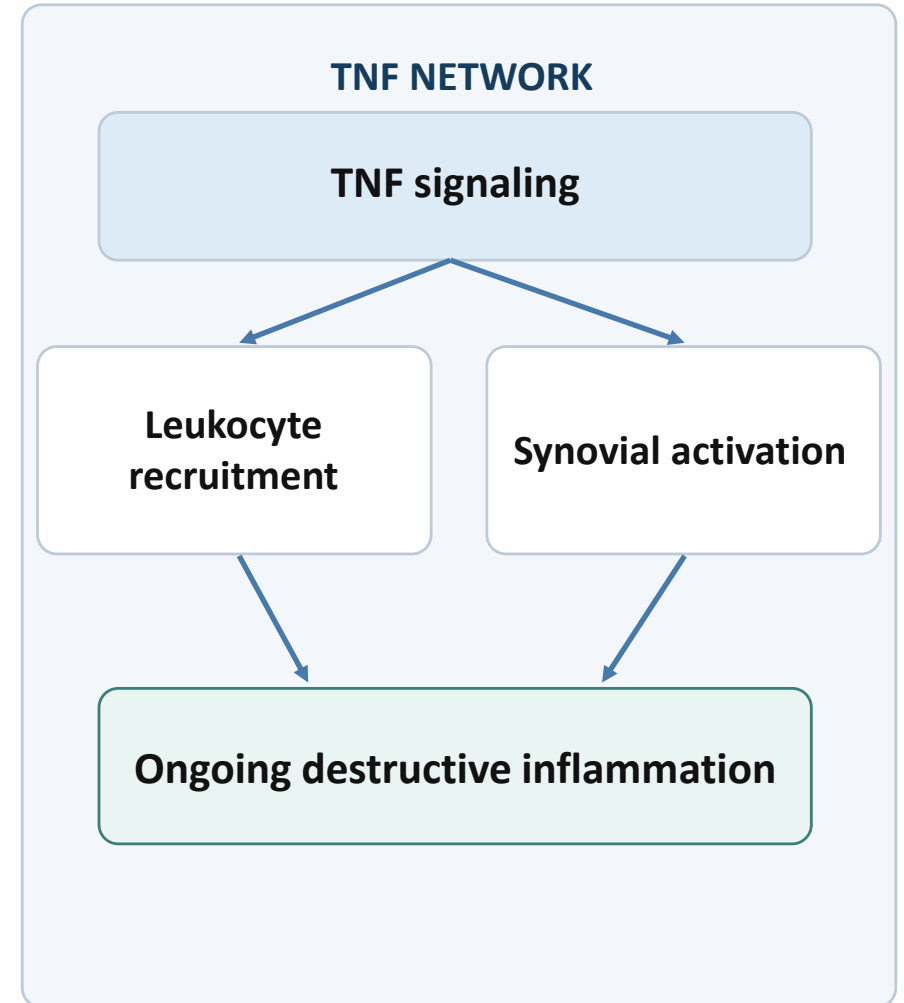
Synovial protease production



Cartilage destruction

TNF is a central inflammatory amplifier

- TNF participates in leukocyte recruitment and tissue inflammation.
- Its activity is implicated in cartilage and joint damage.
- Clinical benefit from TNF antagonists supports its pathogenic importance.
- The response to treatment does not imply that TNF is the sole disease driver.



Proteases link synovitis to cartilage erosion

- Inflammatory cytokines stimulate synovial cells to make proteases.
- These enzymes degrade the extracellular matrix of hyaline cartilage.
- Cartilage loss narrows the functional articulating space.
- Inflammation therefore directly changes load-bearing joint architecture.

PROTEOLYTIC INJURY

Cytokine-exposed synovium



Matrix-degrading proteases



Cartilage matrix loss



Progressive joint damage

RANKL promotes osteoclastic bone resorption

- Activated T cells can express receptor activator of NF- κ B ligand (RANKL).
- RANKL stimulates osteoclast formation or activation.
- Activated osteoclasts resorb bone adjacent to inflamed synovium.
- This provides a cellular mechanism for periarticular erosions.

BONE RESORPTION AXIS

Activated T cell



RANKL expression



Osteoclast activation



Periarticular bone erosion

Antibodies may participate in joint inflammation

- Synovial B cells and plasma cells can secrete autoantibodies.
- RF-containing complexes may accumulate in joint tissues.
- The source considers humoral immunity contributory but not the only injury mechanism.
- Serologic activity and morphologic injury must be interpreted together.

HUMORAL COMPONENT

Autoantibody synthesis



Immune complexes



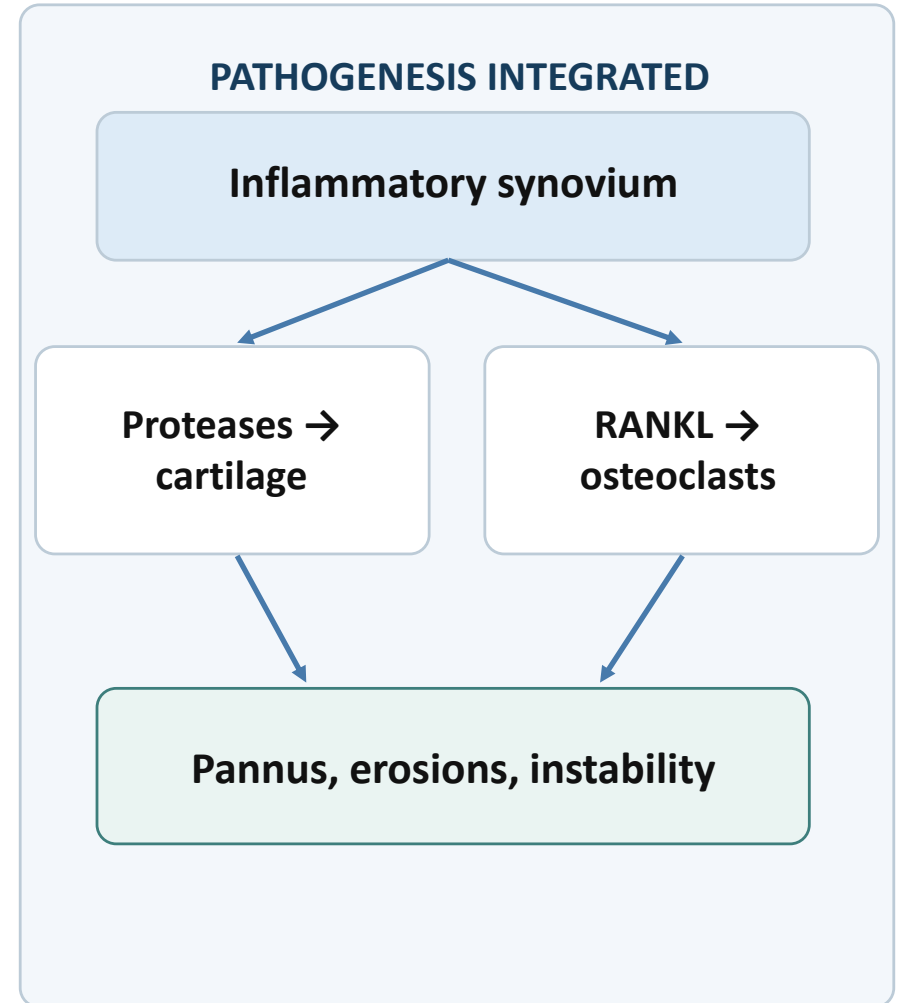
Local inflammatory response



Potential synovial injury

Multiple mechanisms converge at the synovium

- CD4⁺ T-cell cytokines recruit and stimulate inflammatory cells.
- Macrophage mediators drive protease release and cellular activation.
- Osteoclasts erode bone; Proliferating synovium erodes cartilage.
- The integrated lesion is a chronically inflamed, destructive pannus.

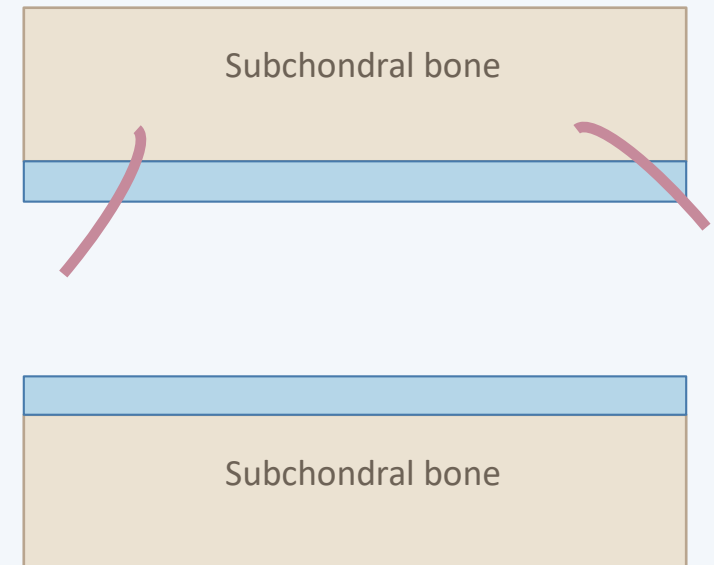


Normal joint anatomy defines the target tissues

- Articular cartilage covers the opposing bone surfaces.
- Synovial lining borders the noncartilaginous inner joint surface.
- Subchondral bone supports the articular cartilage.
- RA preferentially creates proliferative inflammatory synovium at these interfaces.

ANATOMIC REFERENCE

Joint section — schematic



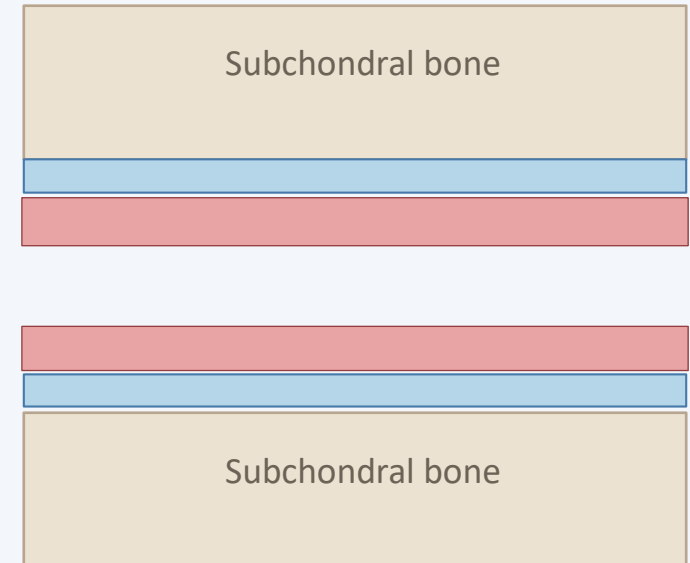
Intact cartilage + thin synovium

Early synovitis begins with edema and thickening

- The synovial membrane becomes edematous and expanded.
- Synovial cells proliferate, creating an abnormally thick lining.
- Chronic inflammation accumulates beneath the lining.
- These early changes precede advanced structural destruction.

EARLY MORPHOLOGY

Joint section — schematic



Synovial expansion

Synovial lining hyperplasia is a hallmark

- The normally thin synovial cell population undergoes proliferation.
- Thickened lining increases the volume of actively inflamed synovium.
- The surface no longer retains its usual smooth appearance.
- Hyperplasia contributes to pannus rather than forming a benign neoplastic mass.

HISTOLOGIC FEATURE 1

Synovial cell proliferation

Thickened lining surface

Inflammatory stromal expansion

Foundation for pannus

Villous change reflects synovial proliferation

- The expanded synovium forms delicate or bulbous villous projections.
- The villi contain inflamed and often vascular stromal tissue.
- This describes gross/microscopic synovial architecture, not osteophyte formation.
- The resulting membrane can extend over articular surfaces.

SYNOVIAL ARCHITECTURE

Synovial edema



Lining hyperplasia



Bulbous / delicate villi



Expanding inflamed membrane

Inflammatory infiltrates are mixed and chronic

- CD4⁺ T cells, B cells, plasma cells, dendritic cells, and macrophages are prominent.
- Cellular infiltrates often become dense in the synovium.
- B cells may organize into follicle-like aggregates.
- The infiltrate is a substrate for locally amplified immune responses.

HISTOLOGIC FEATURE 2

CD4⁺ helper T cells

B cells and plasma cells

Dendritic cells

Macrophages

Lymphoid follicle formation indicates organization

- Synovial B cells can form secondary lymphoid follicle-like structures.
- Germinal-center-type organization is described in RA synovium.
- Plasma cells are often abundant in surrounding inflammatory tissue.
- Such organization helps explain local autoantibody production.

FOLLICULAR IMMUNITY

B-cell accumulation



Lymphoid follicle formation



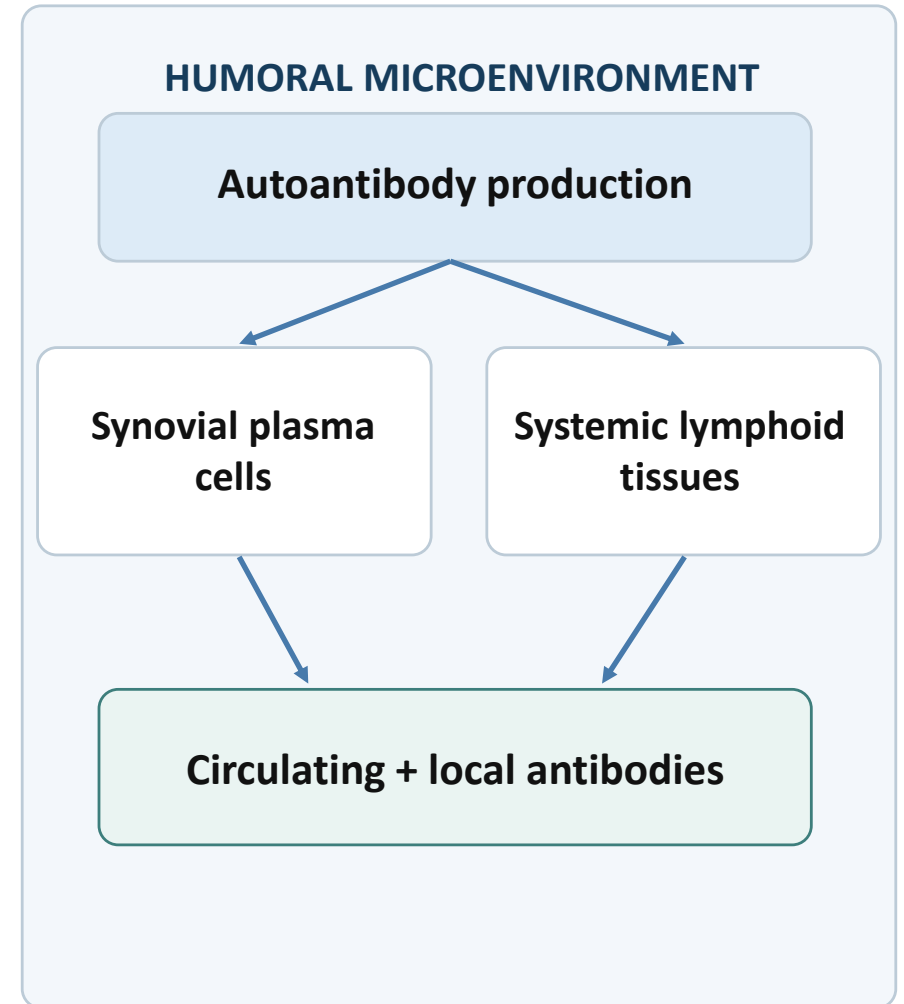
Plasma cell differentiation



Local antibody production

Synovial plasma cells sustain humoral activity

- Plasma cells within RA synovium secrete immunoglobulins.
- A proportion of these immunoglobulins recognize self-antigens.
- Autoantibody production also occurs in lymphoid organs outside joints.
- Local antibodies coexist with cellular cytokine-driven tissue destruction.



Angiogenesis sustains the inflammatory pannus

- The synovium develops increased vascularity through angiogenesis.
- New vessels accompany chronically inflamed proliferating tissue.
- The vascular network facilitates continued arrival of leukocytes.
- Angiogenesis is one of the characteristic histologic changes in RA.

HISTOLOGIC FEATURE 3

Chronic synovitis



Angiogenic response



Expanded vascular supply



Sustained cell recruitment

Fibrin-rich surface exudate is characteristic

- Fibrin-rich exudates may cover the synovial and joint surfaces.
- Neutrophils can be present within the exudate.
- This feature is compatible with inflammatory synovitis despite the term “nonsuppurative.”
- It must not be confused with the purulent fluid of bacterial septic arthritis.

HISTOLOGIC FEATURE 4

Surface fibrin

Neutrophils in exudate

Chronically inflamed synovium

Not equivalent to septic pus

Osteoclasts create marginal bone erosions

- Osteoclastic activity increases in adjacent subchondral bone.
- Inflamed synovium can extend into areas of bone resorption.
- Periarticular erosions and subchondral cysts may result.
- The bone loss contrasts with osteophytic remodeling in OA.

HISTOLOGIC FEATURE 5

Synovial inflammation



RANKL / osteoclast response



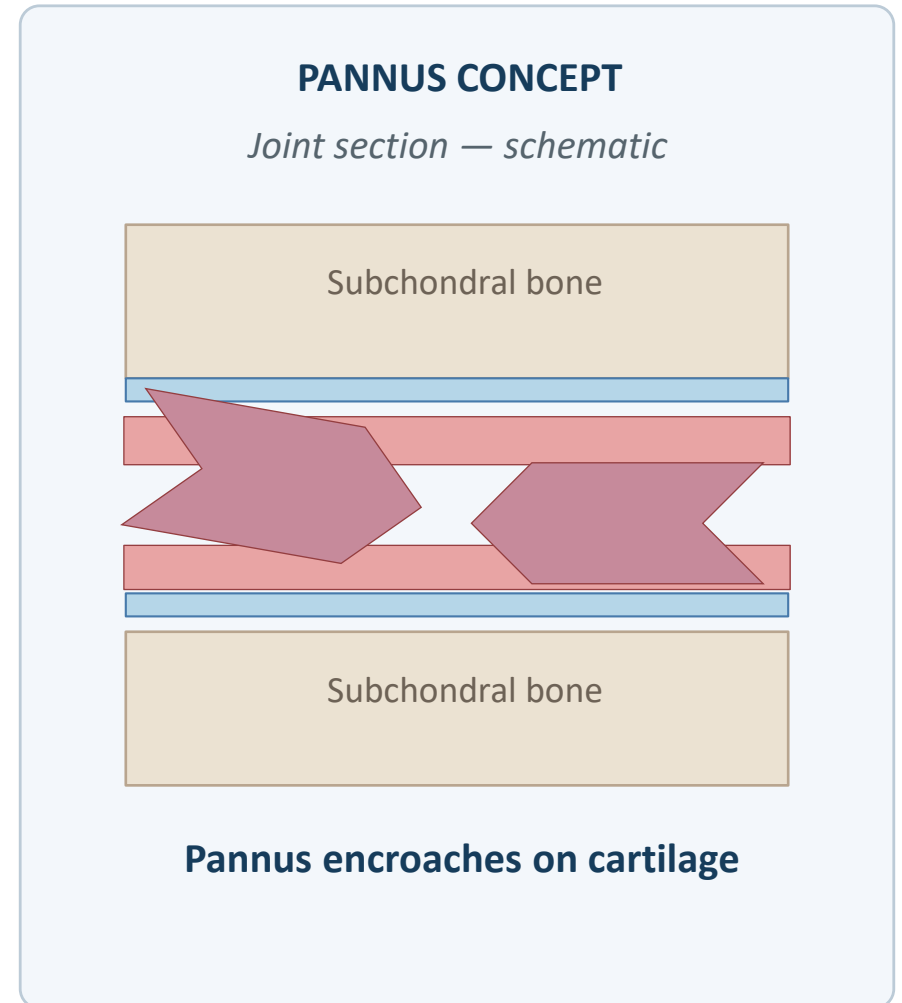
Bone resorption



Marginal erosion + cyst

Pannus is destructive inflammatory tissue

- Pannus contains edematous synovium, inflammatory cells, fibroblasts, and granulation tissue.
- It grows across articular cartilage rather than remaining confined to the lining.
- Proteolysis and cellular invasion progressively damage cartilage.
- Pannus is the defining structural bridge from synovitis to articular destruction.



Pannus extension explains progressive cartilage loss

- Proliferating synovium advances over the joint surface.
- Inflammatory proteases degrade the cartilage matrix.
- Joint-space narrowing follows as cartilage is lost.
- Cartilage erosion and bone resorption contribute to deformity and loss of function.

LOCAL DAMAGE PROGRESSION

Villous proliferative synovium



Pannus over cartilage



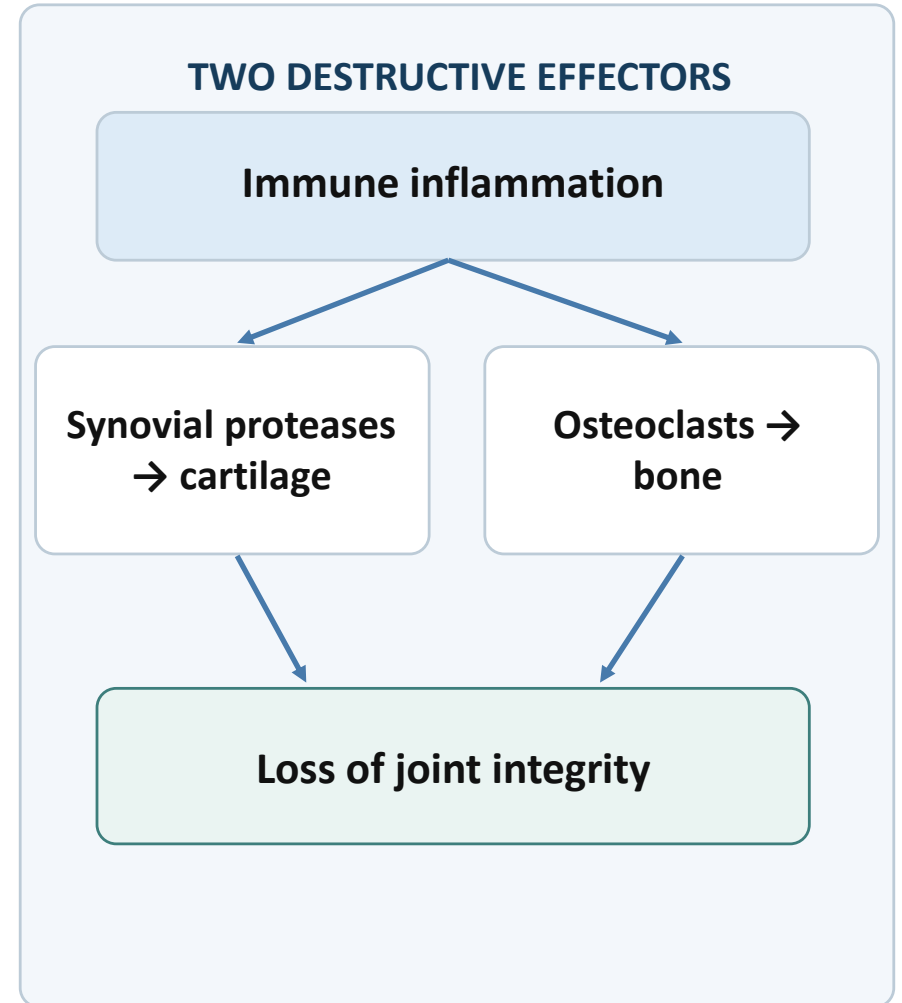
Proteolytic matrix damage



Joint-space narrowing

Cartilage injury and bone erosion are coupled

- Matrix degradation predominantly injures cartilage.
- Osteoclast-mediated resorption erodes subchondral or marginal bone.
- Both changes follow immune activation but involve different cellular effectors.
- Combined damage progressively destabilizes the joint.



Ankylosis develops after severe destruction

- After cartilage destruction, pannus may connect opposing bony surfaces.
- Fibrous tissue can bridge the joint, producing fibrous ankylosis.
- Later ossification can produce bony ankylosis and joint fusion.
- Fusion is a possible advanced consequence—not inevitable for every RA patient.

LATE JOINT OUTCOME

Cartilage destruction



Pannus bridges joint



Fibrous ankylosis



Bony ankylosis

Joint remodeling represents a temporal sequence

- Early RA: Edematous, inflamed, hyperplastic synovium.
- Intermediate RA: Destructive pannus with cartilage and bone erosion.
- Advanced RA: Reduced joint space, deformity, or ankylosis.
- The rate and ultimate extent of structural injury vary among patients.

STAGE CONCEPT

Early: Synovitis + villi

Intermediate: Pannus + erosion

Advanced: Deformity ± ankylosis

Five defining morphologic features of RA synovitis

Finding	Tissue process	Pathologic significance
Synovial hyperplasia	Lining-cell proliferation	Expanded intimal membrane
Inflammatory infiltrate	T / B cells, macrophages	Sustained autoimmunity
Angiogenesis	Increased synovial vessels	Chronic inflammatory support
Fibrin-rich exudate	Surface fibrin ± neutrophils	Inflamed joint surface
Osteoclast activity	Bone resorption	Periarticular erosions

Rheumatoid nodules are an extraarticular lesion

- Nodules are described as an infrequent RA manifestation.
- They typically present as small, firm, nontender subcutaneous masses.
- Classic sites include forearms, elbows, occiput, and lumbosacral region.
- Their characteristic pathology differs from destructive synovial pannus.

EXTRAARTICULAR MORPHOLOGY

Forearm / elbow

Occiput

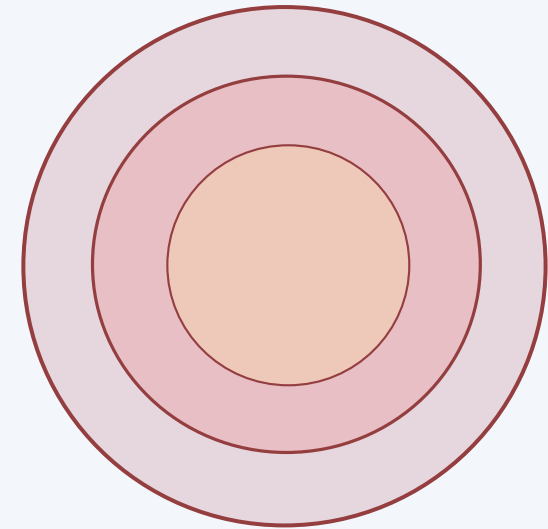
Lumbosacral region

Firm, nontender nodules

Rheumatoid nodules contain central fibrinoid necrosis

- The nodule has a central zone of fibrinoid necrosis.
- Activated macrophages form a surrounding palisading rim.
- Lymphocytes and plasma cells occupy the outer inflammatory zone.
- This organized lesion is a morphologic correlate of systemic RA.

NODULE HISTOARCHITECTURE
Rheumatoid nodule — schematic



Fibrinoid necrosis
Palisaded macrophages

RA-associated vasculitis indicates severe disease

- Severe RA can be associated with leukocytoclastic vasculitis.
- The source describes an acute necrotizing vascular inflammatory pattern.
- Vascular lesions may involve vessels associated with pleura, pericardium, or lung.
- Some organ inflammation can evolve into chronic fibrosis.

SYSTEMIC VASCULAR INJURY

Severe RA



Necrotizing vasculitis



Pleura / pericardium / lung



Possible fibrosing change

Lung and cardiac involvement extend RA beyond joints

- Extraarticular disease may involve the lungs and heart.
- Inflammation in pleural or pericardial regions can occur in severe systemic disease.
- Chronic inflammatory injury can produce fibrosing consequences.
- Organ findings require clinicopathologic interpretation rather than assuming joint-limited illness.

SYSTEMIC DISTRIBUTION

Pulmonary involvement

Pleural inflammation

Pericardial inflammation

Possible chronic fibrosis

Ocular inflammation is a recognized complication

- Uveitis among possible RA-associated ocular findings.
- Keratoconjunctivitis may also develop.
- Dry-eye–type changes can resemble manifestations of Sjögren syndrome.
- Ocular disease is part of the differential assessment of systemic manifestations.

OCULAR INVOLVEMENT

Uveitis

Keratoconjunctivitis

Overlap with sicca patterns

Some patients have a systemic prodrome

- About half of patients are described as developing malaise, fatigue, and generalized pain initially.
- Joint involvement may follow over weeks to months.
- This prodrome can precede an easily recognized inflammatory polyarthritis.
- Clinical chronology therefore contributes to suspicion of RA.

EARLY PRESENTATION

Malaise and fatigue



General musculoskeletal pain



Weeks to months



Inflammatory joint disease

RA usually begins in small peripheral joints

- Symptoms commonly first affect the hands and feet.
- Wrist and ankle involvement may follow.
- Elbow and knee involvement is also described.
- The common distribution is symmetric, although the pattern can vary.

ANATOMICAL DISTRIBUTION

Hands and feet first

Wrists and ankles next

Elbows and knees later

Often symmetric

MCP and PIP joint disease is characteristic

- In the hand, RA commonly affects metacarpophalangeal (MCP) joints.
- Proximal interphalangeal (PIP) joints are another typical site.
- This pattern helps distinguish RA from the characteristic OA distribution.
- Foot small-joint involvement adds diagnostic context.

HAND JOINT PATTERN

Typical hand involvement

MCP

Involved

PIP

Involved

Small foot joints

Involved

DIP

Not emphasized

Inflammatory pain is worse after rest

- Involved RA joints are painful, warm, and swollen.
- Pain commonly worsens in the morning or after inactivity.
- This timing contrasts with pain associated chiefly with joint use in OA.
- Symptoms reflect active synovial inflammation rather than only structural wear.

SYMPTOM QUALITIES

RA pain pattern

Morning or post-rest pain
Warm, swollen joints

OA pain pattern

Use-related mechanical pain
Less primary synovitis

Chronic disease impairs joint movement

- Many patients experience a waxing-and-waning inflammatory course.
- Over time, the joints may enlarge and lose range of motion.
- Progressive cartilage loss, erosions, and deformity impair function.
- A minority—often seronegative—may stabilize or regress.

FUNCTIONAL OUTCOME

Recurrent inflammation



Structural damage



Enlarged / deformed joints



Reduced range of motion

ACPA is useful but does not replace examination

- ACPA detection supports RA among inflammatory polyarthritides.
- The serum test is not positive in every patient.
- Its meaning must be integrated with joint pattern and evidence of inflammation.
- A negative result cannot independently exclude RA.

SEROLOGIC REASONING

Clinical inflammatory arthritis



ACPA testing



Interpret result in context



Integrate with imaging

Rheumatoid factor requires cautious interpretation

- RF supports diagnosis but is not unique to RA.
- A substantial majority of patients may be RF positive.
- Some individuals without RA have measurable RF.
- Absence of RF does not remove the possibility of RA.

TEST LIMITATIONS

RF positive $\neq$ proof of RA

RF negative $\neq$ exclusion

Interpret with ACPA + clinic

Seronegative RA remains a clinical diagnosis

- Approximately 20% of RA patients are seronegative.
- Negative ACPA and RF do not automatically negate clinically compatible RA.
- Joint distribution and characteristic radiographic changes remain important.
- Synovial tissue biopsy is rarely required.

DIAGNOSTIC PITFALL

Inflammatory joint findings



ACPA / RF may be negative



Clinical + radiographic correlation



RA still possible

Imaging reveals accumulated structural injury

- Typical described changes include juxtaarticular osteopenia.
- Periarticular bone erosions provide evidence of destructive arthritis.
- Loss of articular cartilage is associated with joint-space narrowing.
- These changes are complementary to clinical and serologic evaluation.

RADIOGRAPHIC MORPHOLOGY

Juxtaarticular osteopenia

Periarticular erosions

Joint-space narrowing

Cartilage loss

Diagnosis is a synthesis, not a single marker

- Examine for persistent inflammatory and often symmetric peripheral arthritis.
- Assess typical small-joint distribution, swelling, warmth, and post-rest symptoms.
- Use ACPA and RF as supportive laboratory evidence.
- Evaluate imaging for erosions, osteopenia, and joint-space loss.

DIAGNOSTIC WORKFLOW

Clinical pattern



Serology



Radiographic morphology



Integrated RA assessment

Rheumatoid arthritis versus osteoarthritis: Mechanism

Category	Rheumatoid arthritis	Osteoarthritis
Primary driver	Autoimmune synovitis	Mechanical cartilage injury
Inflammation	Central pathogenic component	Often secondary to injury
Structural lesion	Pannus, erosions	Cartilage breakdown, osteophytes
Antibodies	ACPA and/or RF may occur	None characteristic
Systemic disease	Possible lung / heart involvement	Not typical

Rheumatoid arthritis versus osteoarthritis: Presentation

Category	Rheumatoid arthritis	Osteoarthritis
Joint pattern	Small peripheral; Symmetric	Often weight-bearing
Hand pattern	MCP / PIP emphasized	Different hand-joint distribution
Pain timing	Morning / following inactivity	Typically related to use
Pathology	Hyperplastic inflamed pannus	Cartilage fragmentation, osteophytes
Late outcome	Erosions; Possible ankylosis	Degeneration; No typical ankylosis

Therapy targets inflammation and structural injury

- Clinical aims include pain relief and reduction of inflammatory activity.
- Disease-modifying treatment seeks to slow or arrest joint destruction.
- The source describes glucocorticoids and methotrexate among treatments.
- Biologic therapies target mediators or lymphocyte responses.

PATHOLOGY–TREATMENT LINK

Suppress inflammation



Reduce synovial activation



Limit cartilage / bone injury



Preserve joint function

TNF inhibition validates a major disease mechanism

- Therapeutic TNF antagonism provides strong support for TNF-mediated injury.
- Biologic inhibition may control inflammation but does not cure RA.
- Disease flares can follow discontinuation of effective TNF blockade.
- Prolonged anti-TNF therapy increases susceptibility to opportunistic infection, including tuberculosis.

BENEFIT–RISK CONTEXT

TNF blockade



Lower inflammatory signaling



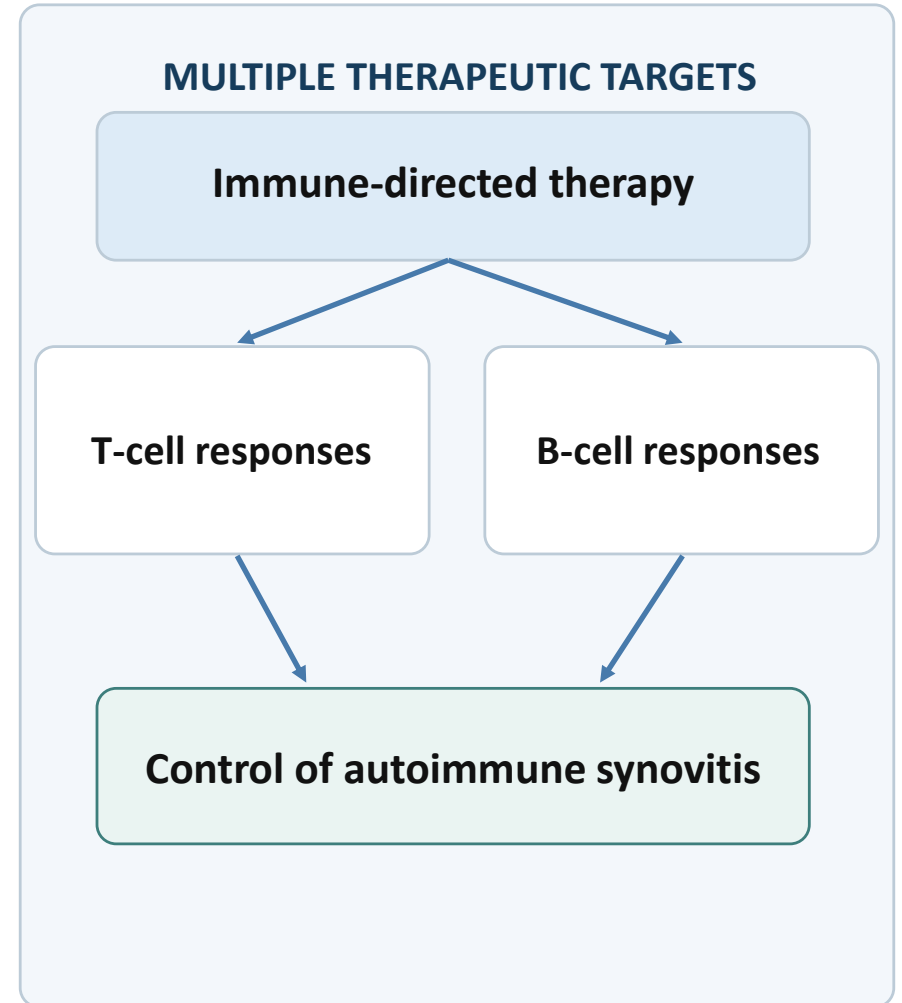
Reduced disease activity



Infection risk: E.g. Tuberculosis

Targeting T and B cells reflects immune complexity

- T cells orchestrate cytokine-mediated inflammation.
- B cells and plasma cells provide an autoantibody component.
- Additional biologic agents that interfere with T- and B-cell responses.
- This mechanistic diversity helps explain why RA cannot be reduced to one cytokine.



Case interpretation: Symmetric small-joint arthritis

An adult has swelling, warmth, and pain in symmetric MCP and PIP joints. Symptoms are most troublesome after waking or prolonged inactivity.

Clinicopathologic questions

- Which aspects favor inflammatory RA over OA?
- What tests and radiographic features would provide additional support?

Case interpretation: Pathology-to-clinic

- Persistent synovitis accounts for warmth, swelling, and post-rest discomfort.
- Hyperplasia, angiogenesis, and immune infiltrates expand synovial tissue.
- Protease-rich pannus produces cartilage loss and joint-space narrowing.
- Osteoclastic activity produces characteristic periarticular erosions.

CASE SOLUTION

Synovitis



Joint warmth + swelling



Pannus + osteoclasts



Cartilage loss + erosion

Case interpretation: Seronegative erosive disease

A patient has persistent symmetric small-joint inflammatory arthritis and erosive radiographic change, but both ACPA and RF are reported negative.

Clinicopathologic questions

- Can rheumatoid arthritis still be considered?
- Why is joint biopsy usually not the next routine step?

Case interpretation: Negative serology is not exclusion

- Antibodies are probabilistic adjuncts, not defining tissue lesions.
- A compatible symmetric inflammatory phenotype can persist despite negative markers.
- Radiographic erosions provide structural corroboration.
- A negative serologic result should prompt integration of all evidence rather than diagnostic closure.

CASE SOLUTION

Clinical phenotype

Radiographic structural injury

Serology interpreted contextually

Synthesis: Immune cells explain morphologic lesions

- Th1 / Th17: IFN- γ and IL-17 support local inflammatory activation and recruitment.
- Macrophages: TNF, IL-1, and IL-6 stimulate destructive synovial responses.
- T-cell RANKL: Osteoclastic bone erosion.
- B cells / plasma cells: ACPA, RF, and possible immune-complex contributions.

IMMUNE → MORPHOLOGY

Autoreactive T / B cells



Cytokines + antibodies



Proliferative synovitis



Pannus / cartilage / bone injury

Synthesis: Recognize the signature phenotype

- Chronic, often symmetric small-joint inflammatory arthritis.
- Hyperplastic villous synovium with chronic immune infiltration and angiogenesis.
- Destructive pannus with cartilage and bone erosions.
- ACPA/RF often supportive; Systemic manifestations and nodules may occur.

FOUR DIAGNOSTIC ANCHORS

Symmetric MCP / PIP pattern

Inflammatory synovitis

Pannus + erosions

± Antibodies / extraarticular disease

Principal reference and image-use statement

Robbins, Cotran & Kumar

Pathologic Basis of Disease · 11th edition (2026)

Chapter 26, “Bones, Joints, and Soft Tissue Tumors”

Rheumatoid Arthritis, printed pp. 1089–1091

Textbook Table 26.5 supplies the RA–OA comparison.

Figures are original editable schematic representations; no histologic specimen has been simulated.