

Sjögren syndrome

Glandular autoimmunity • morphology • clinical consequences

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Connect glandular immune injury to sicca symptoms and microscopic change.
- Recognize the cellular infiltrate, gland destruction, and B-cell evolution.
- Interpret autoantibodies and extraglandular disease without overclaiming specificity.
- Explain why chronic glandular inflammation raises lymphoma concern.

A disease of exocrine-gland injury

- A chronic autoimmune inflammatory disease preferentially affects lacrimal and salivary glands.
- Loss of functioning secretory tissue produces keratoconjunctivitis sicca and xerostomia.
- The same inflammatory process can extend beyond the principal glands.

Lacrimal gland

↓ Tears



Ocular surface injury

Salivary glands

↓ Saliva

The sicca phenotype links two organ systems

Lacrimal system

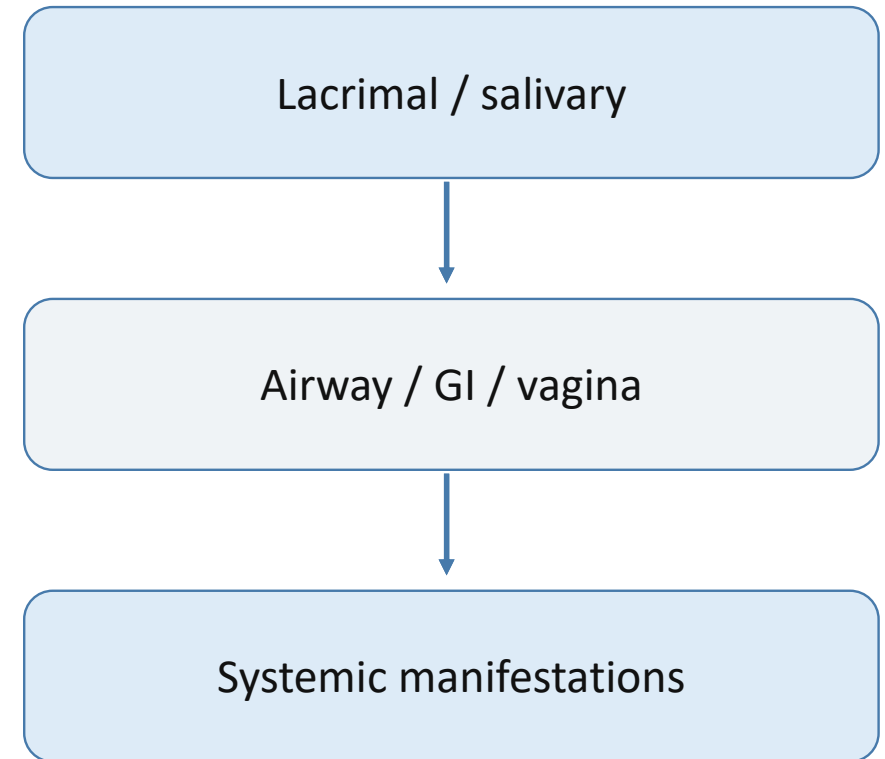
- Reduced tear production
- Ocular surface dryness
- Keratoconjunctivitis sicca

Salivary system

- Reduced salivary secretion
- Oral surface dryness
- Xerostomia

Exocrine targets extend beyond tears and saliva

- The lacrimal and salivary glands are the dominant sites of inflammation.
- Other potentially affected secretory surfaces include respiratory, gastrointestinal, and vaginal mucosa.
- Systemic manifestations are distinct from local dryness, although both belong to the disease spectrum.



Primary and associated presentations

Primary Sjögren syndrome

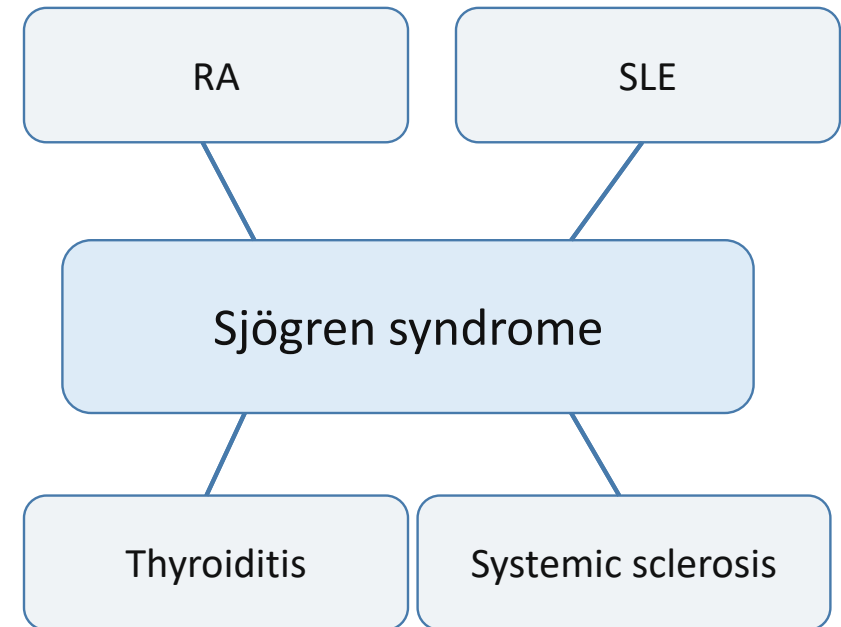
- Occurs as an isolated disorder
- Gland-centered autoimmune manifestations
- Historically described as the “sicca syndrome”

Associated (secondary) form

- Occurs alongside another autoimmune disease
- May coexist with its systemic findings
- Classification depends on the clinical context

Autoimmune diseases reported in association

- Rheumatoid arthritis is the most frequently associated condition in the Robbins description.
- Other associations include systemic lupus erythematosus, systemic sclerosis, myositis, vasculitis, and mixed connective tissue disease.
- Autoimmune thyroiditis also belongs to the reported overlap spectrum.



Patient context and presentation

- Greatest frequency in women aged approximately 50–60 years.
- Presentations may emphasize ocular symptoms, oral symptoms, gland enlargement, or extraglandular findings.
- Clinical pattern and immune markers should be interpreted together rather than in isolation.

Lacrimal gland

↓ Tears

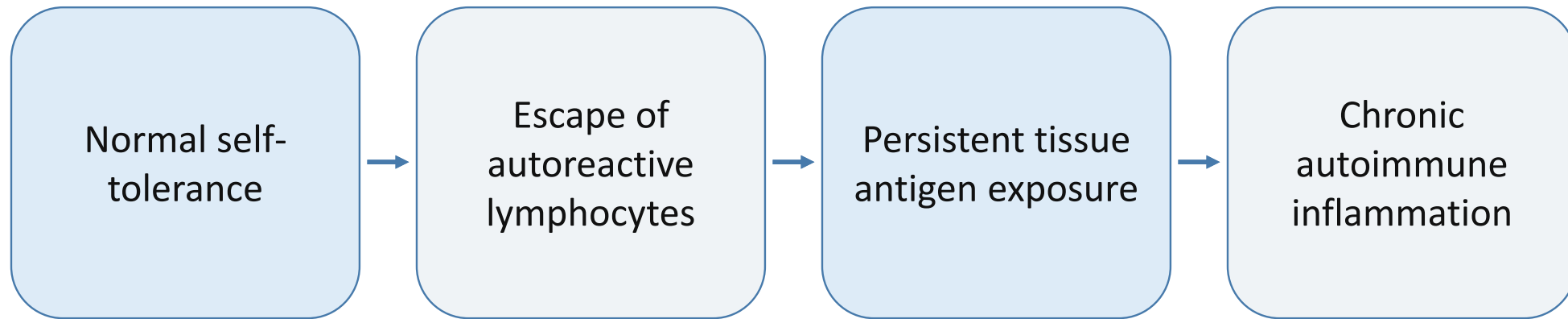


Ocular surface injury

Salivary glands

↓ Saliva

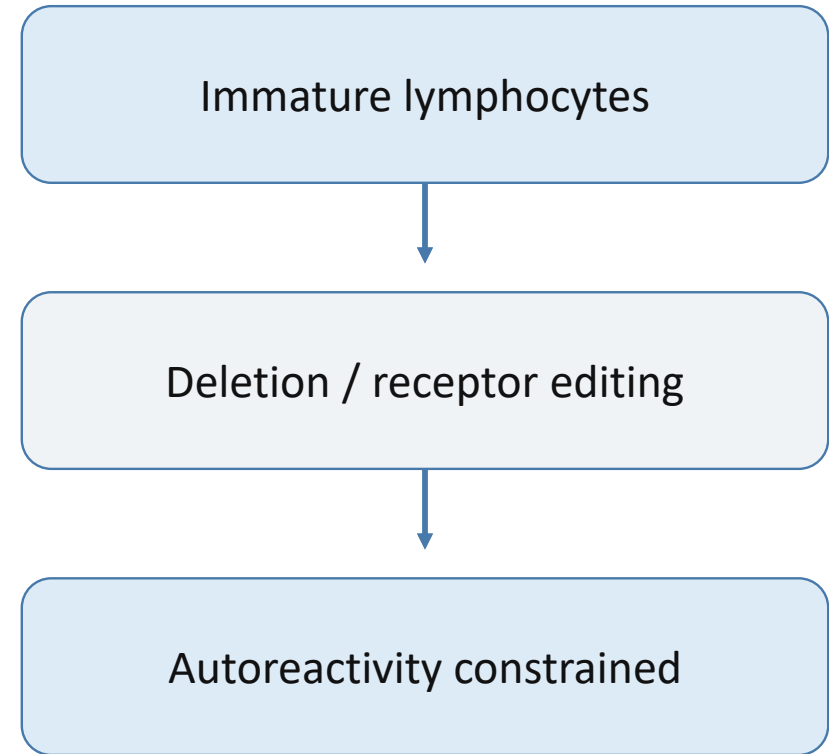
Why self-tolerance matters



Context' autoimmune-tolerance framework; Not a uniquely proven Sjögren pathway.

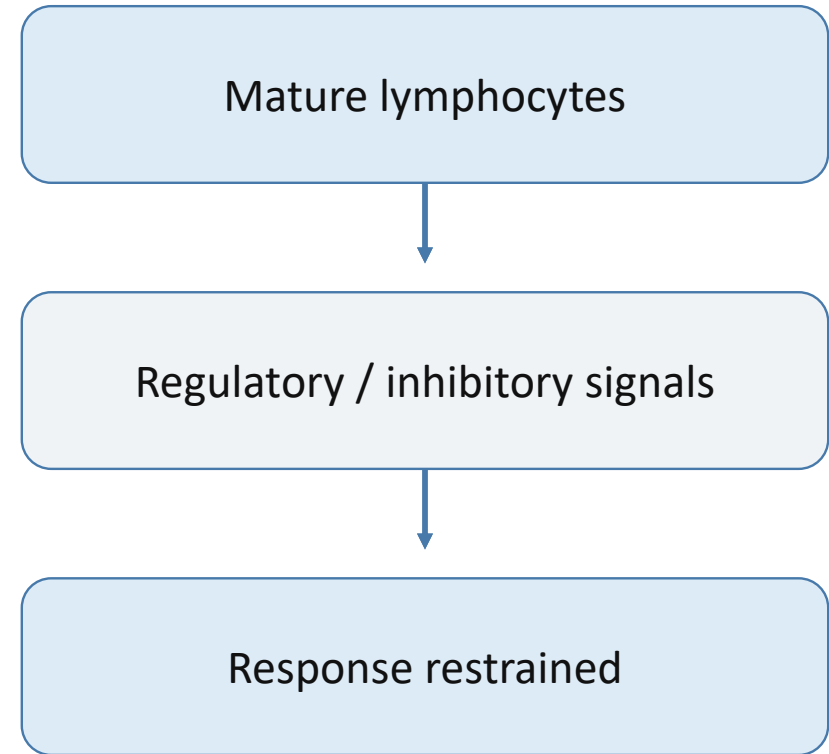
Central tolerance: First safeguard

- Self-reactive immature lymphocytes are normally controlled in generative lymphoid organs.
- Deletion by apoptosis limits persistence of strongly self-reactive clones.
- B-cell receptor editing can replace an autoreactive antigen receptor.



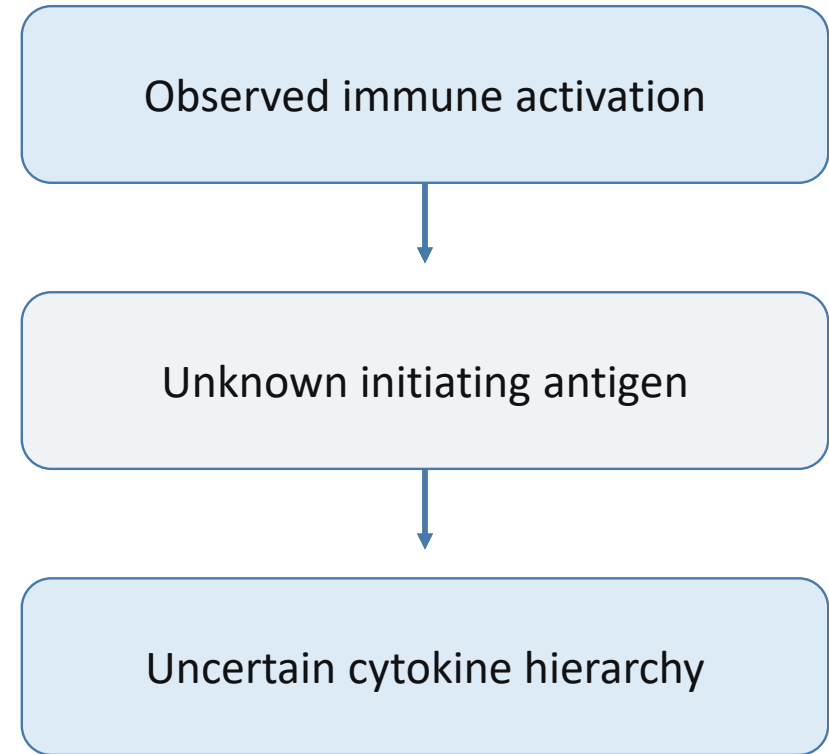
Peripheral tolerance: Secondary safeguard

- Regulatory T cells suppress inappropriate activation of mature lymphocytes.
- Inhibitory signaling through CTLA-4 and PD-1 restrains responses.
- Anergy and apoptosis further reduce responses to self antigens.



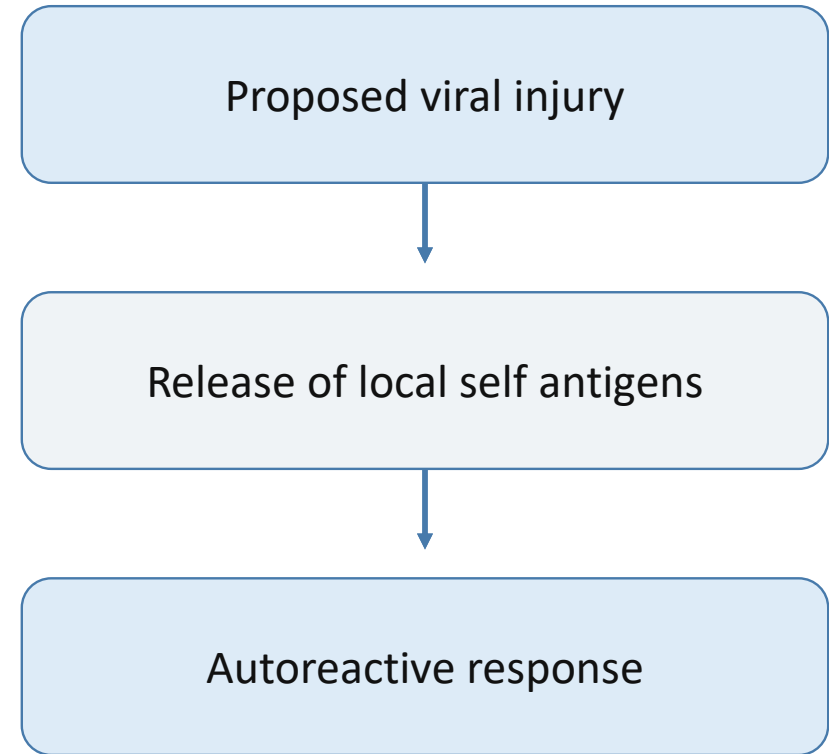
Genetic predisposition is plausible, not deterministic

- Sjögren syndrome has weak reported associations with certain HLA alleles.
- The causal significance of these associations remains uncertain.
- Susceptibility fits the broader autoimmune framework, but no single causal genotype is established here.

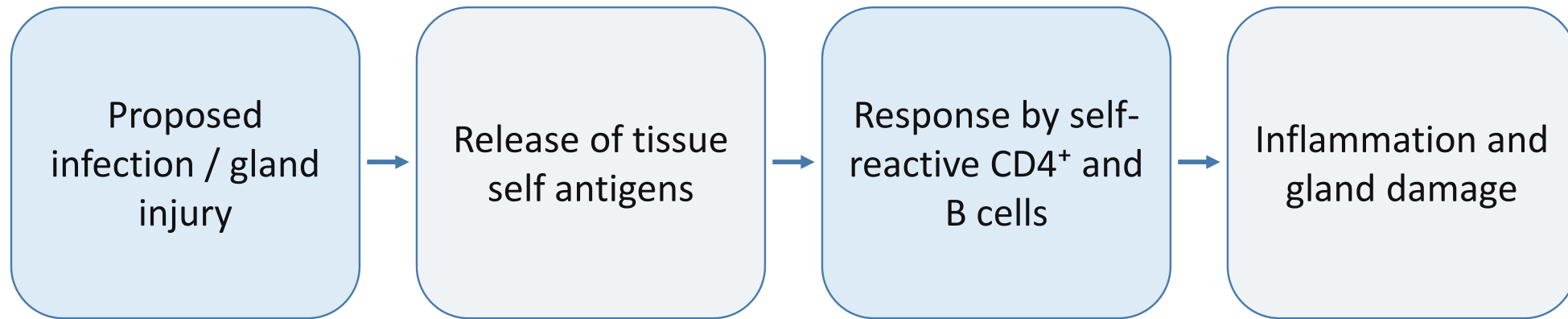


A viral trigger is a hypothesis

- Local salivary-gland infection could injure epithelial cells and expose self antigens.
- Autoreactive lymphocytes that escaped tolerance might respond to those antigens.
- Robbins does not establish a specific virus as the causal agent.



How tissue injury could initiate autoimmunity



Proposed mechanism; Initial trigger and target antigens remain unresolved.

Viral associations are not causal proof

- Sjögren-like presentations have been described with HTLV, HIV, and hepatitis C virus infections.
- The relationship of these infections to the autoimmune disease remains obscure.
- Phenotypic similarity must not be treated as evidence that one infection causes all Sjögren syndrome.

Observed immune activation



Unknown initiating antigen



Uncertain cytokine hierarchy

Mechanistic boundaries

Supported disease features

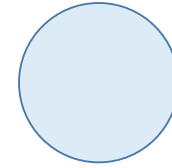
- Aberrant T-cell and B-cell activation
- Glandular immune infiltration
- Progressive destruction and fibrosis

Not yet established

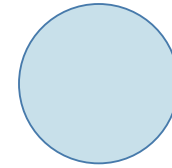
- Initiating autoantigens
- Necessary cytokine or T-helper subsets
- A unique infectious cause

Cellular composition of the infiltrate

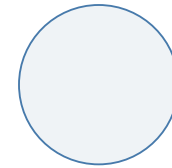
- Activated CD4⁺ helper T cells predominate in involved glands.
- B lymphocytes and plasma cells also contribute to the infiltrate.
- The mixture explains why both cellular injury and circulating autoantibodies are prominent.



CD4⁺ T cell



B lymphocyte

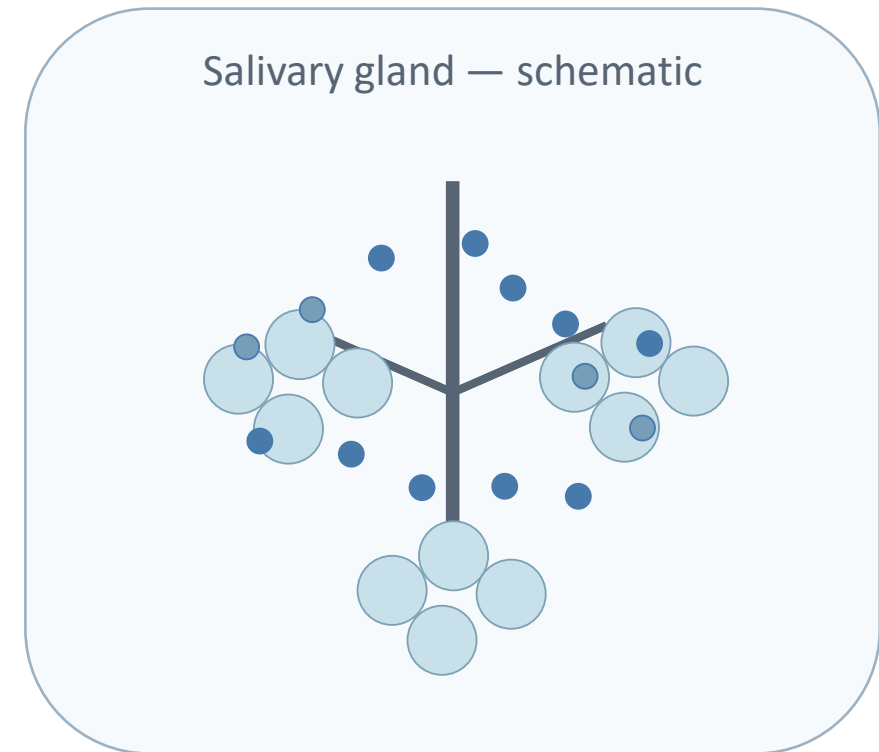


Plasma cell

Mixed immune-cell infiltrate

The gland is the site of the immune reaction

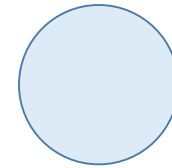
- Inflammatory cells accumulate in relation to glandular ducts and blood vessels.
- Prolonged tissue inflammation progressively compromises gland architecture.
- Secretory failure is therefore an anatomic consequence of immune injury.



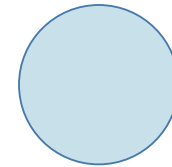
Secretory acini Duct / immune infiltrate
Original conceptual schematic; Not a histologic specimen

Activated CD4⁺ T cells are prominent

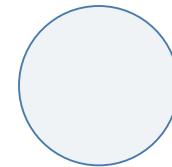
- A CD4⁺-rich infiltrate is a central morphologic observation.
- The specific self antigens recognized by participating T cells remain unknown.
- The roles of proposed cytokines or precise T-cell subsets are not resolved by the source.



CD4⁺ T cell



B lymphocyte



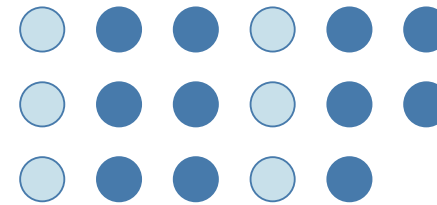
Plasma cell

Mixed immune-cell infiltrate

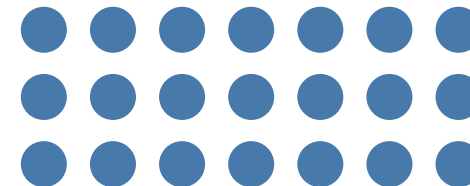
B cells participate from early inflammation

- Early salivary-gland infiltrates contain a mixture of polyclonal T and B cells.
- B-cell stimulation contributes to a broad autoantibody repertoire.
- Persistence of this response creates a setting for clonal B-cell selection.

Initially mixed infiltrate

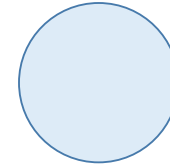


Potential dominant B-cell clone

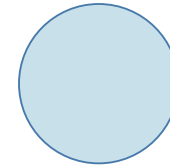


Plasma cells connect tissue and serology

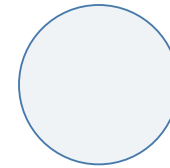
- Plasma cells are present within inflammatory gland infiltrates.
- Humoral autoimmunity can be detected through RF, ANA, and anti-Ro/anti-La assays.
- A positive antibody result is a marker of immune activity, not direct proof of its pathogenic role.



CD4⁺ T cell



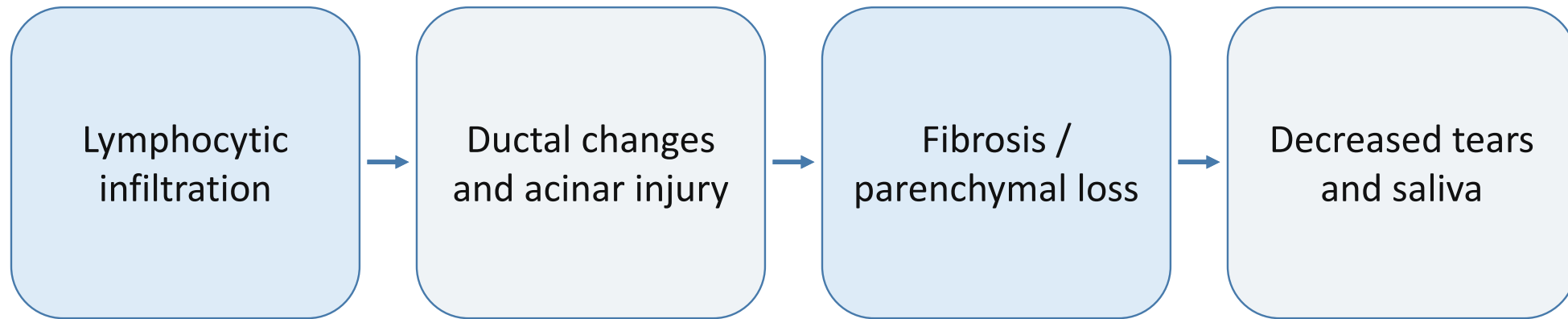
B lymphocyte



Plasma cell

Mixed immune-cell infiltrate

Sustained inflammation impairs secretion



Anatomic sequence integrating Robbins' morphology with its clinical consequences.

Rheumatoid factor is frequent but nonspecific

- Approximately 75% of patients have rheumatoid factor.
- Rheumatoid factor reacts with self IgG.
- Its detection does not imply that the patient also has rheumatoid arthritis.

RF

IgG-reactive
autoantibody

ANA

Broad nuclear reactivity

Ro / La

Ribonucleoprotein
antigens

Antinuclear antibodies are common

- ANA positivity is reported in roughly 50–80% by immunofluorescence assay.
- ANA is a broad serologic finding shared by several autoimmune diseases.
- A positive ANA alone cannot establish Sjögren syndrome.

RF

IgG-reactive
autoantibody

ANA

Broad nuclear reactivity

Ro / La

Ribonucleoprotein
antigens

Anti-SS-A/Ro and anti-SS-B/La

- SS-A (Ro) and SS-B (La) are ribonucleoprotein-associated autoantigens.
- Antibodies targeting these antigens are important serologic markers in the Robbins account.
- Detection varies by assay; The text describes positivity in as many as 90% using sensitive techniques.

RF

IgG-reactive
autoantibody

ANA

Broad nuclear reactivity

Ro / La

Ribonucleoprotein
antigens

Serologic specificity has limits

What positive Ro/La supports

- An autoimmune sicca context
- A disease-associated humoral response
- Useful supportive serology

What it does not prove

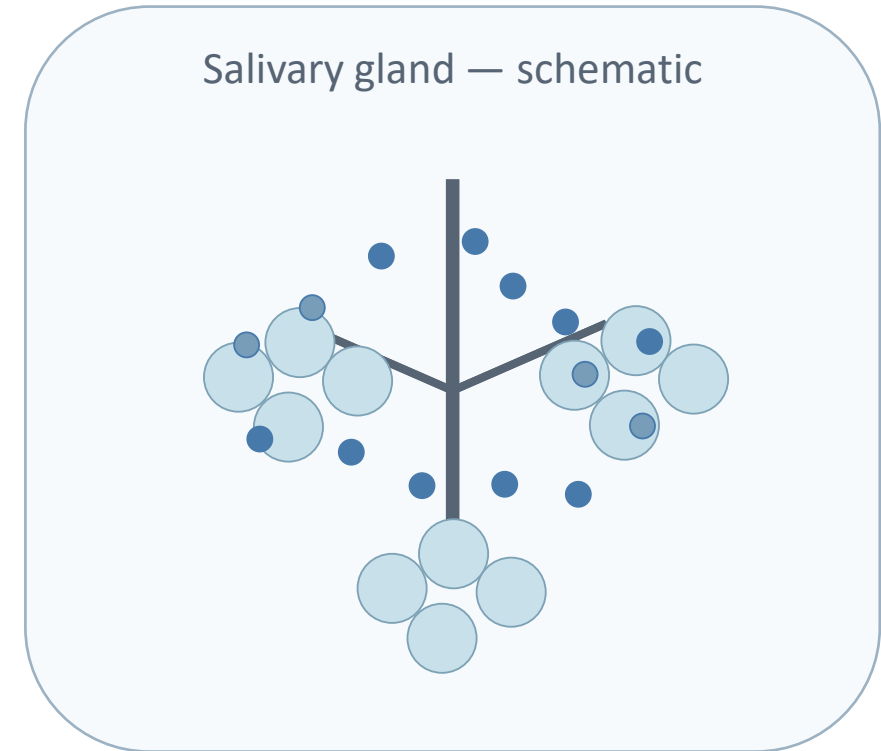
- Exclusive specificity for Sjögren syndrome
- That glandular injury is antibody-mediated
- A complete diagnosis without clinical context

Interpret serologic results as a pattern

Marker	Robbins frequency	Interpretive caution
Rheumatoid factor	About 75%	Not synonymous with rheumatoid arthritis
ANA (IFA)	50–80%	Broad autoimmune marker
Ro/La antibodies	Up to 90% by sensitive methods	May occur in SLE

Earliest salivary-gland lesion

- The earliest described finding is periductal and perivascular lymphocytic infiltration.
- An initially localized infiltrate precedes widespread architectural loss.
- The spatial distribution is important because it links inflammation to ducts and vessels.



Secretory acini

Duct / immune infiltrate

Original conceptual schematic; Not a histologic specimen

Periductal and perivascular are different landmarks

Periductal

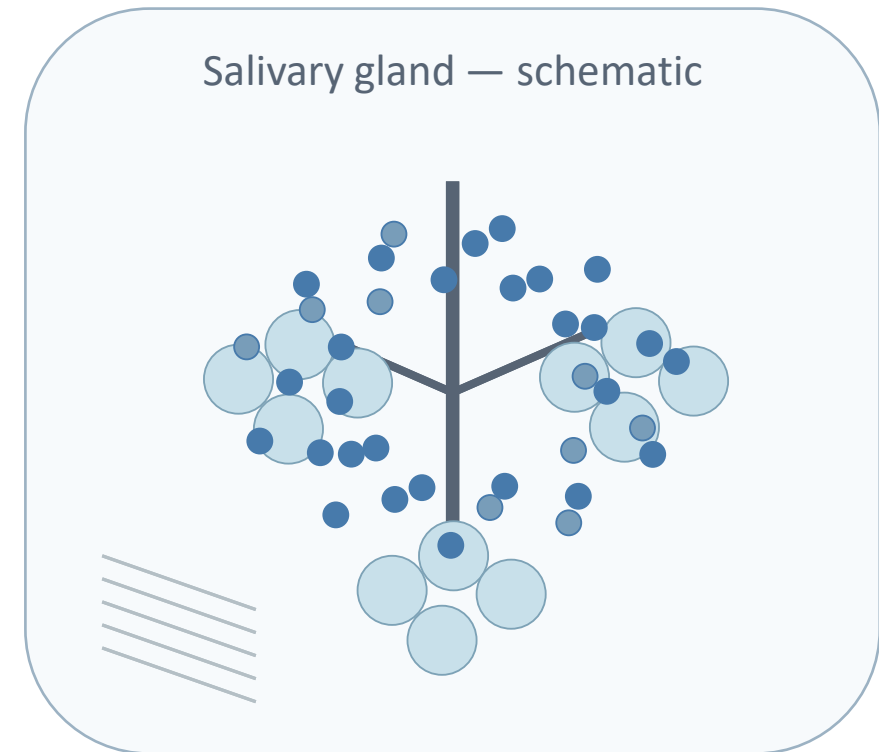
- Immune cells collect around ducts
- Duct epithelium may subsequently proliferate
- Obstruction may follow epithelial hyperplasia

Perivascular

- Immune cells collect near vessels
- Occurs early in involved glands
- A second landmark of localized inflammation

Inflammatory infiltrates may become extensive

- With progression, lymphocytes occupy increasing portions of glandular parenchyma.
- The expansion occurs alongside loss of normal acinar organization.
- The density of lymphocytes can eventually resemble a lymphoid neoplasm.



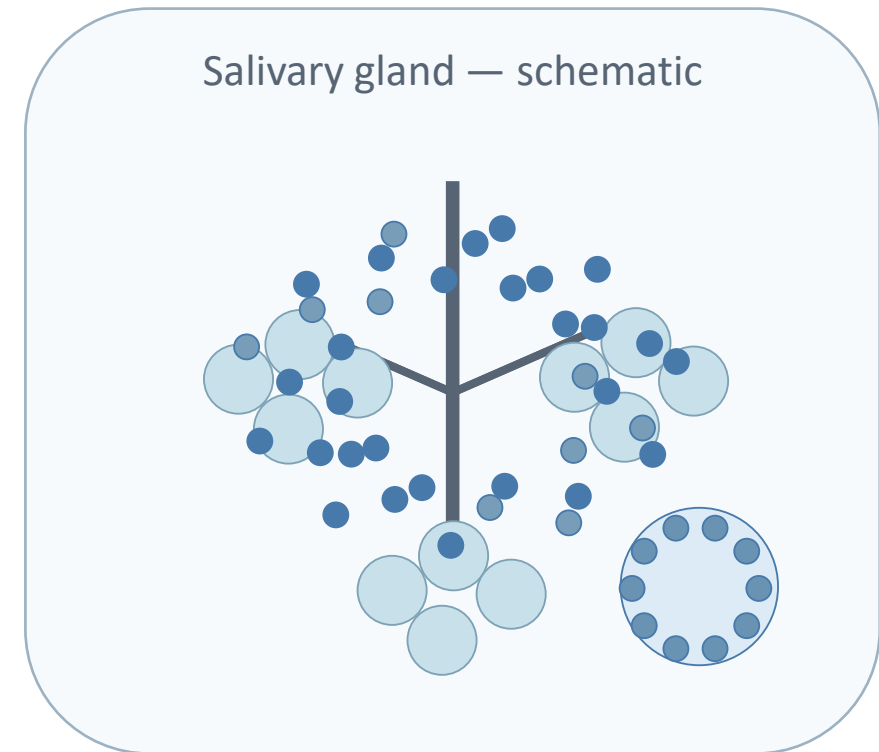
Secretory acini

Duct / immune infiltrate

Original conceptual schematic; Not a histologic specimen

Lymphoid follicles may form

- Lymphoid follicles, sometimes with germinal centers, may appear in affected glands.
- This represents organized lymphoid tissue within a chronically inflamed organ.
- Follicle formation underscores persistent B-cell activity but is not itself a lymphoma diagnosis.



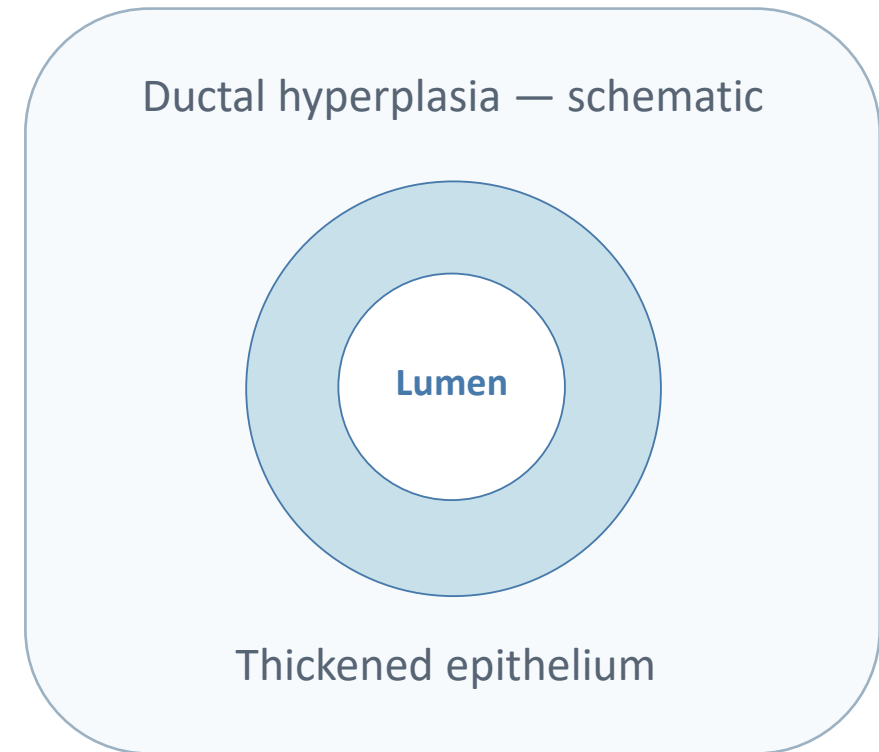
Secretory acini

Duct / immune infiltrate

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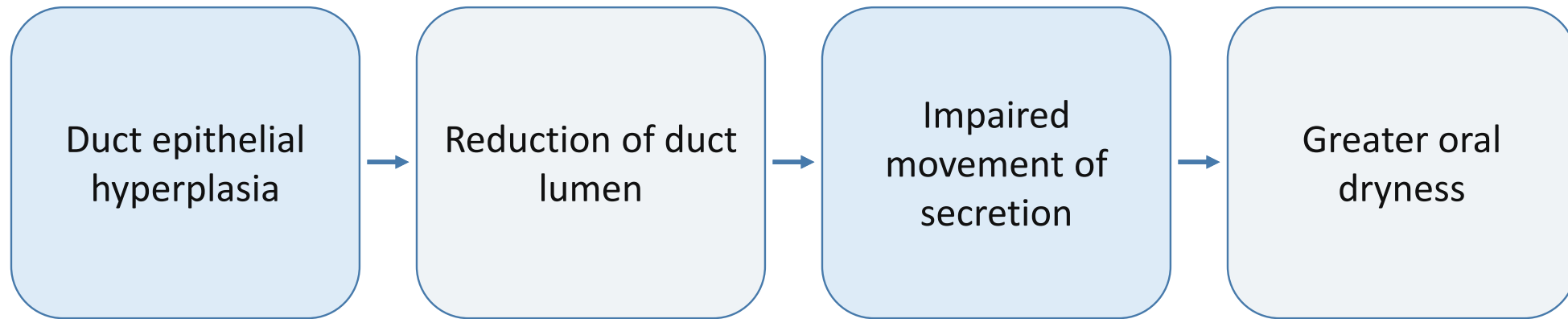
Ductal epithelial hyperplasia

- The epithelial lining of salivary ducts may become hyperplastic.
- Luminal narrowing or obstruction can result from this proliferation.
- Secretory dysfunction therefore reflects both parenchymal damage and altered ductal architecture.



Original conceptual schematic; Not a histologic specimen

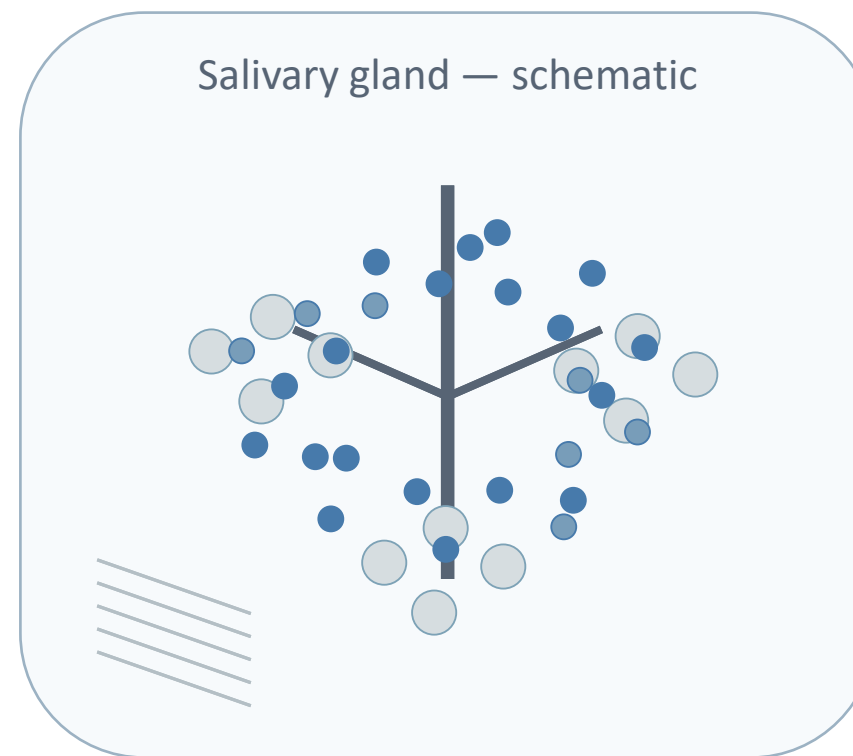
Duct obstruction amplifies gland dysfunction



Mechanistic consequence of the ductal changes.

Acinar atrophy marks loss of secretory capacity

- Secretory acini atrophy as inflammatory injury progresses.
- Fewer functioning acini reduce the capacity to produce tears or saliva.
- Structural loss explains why established dryness may be persistent.



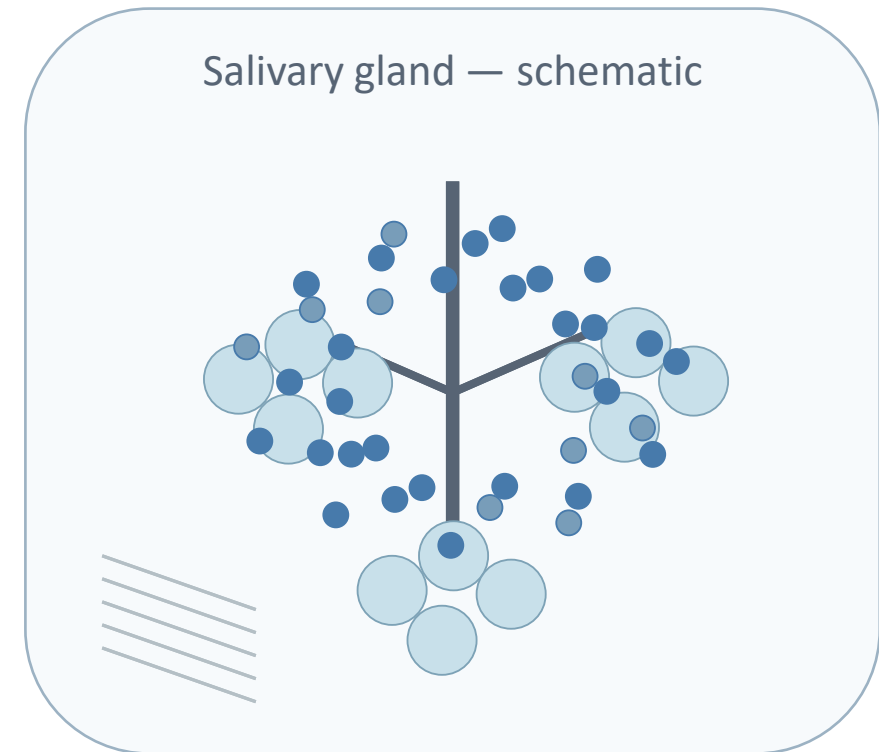
Secretory acini

Duct / immune infiltrate

Original conceptual schematic; Not a histologic specimen

Fibrosis and hyalinization follow injury

- Later glands show fibrosis and hyalinization.
- Replacement of functioning tissue by scar further limits secretion.
- Fibrotic remodeling is a consequence of sustained tissue injury, not the initiating lesion.



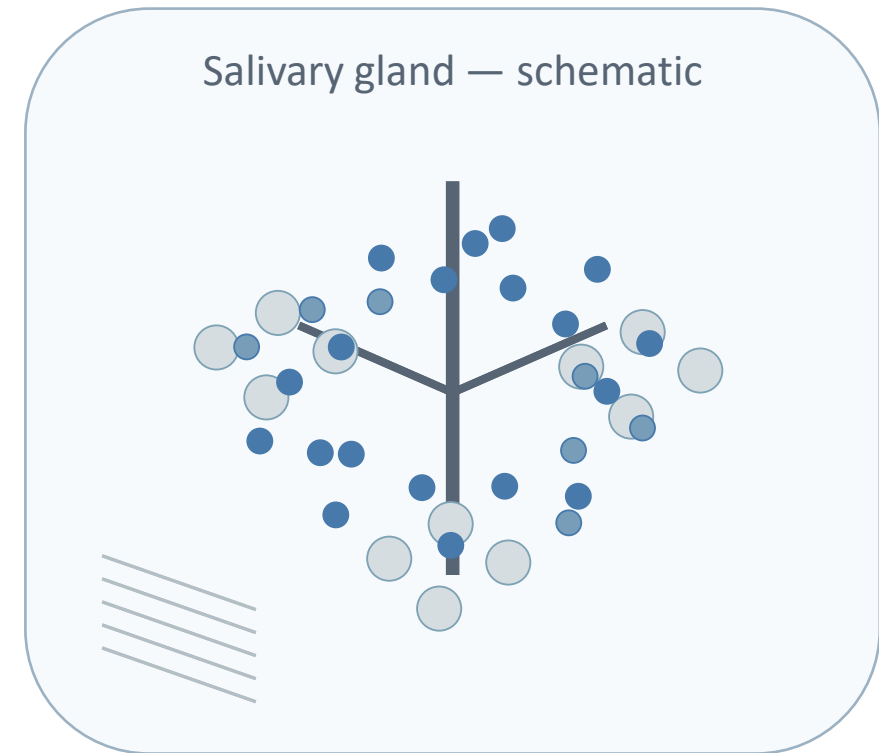
Secretory acini

Duct / immune infiltrate

Original conceptual schematic; Not a histologic specimen

Late parenchyma may be replaced by fat

- Advanced disease may show atrophy with fatty replacement of glandular tissue.
- Loss of acini, fibrosis, and fat collectively reflect chronic tissue remodeling.
- This appearance is part of the later morphologic spectrum rather than a defining early change.

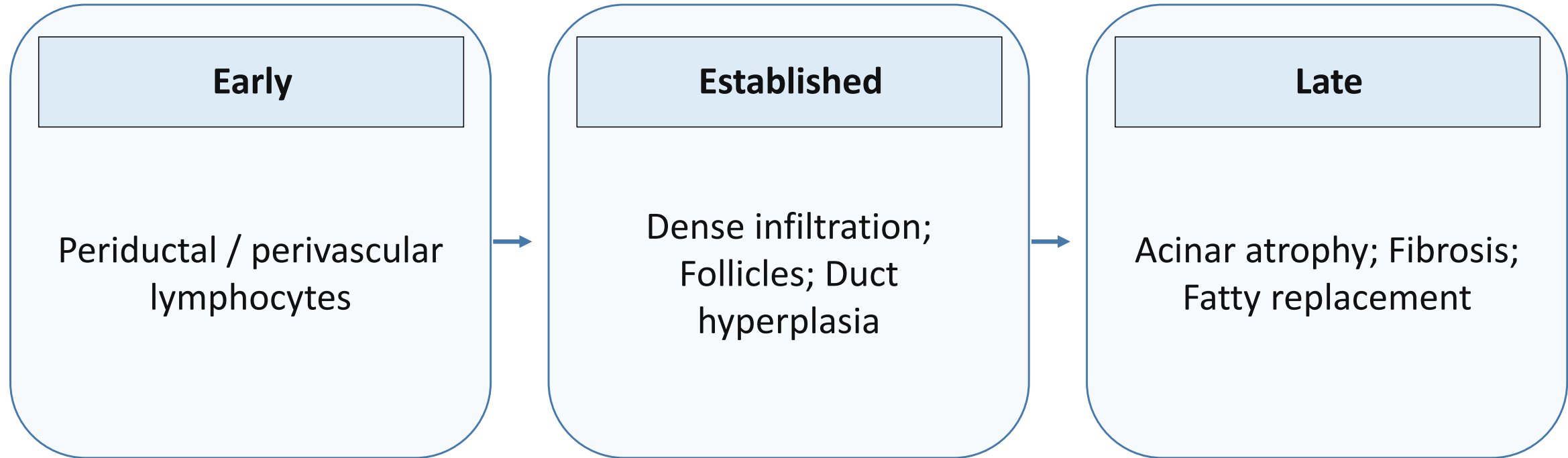


Secretory acini

Duct / immune infiltrate

Original conceptual schematic; Not a histologic specimen

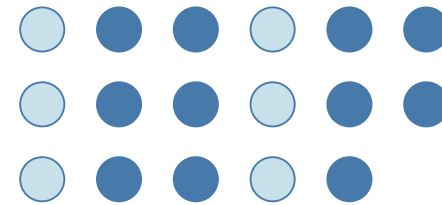
Histologic progression at a glance



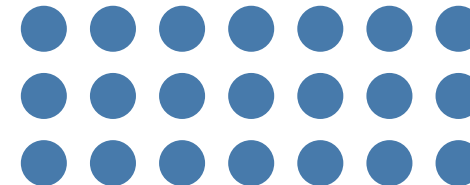
Lymphoid-rich tissue is not automatically lymphoma

- Dense reactive lymphoid infiltrates may resemble lymphoid neoplasia.
- Early lesions can contain mixed polyclonal T and B lymphocytes.
- A dominant expanding B-cell clone raises concern for true marginal zone lymphoma.

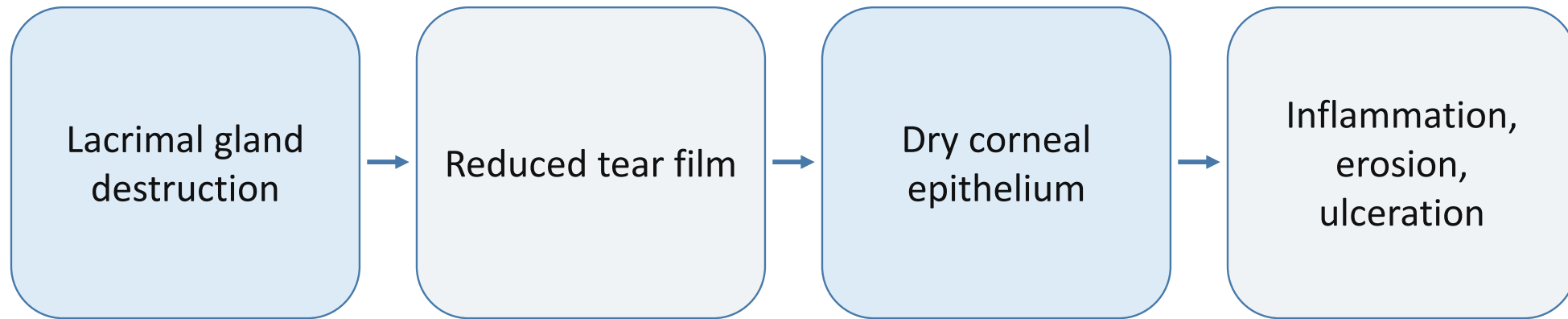
Initially mixed infiltrate



Potential dominant B-cell clone



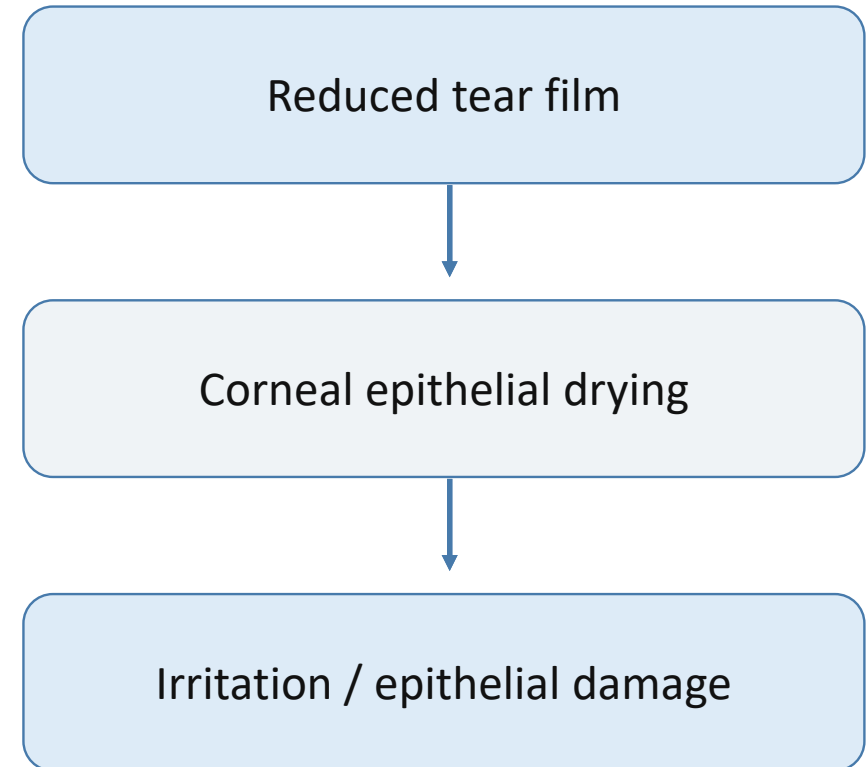
Reduced tears injure the ocular surface



The cornea is injured secondarily to impaired lacrimal secretion.

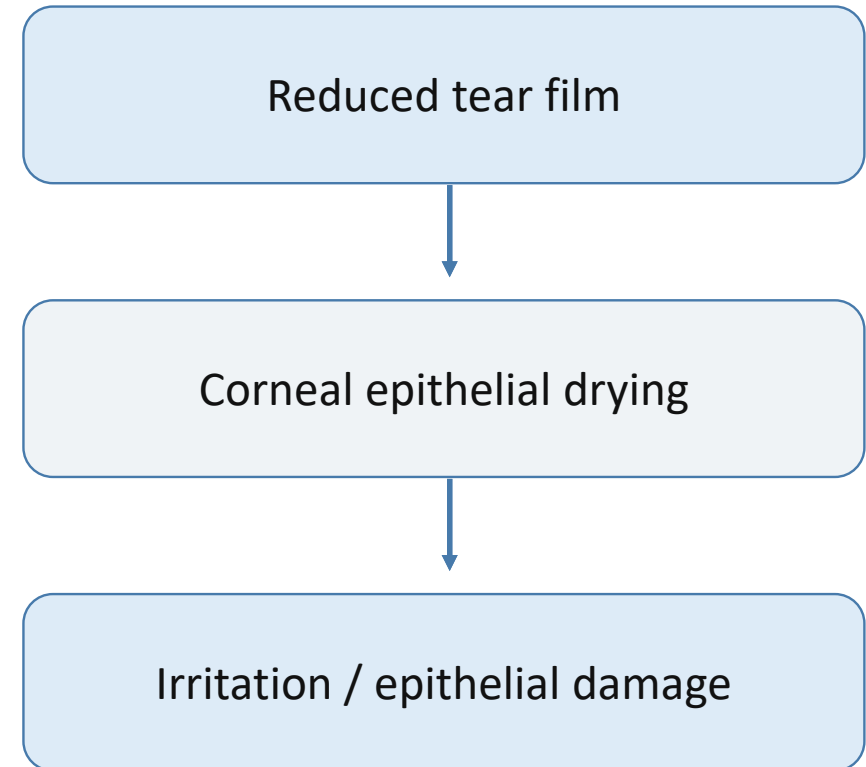
Ocular symptoms follow keratoconjunctivitis sicca

- Burning and itching reflect irritation of the dry ocular surface.
- Blurred vision may accompany corneal epithelial damage.
- Thick secretions may accumulate in the conjunctival sac.

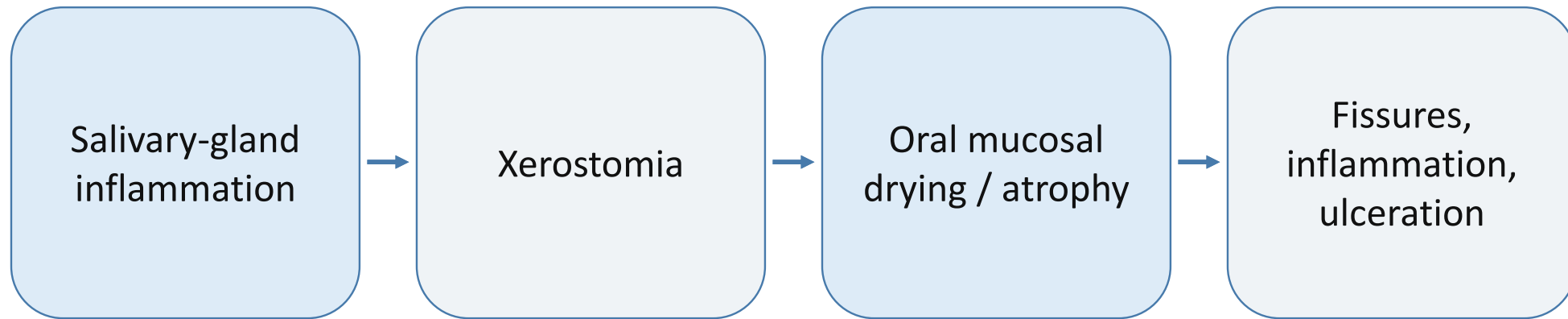


Corneal injury can progress beyond discomfort

- Reduced lubrication contributes to epithelial drying and inflammation.
- Erosions and even ulceration are described in the source.
- Clinical concern extends from symptoms to structural ocular-surface injury.



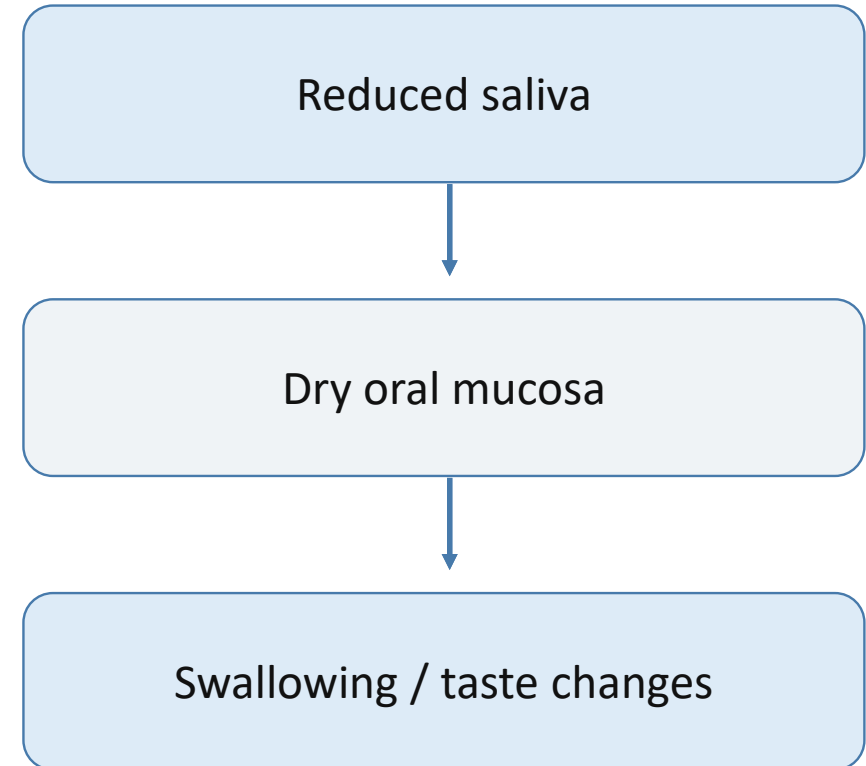
Salivary loss injures the oral mucosa



The mucosal lesions are a downstream effect of reduced salivary protection.

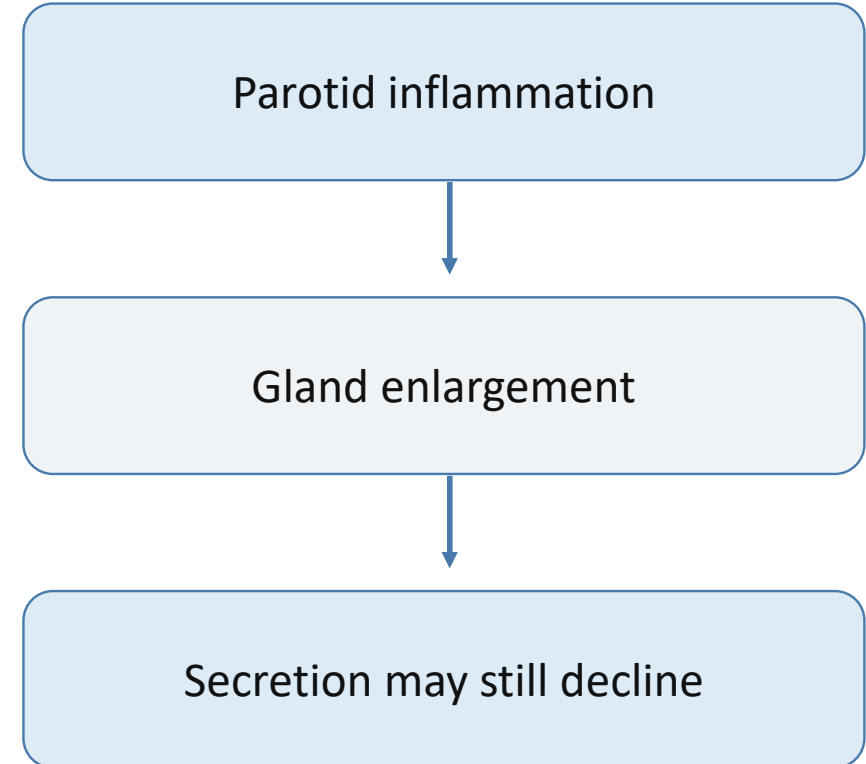
Xerostomia alters everyday function

- Swallowing solid foods may become difficult.
- Patients may report diminished taste.
- Dry buccal mucosa and oral cracks or fissures are characteristic consequences.



Parotid enlargement is an important clue

- Parotid enlargement in about one-half of patients.
- Inflammatory gland enlargement can coexist with declining secretion.
- The later emergence of a dominant B-cell clone changes the interpretation of a persistent gland mass.

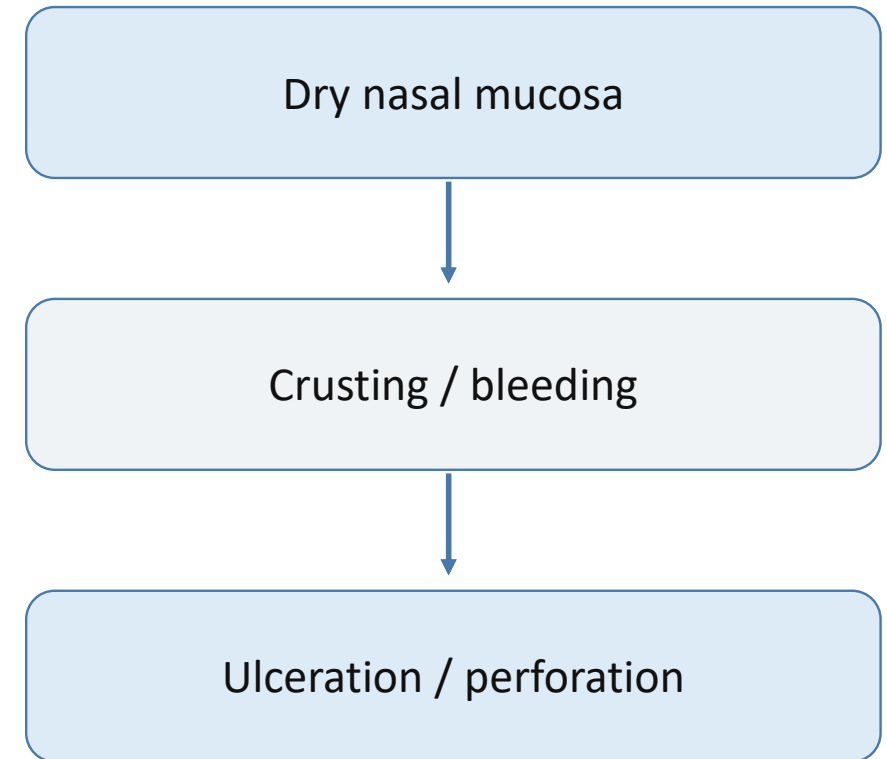


Other exocrine surfaces can be affected

Exocrine site	Possible consequence	Source-supported context
Nasal mucosa	Dryness; Crusting	Ulceration or septal perforation can occur
Airway mucosa	Dryness / airway symptoms	Recurrent bronchitis, pneumonitis
Gastrointestinal / vaginal	Additional mucosal dryness	Other exocrine glands may be involved

Nasal dryness can damage local tissue

- Dryness and crusting of the nose may lead to erosive mucosal damage.
- Epistaxis is among the reported symptoms.
- Severe local disease may cause ulceration or nasal septal perforation.



Respiratory presentations have more than one mechanism

Airway/exocrine involvement

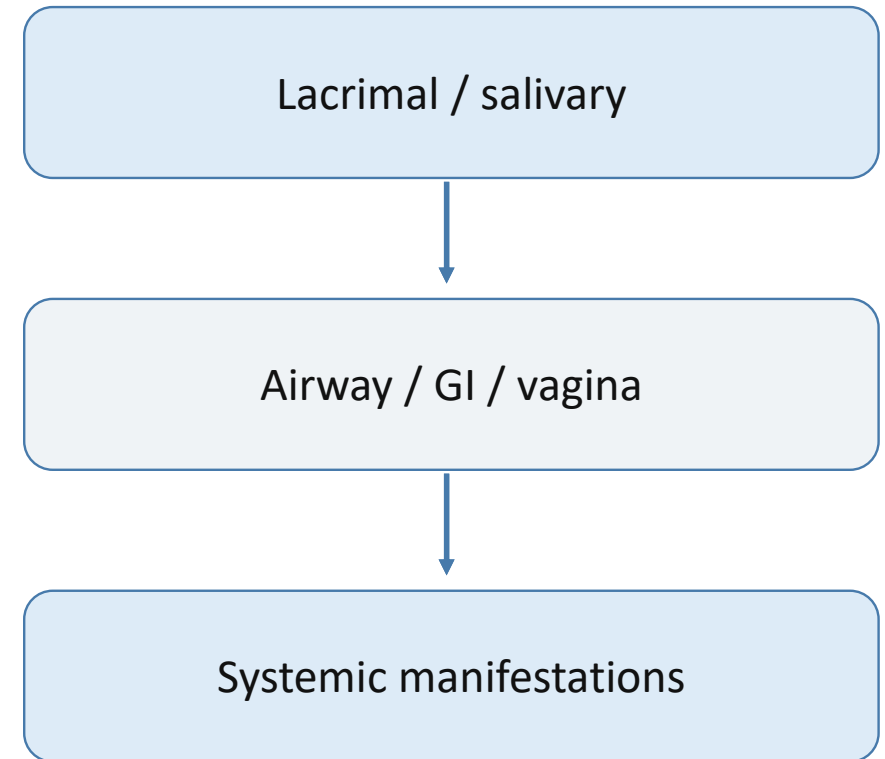
- Dry respiratory mucosa
- Recurrent bronchitis
- Pneumonitis

Extraglandular involvement

- Diffuse pulmonary fibrosis
- Part of systemic disease
- Separate from isolated mucosal dryness

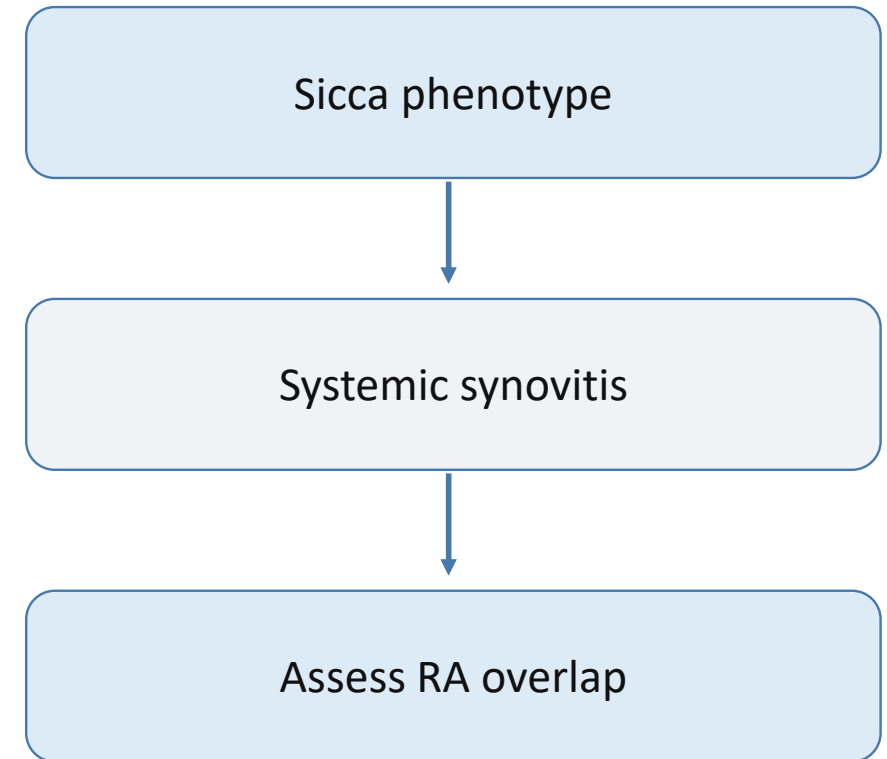
Extraglandular disease affects a substantial minority

- Manifestations outside the principal glands in approximately one-third of patients.
- Examples include synovitis, diffuse pulmonary fibrosis, and peripheral neuropathy.
- Systemic findings are described as more frequent with high anti-SS-A titers.



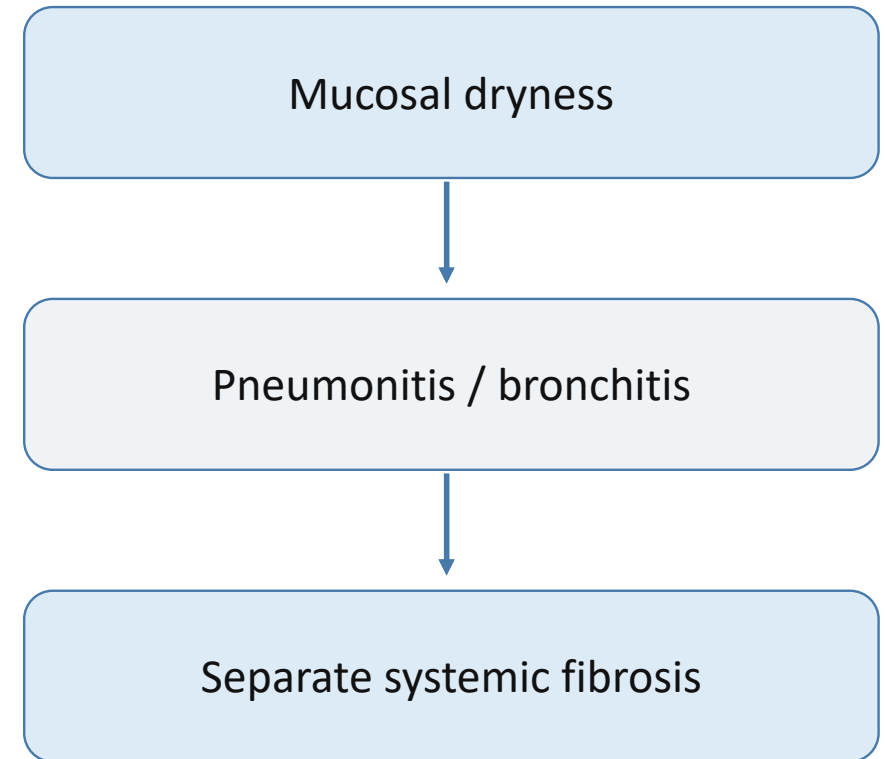
Synovitis belongs to the systemic spectrum

- Inflammatory joint involvement may accompany ocular and oral dryness.
- Synovitis can arise as an extraglandular Sjögren manifestation.
- Coexisting rheumatoid arthritis must remain a separate diagnostic consideration.



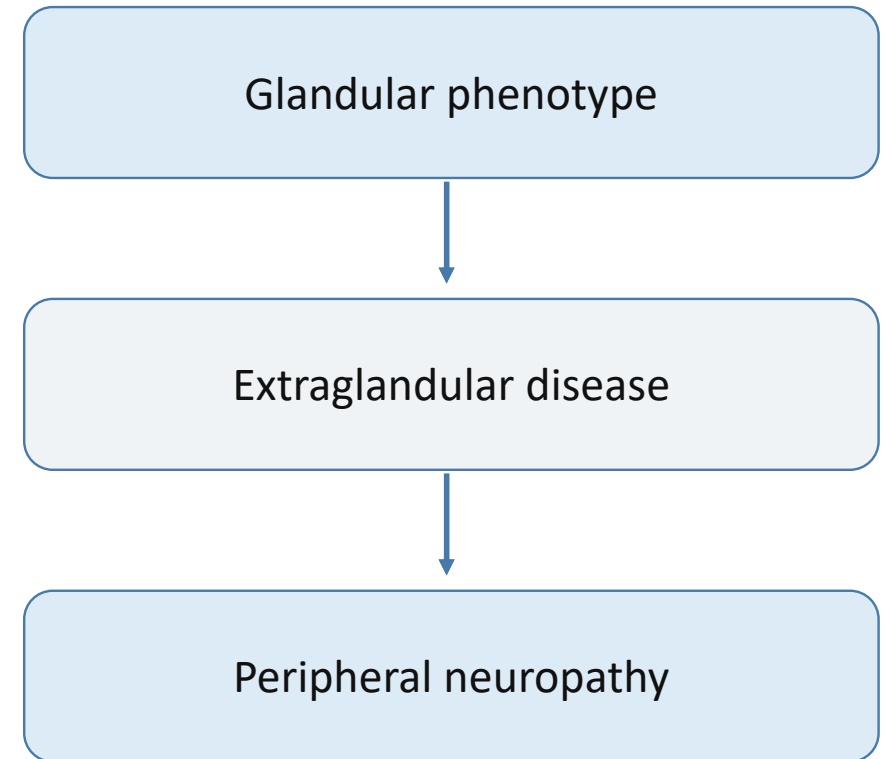
Pulmonary fibrosis indicates systemic extension

- Diffuse pulmonary fibrosis is included among extraglandular manifestations.
- It should not be conflated with bronchitis arising from exocrine-airway dryness.
- The distinction matters when interpreting respiratory disease in a patient with sicca symptoms.



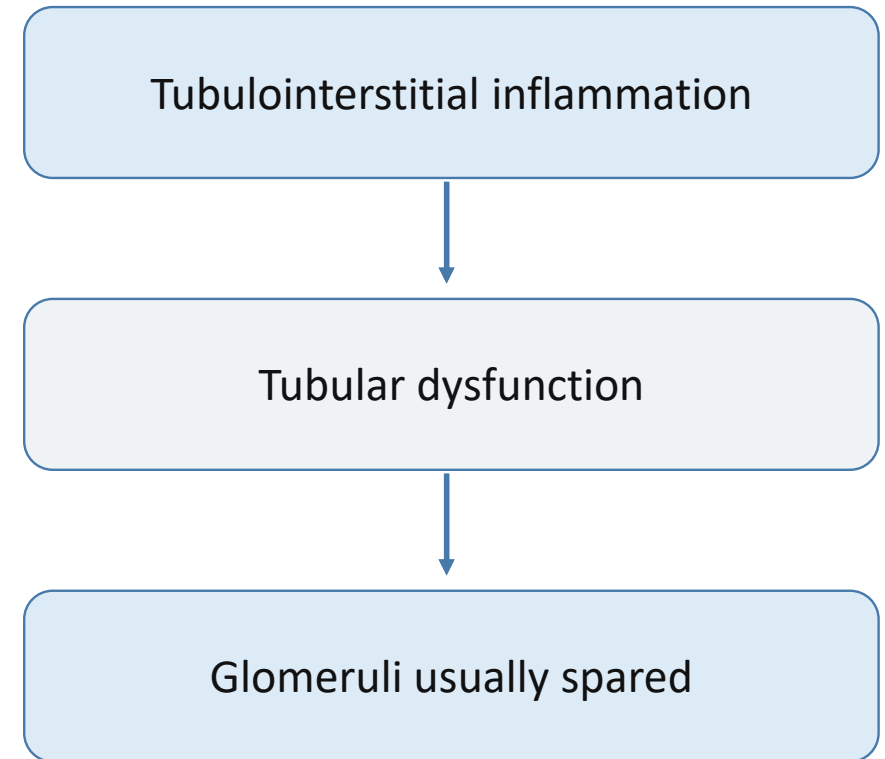
Peripheral neuropathy is another systemic clue

- Peripheral nerve involvement appears in the Robbins extraglandular list.
- Neurologic complaints cannot be explained solely by tear or saliva deficiency.
- Their presence should prompt consideration of multisystem autoimmune disease.



Renal involvement favors the tubulointerstitium

- Renal tubular acidosis, uricosuria, and phosphaturia are described tubular abnormalities.
- The reported association is tubulointerstitial nephritis.
- Robbins specifically distinguishes this pattern from the glomerular lesions typical of lupus.



Tubular injury is distinct from glomerular injury

Sjögren pattern

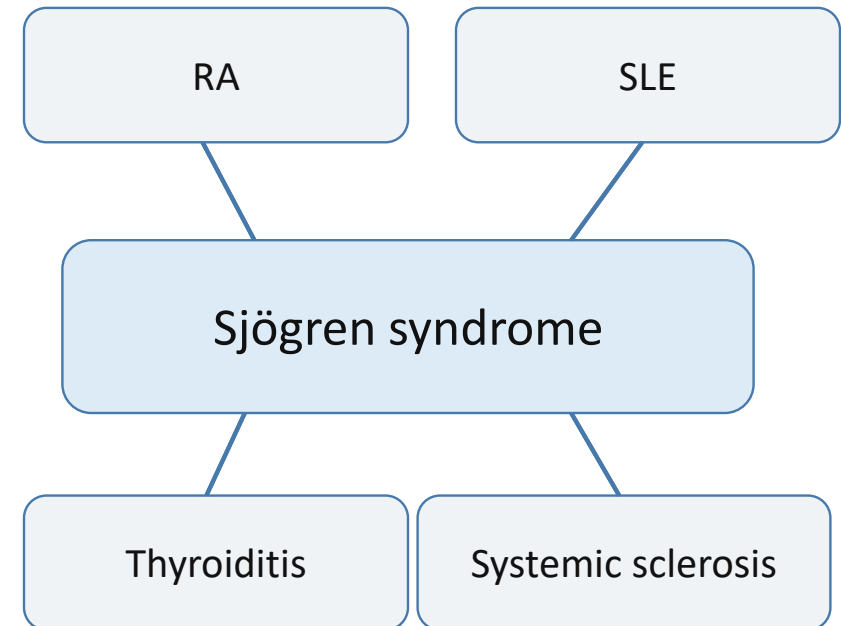
- Tubular functional defects
- Associated interstitial nephritis
- Glomerular lesions extremely rare

Contrast with SLE

- Immune-complex glomerular injury prominent
- Glomerular disease is a key source feature
- Different major pathologic compartment

Coexisting autoimmunity modifies the phenotype

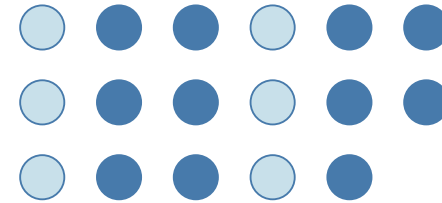
- More than one-half of patients in the Robbins account have another autoimmune disorder.
- They may exhibit both sicca findings and manifestations of the accompanying condition.
- Do not attribute every joint, skin, or renal abnormality automatically to Sjögren syndrome.



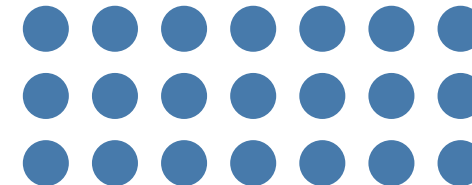
Persistent B-cell stimulation is a lymphoma risk

- Early infiltrates are mixed and polyclonal.
- Continued stimulation may favor expansion of a dominant B-cell clone.
- Marginal zone lymphoma is a characteristic malignancy arising in this setting.

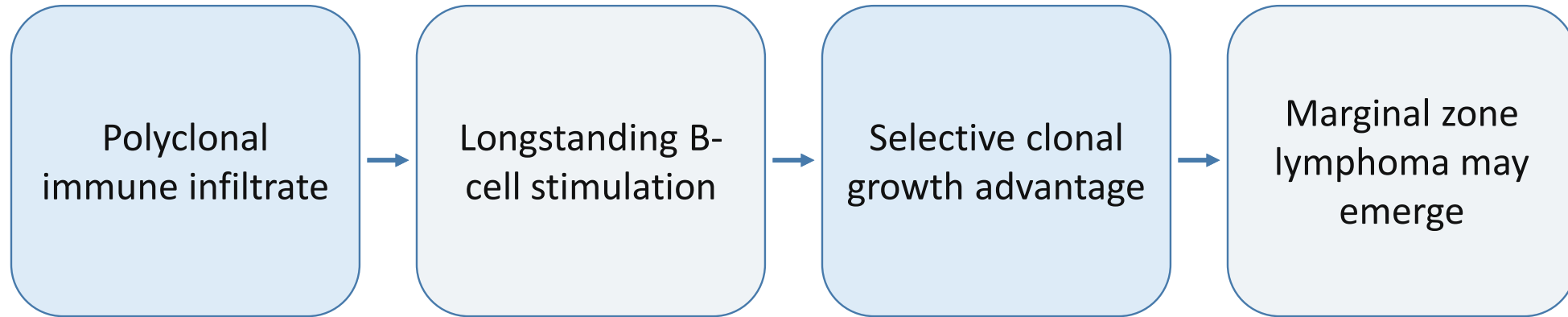
Initially mixed infiltrate



Potential dominant B-cell clone



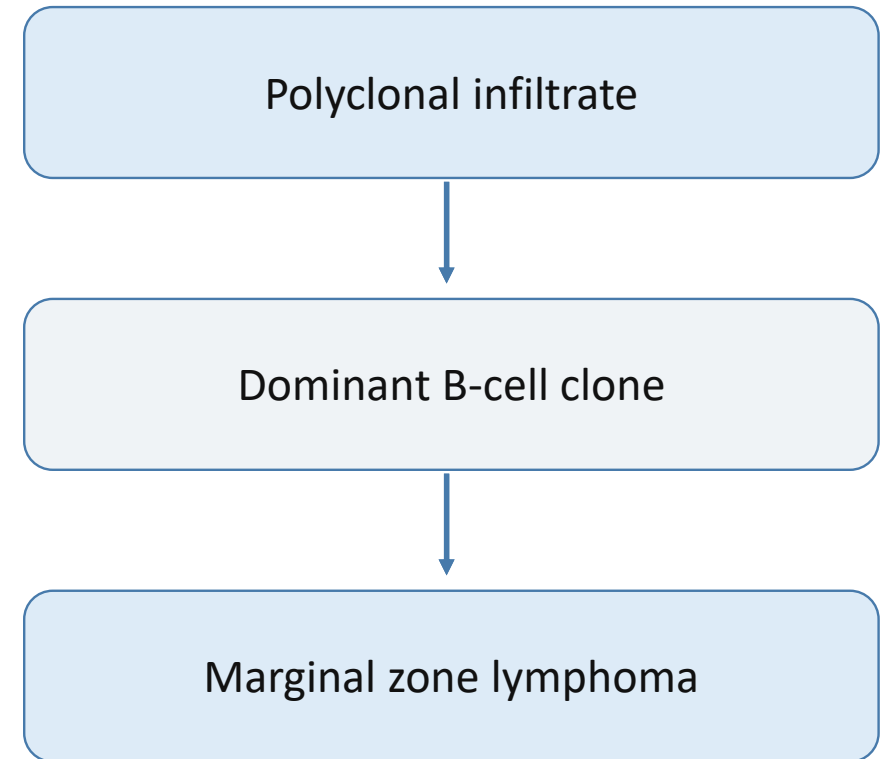
From chronic inflammation to dominant clone



Somatic mutations as a presumptive mechanism for clonal advantage.

The magnitude of lymphoma risk

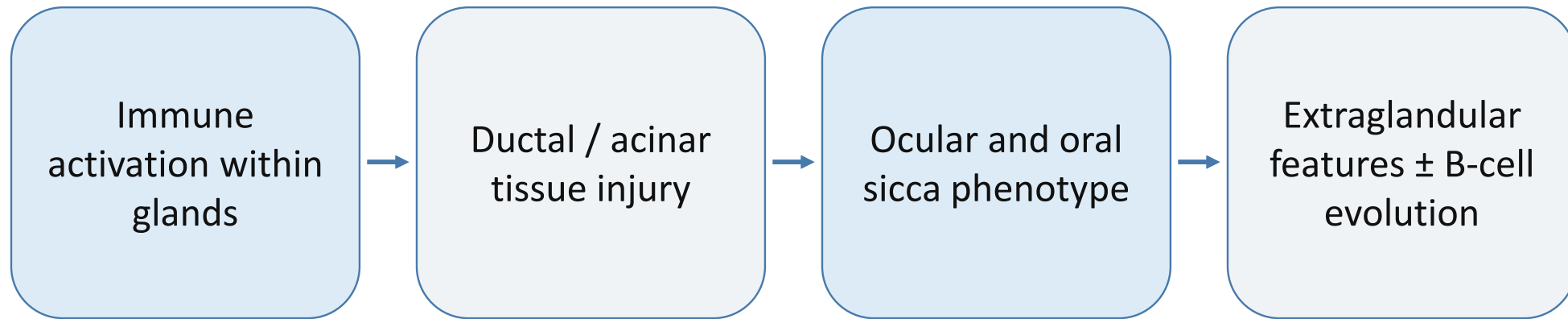
- Lymphoma development in approximately 5% of patients.
- Its reported incidence is about 40-fold higher than normal.
- These textbook estimates underscore surveillance relevance; They are not individualized predictions.



Reactive infiltrate versus lymphoma: Diagnostic reasoning

Feature	Inflammatory disease	Concern for lymphoma
Population	Early mixed, polyclonal T and B cells	Dominant B-cell clone
Architecture	Inflammatory lymphoid aggregates / follicles	Evolving clonal lymphoid expansion
Interpretation	Chronic autoimmunity	Separate neoplastic event

Clinicopathologic integration



Final clinical phenotype depends on gland damage, systemic involvement, and any associated autoimmunity.

Case: Sicca symptoms and parotid swelling

Clinical vignette

A woman in her late fifties reports persistent burning eyes, difficulty swallowing dry foods, and painless enlargement of a parotid gland.

Reason through the case

- Which two gland systems are principally affected?
- Which histologic distribution would support the expected autoimmune process?
- Why can swelling coexist with poor secretion?

Case interpretation: Connect structure to function

- Lacrimal and salivary immune injury unifies eye and mouth symptoms.
- Periductal/perivascular lymphocytes, later duct changes, and acinar atrophy fit the source morphology.
- Gland enlargement reflects inflammation; It does not demonstrate normal gland function.

Lacrimal gland

↓ Tears



Ocular surface injury

Salivary glands

↓ Saliva

Case: Anti-Ro positive with overlapping disease

Clinical vignette

A patient has xerostomia, positive ANA and anti-SS-A, and manifestations that also suggest systemic lupus erythematosus.

Reason through the case

- Does anti-SS-A positivity alone prove Sjögren syndrome?
- What diagnosis must remain in the differential?
- Why does the clinical context matter?

Case interpretation: Avoid serologic overreach

- Anti-SS-A supports an autoimmune disease but is not fully specific to Sjögren syndrome.
- Robbins documents Ro/La antibodies in a subset of patients with SLE.
- Interpret antibody results alongside sicca findings and the features of associated disease.

RF

IgG-reactive
autoantibody

ANA

Broad nuclear reactivity

Ro / La

Ribonucleoprotein
antigens

Case: Tubular dysfunction with sicca symptoms

Clinical vignette

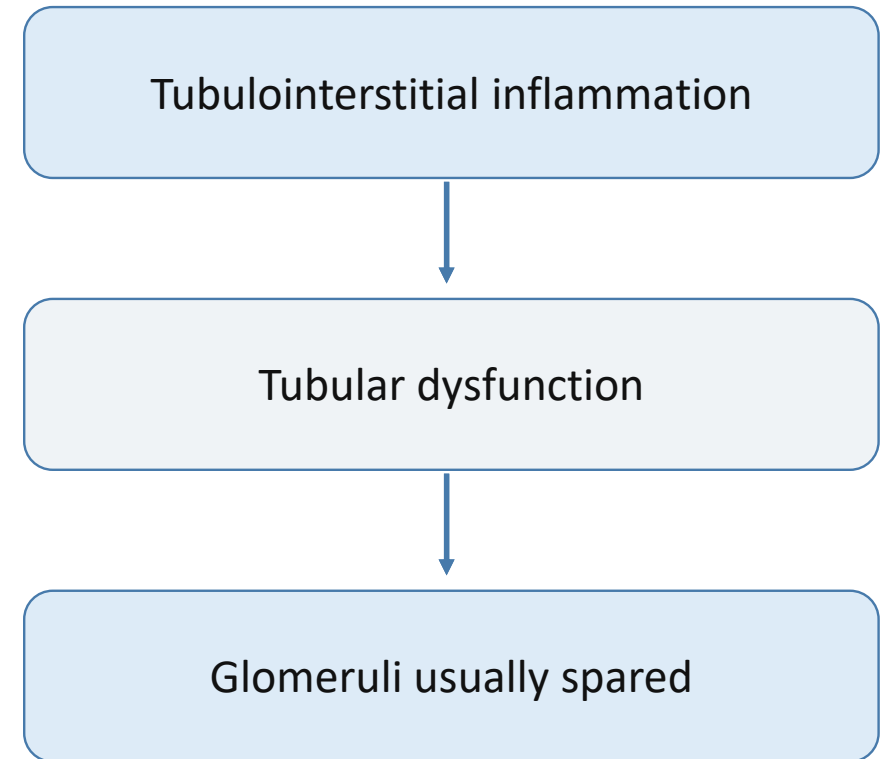
A patient with longstanding dry eyes and dry mouth develops a renal tubular acidification defect but no evidence of a glomerular syndrome.

Reason through the case

- Which renal compartment is implicated in Sjögren syndrome?
- What associated lesion does Robbins describe?
- How does this differ from the classic lupus pattern?

Case interpretation: Compartment is informative

- Tubular dysfunction fits the reported Sjögren-associated tubulointerstitial process.
- Tubulointerstitial nephritis is the source-associated renal lesion.
- Clinically prominent glomerular injury would warrant consideration of other causes, including SLE.



Case: An enlarging salivary-gland mass

Clinical vignette

A patient with established Sjögren syndrome develops a persistent, progressively enlarged salivary gland with an unusually dense lymphoid infiltrate.

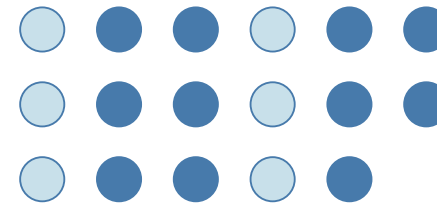
Reason through the case

- Why is reactive inflammation not the only possibility?
- Which B-cell neoplasm is especially relevant?
- What cellular change signals escalation in concern?

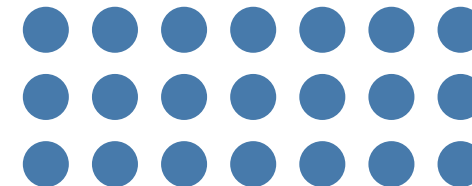
Case interpretation: Clonal evolution matters

- Longstanding B-cell activation can select a dominant lymphocyte clone.
- Marginal zone lymphoma is a recognized complication in the affected tissue.
- A dense infiltrate alone is not sufficient to conclude that lymphoma is present.

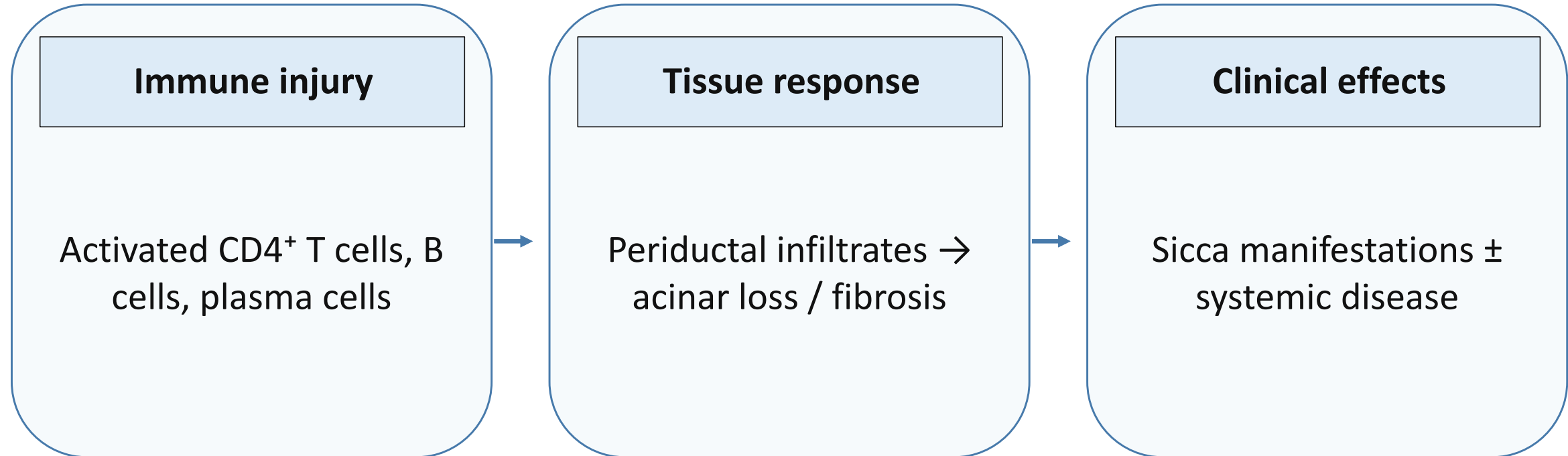
Initially mixed infiltrate



Potential dominant B-cell clone



Five concepts that organize the disease



Diagnostic and prognostic boundaries

Supported clinical / diagnostic clues

- Dry eye and mouth syndrome
- Glandular immune pathology
- Ro/La and other autoimmune serology

What needs careful interpretation

- Assays are not fully specific
- Mechanism remains partly unresolved
- B-cell clonality changes risk assessment

Primary textbook reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) • Chapter 6: Diseases of the Immune System

Sjögren syndrome: pathogenesis, morphology, and clinical features

Additional context: Immunologic Tolerance and Autoimmunity; Table 6.10; tubulointerstitial nephritis discussion in Chapter 20.