

Hashimoto thyroiditis

Autoimmune injury · Morphology · Clinicopathologic correlation

A source-grounded thyroid pathology lecture

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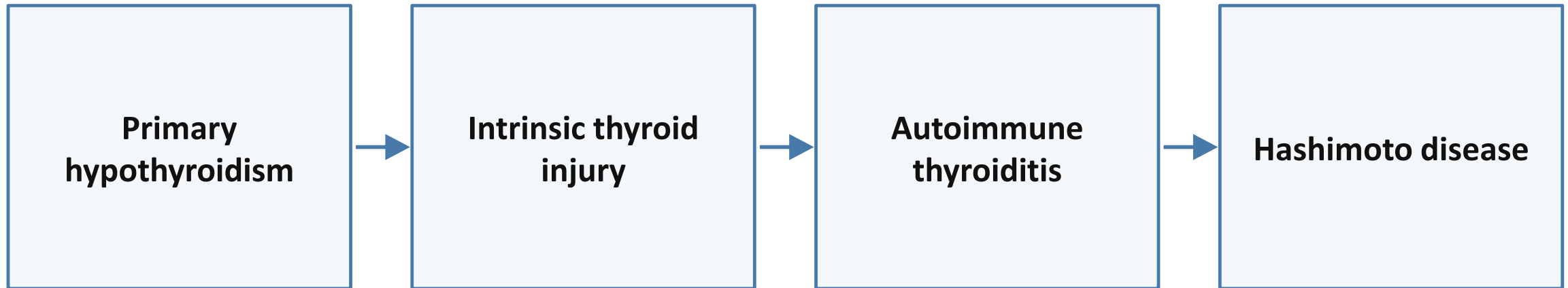
Learning objectives

- Explain the breakdown of thyroid self-tolerance and the principal effector mechanisms.
- Recognize the characteristic gross, microscopic and cytologic findings.
- Link progressive follicular loss to the thyroid-function trajectory.
- Distinguish Hashimoto thyroiditis from other common thyroiditides and Graves disease.

Definition: Chronic autoimmune thyroid injury

- Hashimoto thyroiditis is immune-mediated destruction of the thyroid gland.
- Follicular epithelial loss accumulates over time, causing progressive thyroid failure.
- Lymphoplasmacytic inflammation, oncocytic metaplasia and variable fibrosis form the morphologic signature.

Where Hashimoto fits in hypothyroidism



Hashimoto disease is a major autoimmune cause of primary hypothyroidism in iodine-sufficient settings.

Why iodine sufficiency changes the differential

Context	Important thyroid failure mechanism
Iodine-sufficient areas	Autoimmune hypothyroidism, mostly Hashimoto thyroiditis
Iodine-deficient areas	Deficient substrate for thyroid-hormone synthesis
After gland ablation	Loss of thyroid tissue from surgery or irradiation

Cause of hypothyroidism depends on population and clinical context.

Age distribution and clinical setting

- Most prevalent in adults aged 45–65 years.
- Occurs across ages; Adult predominance does not exclude pediatric disease.
- Many patients come to attention because of a painless goiter and evolving thyroid dysfunction.

Marked female predominance

Sex distribution

A female-to-male ratio of approximately 10:1–20:1.

Interpretation

Female predominance supports epidemiologic suspicion but is not diagnostic.

Practice point

A male patient with compatible morphology may still have Hashimoto thyroiditis.

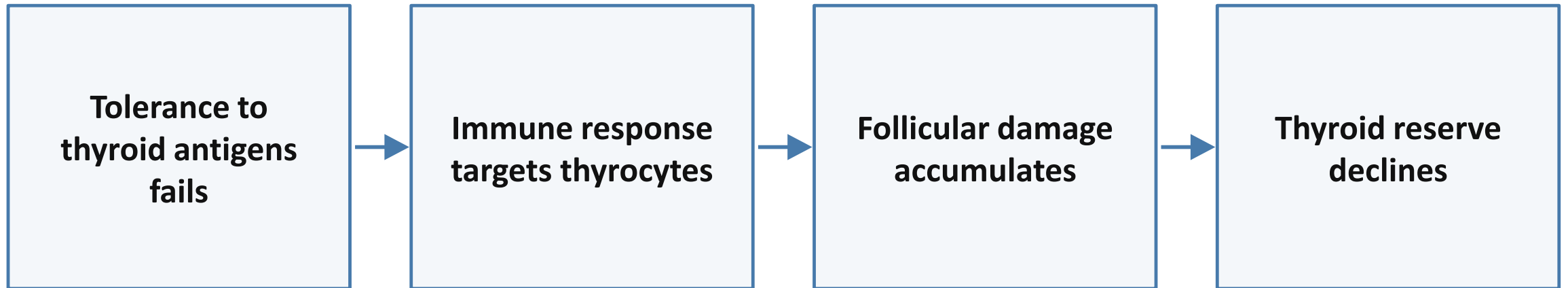
Pediatric Hashimoto thyroiditis

- Hashimoto thyroiditis occurs in children as well as adults.
- It is an important cause of nonendemic goiter during childhood.
- The underlying process remains autoimmune damage of thyroid parenchyma.

Historical descriptor: Struma lymphomatosa

- Hashimoto described goitrous thyroid glands with prominent lymphocytic infiltration in 1912.
- “Struma lymphomatosa” reflects the dense lymphoid reaction, not a diagnosis of lymphoma.
- Modern interpretation integrates this morphology with autoimmune follicular destruction.

Initiating abnormality: Lost self-tolerance



The precise initiating events remain unresolved.

Two autoantigen targets

Thyroid peroxidase (TPO)

Thyroid enzyme frequently recognized by circulating autoantibodies.

Thyroglobulin (Tg)

Thyroid follicular protein also targeted by circulating autoantibodies.

Important distinction

Antibody presence demonstrates autoimmunity; It does not establish how much injury antibodies cause.

Autoantibodies: Evidence versus mechanism

Established observation

Anti-TPO and anti-Tg often detectable

Autoimmune thyroid disease established by integrated findings

Useful etiologic evidence

Unresolved mechanism

Antibodies may participate in injury—or result from injured tissue

Direct antibody cytotoxicity is not proved by seropositivity

Cannot replace functional and morphologic assessment

Do not equate an antibody marker with a proven pathogenic effector.

Genetic susceptibility is polygenic

- Hashimoto thyroiditis has a strong genetic component.
- Associated polymorphisms affect genes involved in immune regulation.
- CTLA4, PTPN22 and IL2RA as examples.
- Association with susceptibility does not imply a single-gene deterministic disease.

CTLA4: An immune-regulatory association

CTLA4

Encodes cytotoxic T-lymphocyte–associated antigen 4.

Relevance

Part of the machinery regulating T-cell responses.

Clinical interpretation

Susceptibility association; Not a standalone diagnostic test.

PTPN22: T-cell response regulation

PTPN22

Encodes protein tyrosine phosphatase non-receptor type 22.

Relevance

Immune regulation contributes to autoimmune susceptibility.

Clinical interpretation

Genetic predisposition is distinct from an established initiating trigger.

IL2RA: Regulatory immune pathways

IL2RA

Encodes the interleukin-2 receptor α chain.

Relevance

Another immune-response regulator implicated by susceptibility polymorphisms.

Clinical interpretation

Interpret as a risk association rather than direct proof of thyrocyte injury.

The initiating event remains uncertain

Proposed possibility	Evidence level in Robbins
Regulatory T-cell abnormality	Suggested, not established as a universal trigger
Exposure of sequestered thyroid antigens	Proposed, not a demonstrated initiating sequence
Immune-regulation gene variants	Supported susceptibility association; do not infer determinism

Keep proposed initiation mechanisms separate from established tissue injury.

Immune injury has several effector routes

Common initiating context

Breakdown of self-tolerance allows autoreactive immune responses to thyroid antigens.

Direct cytotoxic route

CD8⁺ T cells can destroy follicular epithelial cells.

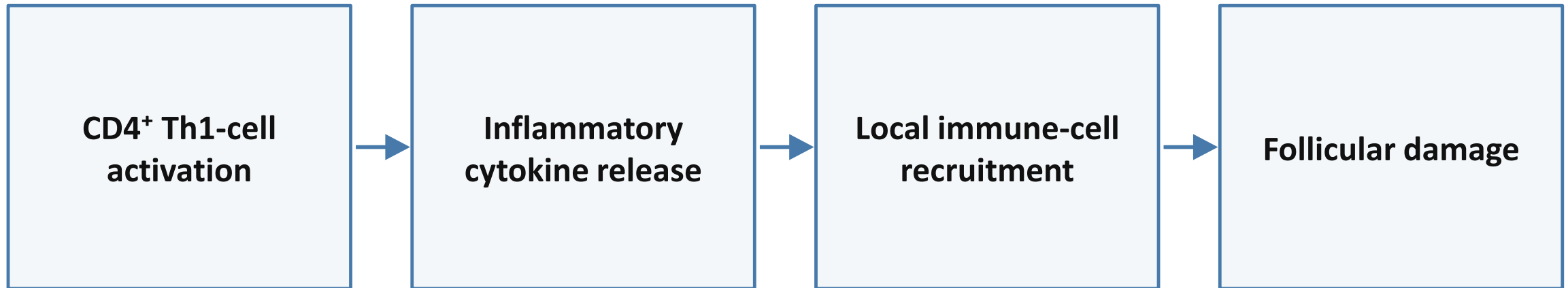
Inflammatory cytokine route

CD4⁺ Th1 signals recruit and activate macrophages; Routes converge on follicular injury.

CD8⁺ cytotoxic lymphocytes

- Cytotoxic CD8⁺ T cells can directly damage thyroid follicular epithelial cells.
- Repeated killing reduces the population of functioning thyrocytes.
- This contributes to the depletion of thyroid follicles seen microscopically.

CD4⁺ Th1 immune activation



CD4⁺ T-cell activity amplifies local inflammatory injury rather than simply forming an inert infiltrate.

Interferon- γ and macrophage recruitment

- Th1 cells produce inflammatory cytokines, including interferon- γ .
- These signals recruit and activate macrophages within the thyroid.
- Local cytokine-associated injury contributes to destruction of follicles.

What is uncertain about antibody-mediated damage?

Hypothesized route	Critical interpretation
Antibody-dependent cellular cytotoxicity	Historically proposed; pathogenic importance uncertain
Complement-dependent damage	Possible, but not established as the dominant cause
Anti-TPO / anti-Tg seropositivity	Robust autoimmune association without proven causality for each antibody

Robbins explicitly cautions that antibodies may be cause or consequence of injury.

Injury evolves into tissue remodeling



Autoimmune activity Lymphocytic inflammation develops

Follicular loss Thyrocytes are progressively depleted

Remodeling Parenchyma is replaced by inflammation and fibrosis

Integrative pathogenesis schematic

Immune dysregulation



Genetic susceptibility and lost tolerance

Cell-mediated injury



CD8⁺ killing and CD4⁺ / Th1 inflammation

Morphology



Atrophy, lymphoid aggregates, oncocytic change

Function



Declining thyroid reserve and primary hypothyroidism

Gross morphology: Enlargement without invasion

- The gland is usually diffusely enlarged and remains sharply separated from adjacent structures.
- Gross cut surface is characteristically pale, yellow-tan and firm.
- A somewhat nodular cut appearance may be present, even without a discrete neoplasm.

Interpreting the gross cut surface

Diffuse increase in size

Often reflects chronic inflammatory enlargement.

Pale, firm texture

Consistent with inflammatory remodeling and variable fibrosis.

Well-defined gland edge

Classic fibrosis remains within the gland rather than invading adjacent neck structures.

Macroscopic differential: Localized enlargement

- Hashimoto enlargement is usually symmetric and diffuse.
- In some patients, the enlargement is sufficiently localized to simulate a thyroid neoplasm.
- Apparent nodularity therefore requires clinicopathologic correlation; The label “Hashimoto” alone is insufficient.

Microscopy: Three linked compartments

Follicular compartment

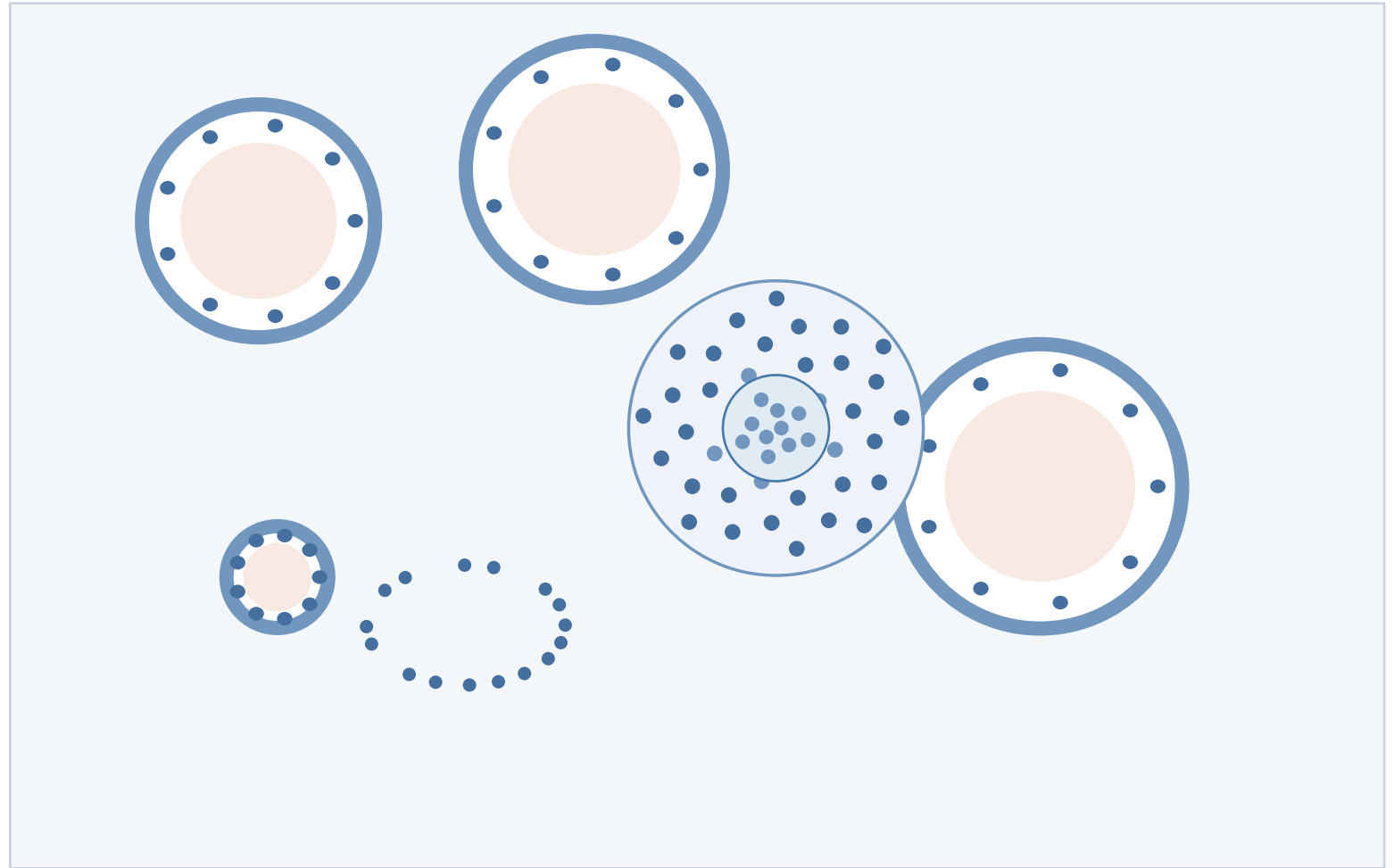
Residual follicles alongside inflammation

Immune compartment

Lymphoid aggregates with germinal centers

Stromal compartment

Variable connective-tissue increase



Schematic architecture — not a histologic specimen

Lymphoplasmacytic infiltration

- Extensive mononuclear inflammation replaces portions of thyroid parenchyma.
- The infiltrate contains small lymphocytes and plasma cells.
- Lymphoid aggregates may organize into follicle-like structures with germinal centers.

Germinal centers within the thyroid

Lymphoid follicles

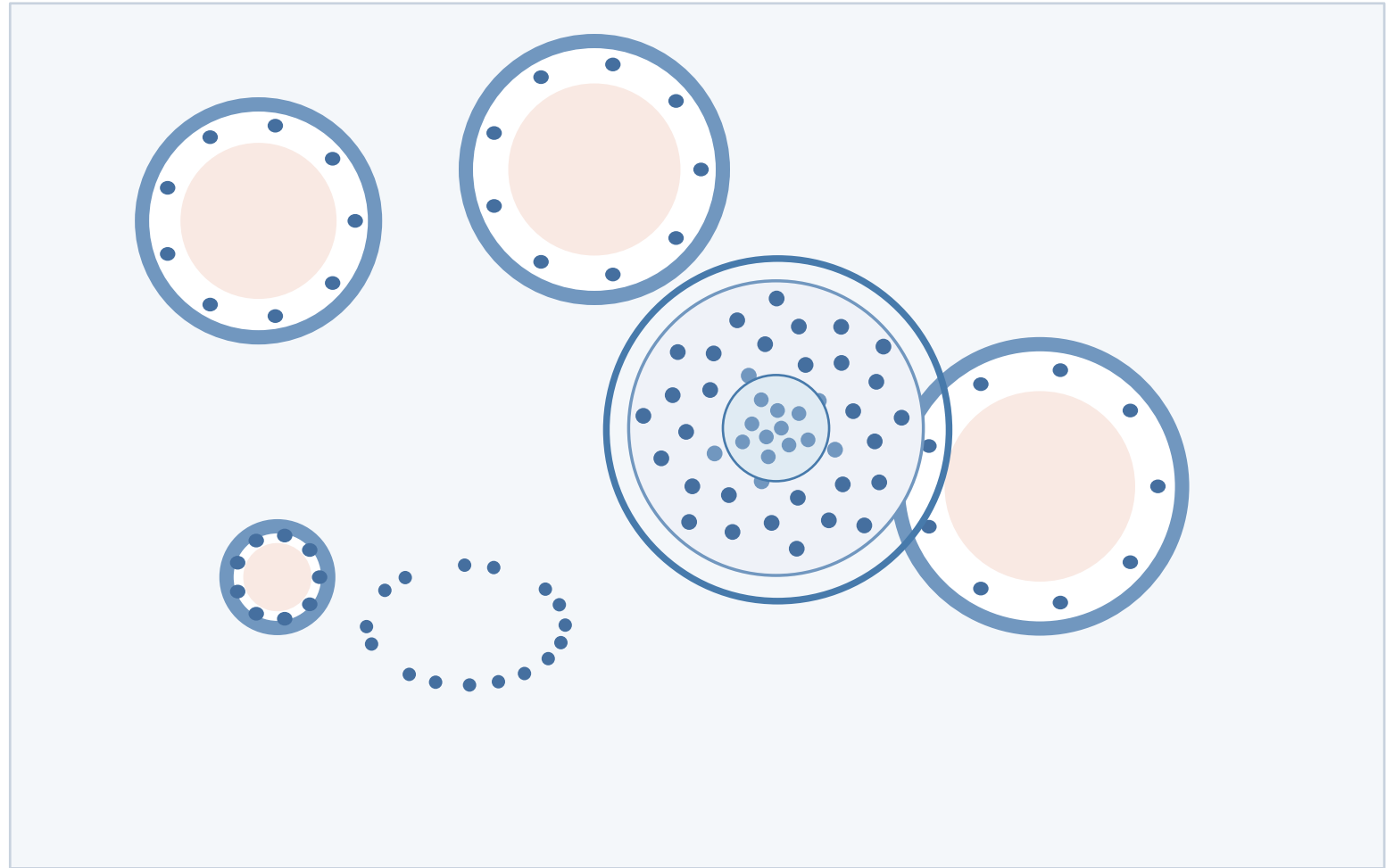
Organized collections of small lymphocytes

Germinal centers

Paler reactive central zones

Context

Surrounded by altered thyroid follicles



Schematic architecture — not a histologic specimen

Why organized lymphoid follicles matter

Morphologic clue

Prominent germinal centers support a sustained autoimmune inflammatory process.

Site matters

These structures are within thyroid tissue;
They are not native thyroid follicles.

Interpretation

Assess in the company of epithelial atrophy, oncocytic change and fibrosis.

Progressive thyroid follicular atrophy

Small follicles

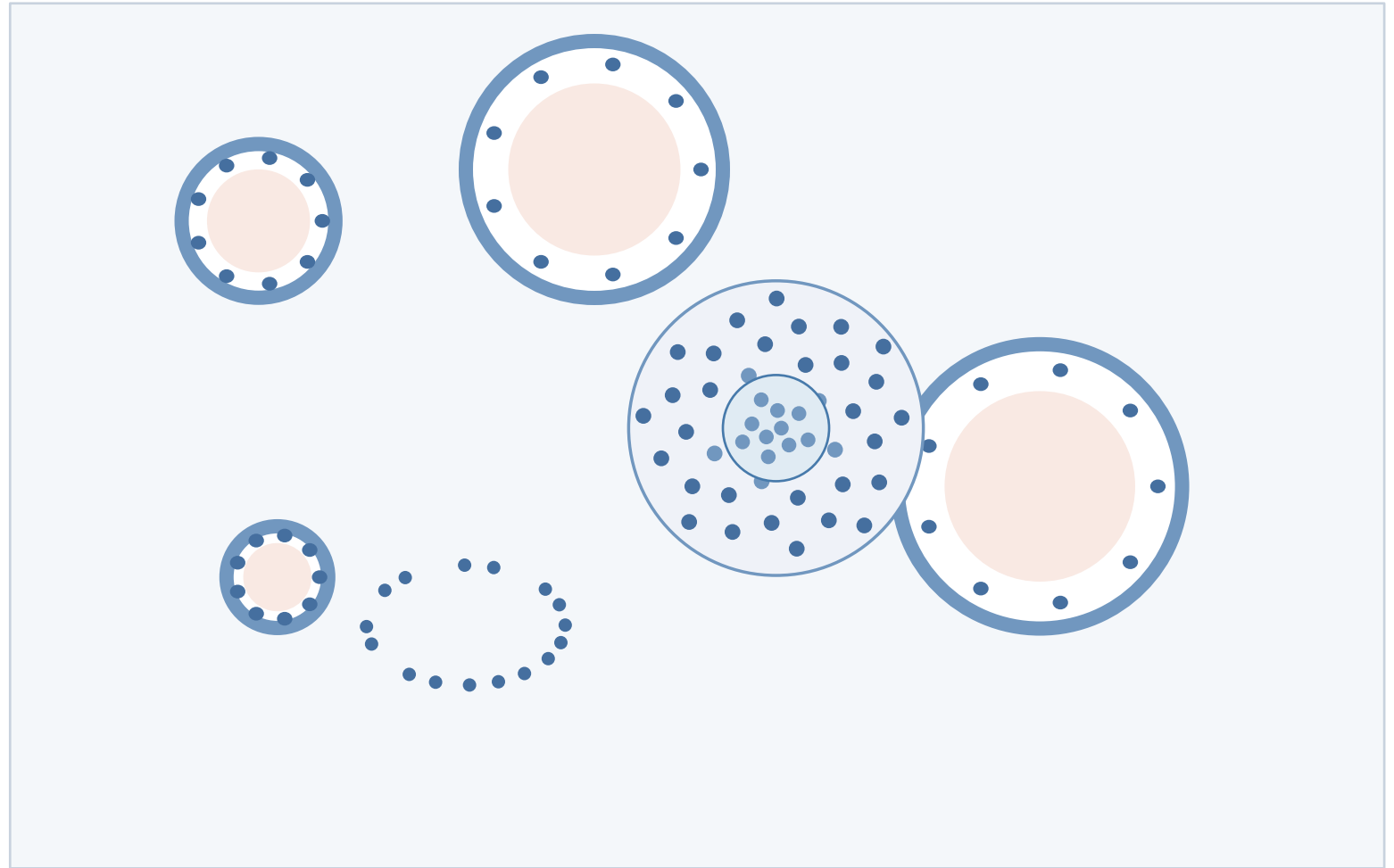
Loss of epithelium diminishes
functioning units

Parenchymal replacement

Inflammation occupies previously
follicular space

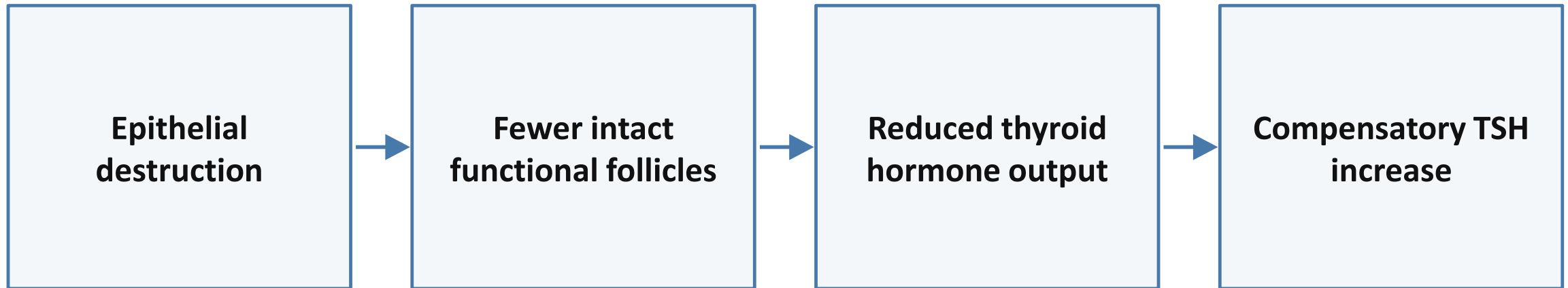
Consequence

Functional reserve falls
progressively



Schematic architecture — not a histologic specimen

Follicular loss explains functional decline



The structure–function link explains the usual gradual evolution to primary hypothyroidism.

Oncocytic metaplasia of follicular epithelium

Residual lining

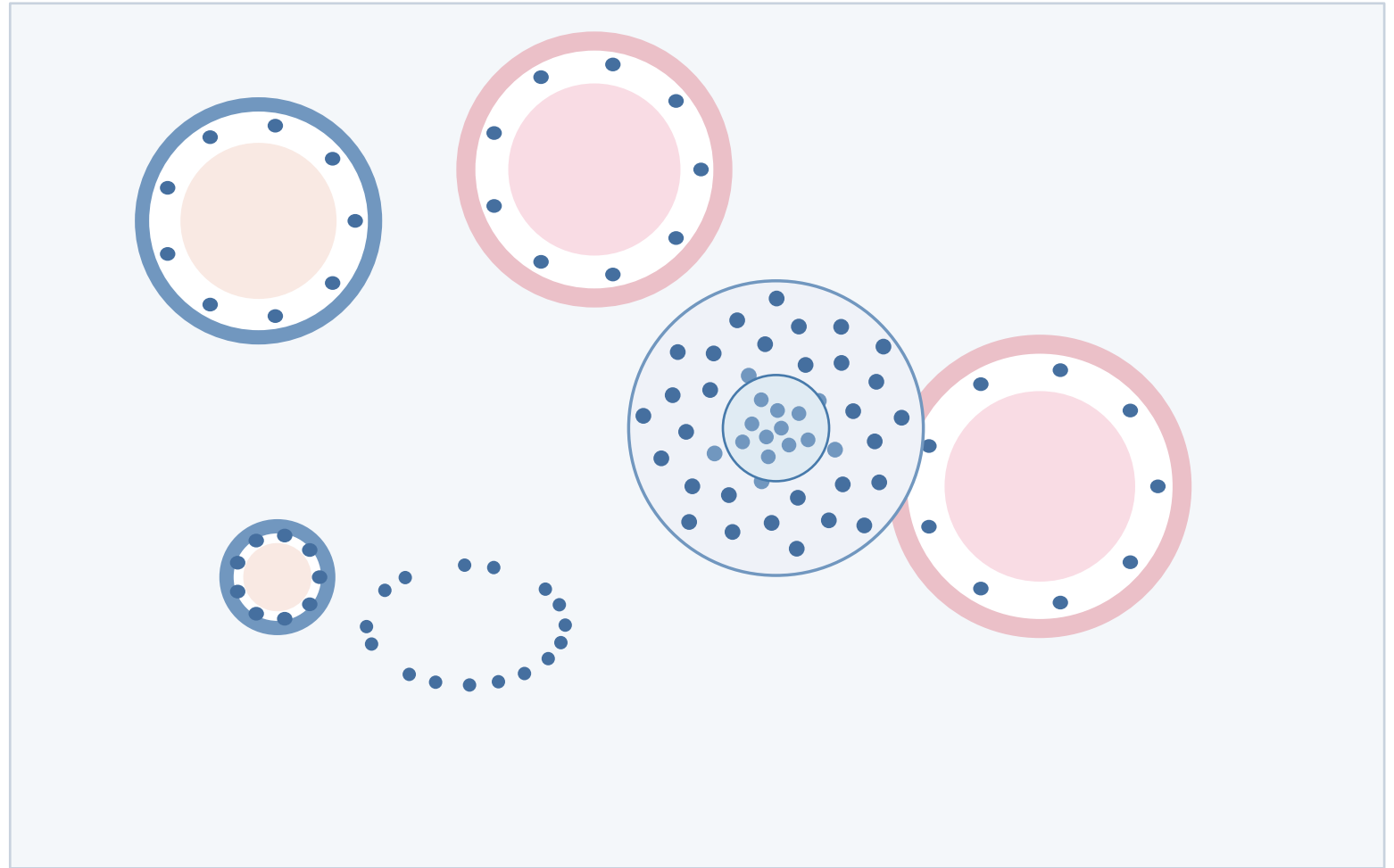
Abundant granular eosinophilic cytoplasm

Older term

Hürthle-cell change

Interpretation

Metaplastic response to chronic injury



Schematic architecture — not a histologic specimen

Recognizing oncocytes

- Residual follicles are often lined by cells with abundant eosinophilic, granular cytoplasm.
- These cells are termed oncocytes; The older term is Hürthle cells.
- Robbins interprets the change as metaplasia in response to chronic epithelial injury.

Oncocytic change is not synonymous with cancer

Observation	Interpretation
Oncocytes in inflamed residual follicles	Expected in Hashimoto thyroiditis
Abundant granular eosinophilic cytoplasm	Epithelial phenotype, not an independent malignancy criterion
Focal thyroid enlargement with oncocytes	Correlate with tissue architecture and clinical features

Cytomorphology must be interpreted in its inflammatory context.

Interstitial fibrosis: The tissue boundary

Stromal remodeling

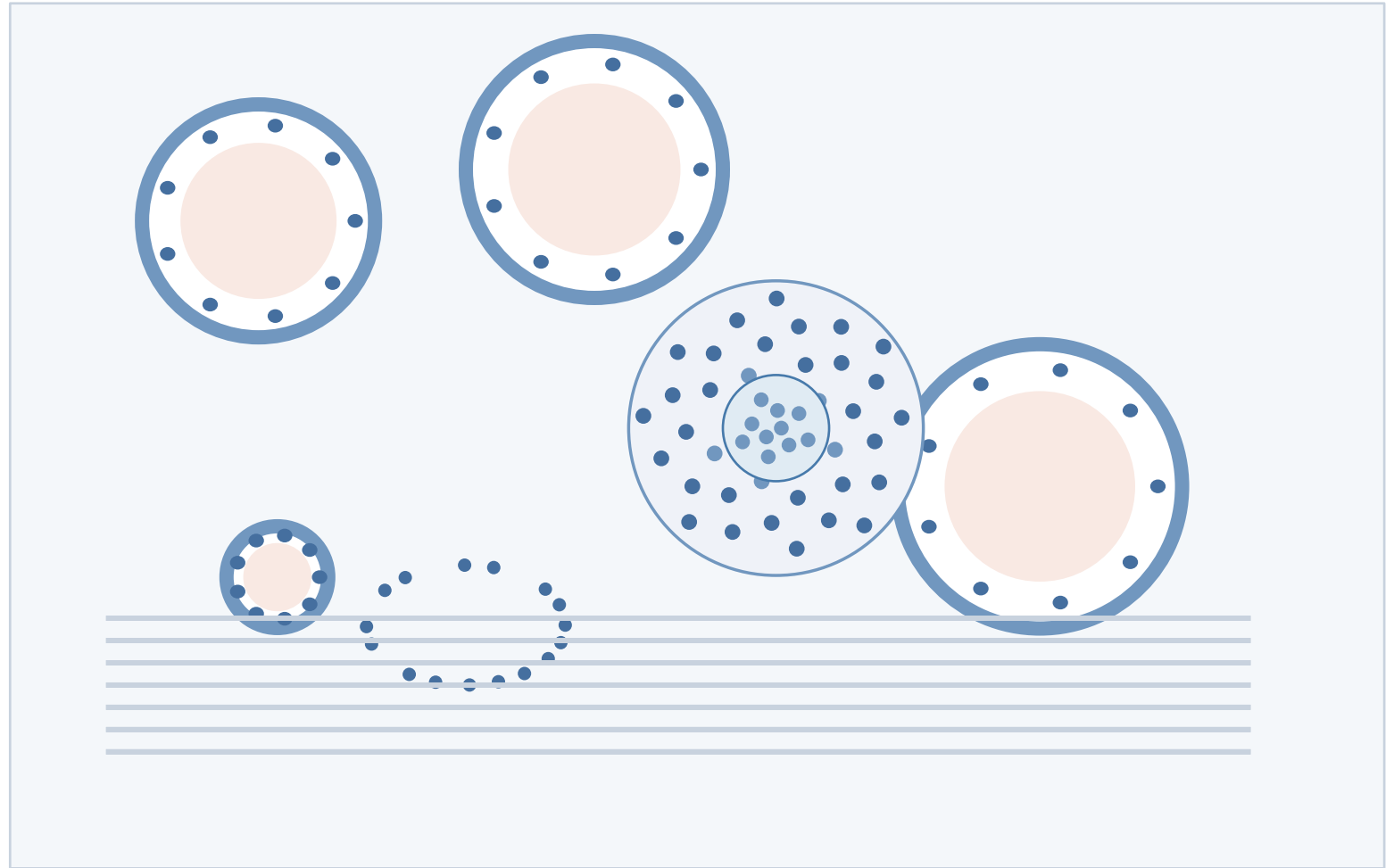
Variable intrathyroidal collagen deposition

Peripheral border

Classic disease remains gland-confined

Comparison

Riedel fibrosis extends beyond gland



Schematic architecture — not a histologic specimen

Fibrosis in Hashimoto versus Riedel

Classic Hashimoto thyroiditis

Fibrosis may be abundant inside the thyroid

Gland remains well demarcated

Prominent lymphoid inflammation and oncocytes

Riedel thyroiditis

Dense fibrosis includes adjacent neck structures

Hard, fixed mass may simulate carcinoma

Extensive invasive fibrosclerosis is dominant

The peripheral extent of fibrosis is a major distinguishing principle.

Fine-needle aspirate: A characteristic pairing

Epithelial population

Oncocytes with granular eosinophilic cytoplasm.

Inflammatory population

Heterogeneous lymphocytes accompanying the oncocytes.

Interpretation

The combination is characteristic of Hashimoto thyroiditis in an appropriate clinical setting.

Cytologic interpretation requires context

- Oncocytes are not sufficient alone to classify a lesion as Hashimoto thyroiditis.
- Mixed lymphocytes reinforce the chronic thyroiditis pattern.
- Localized enlargement can raise the suspicion of neoplasia, so interpretation is integrated rather than isolated.

The classic clinical presentation

- Painless thyroid enlargement is a common mode of presentation.
- The gland is generally diffusely and symmetrically enlarged.
- Some degree of thyroid hypofunction may already be present at first assessment.

A gradual course is typical



Autoimmune injury

Inflammation begins before reserve is exhausted

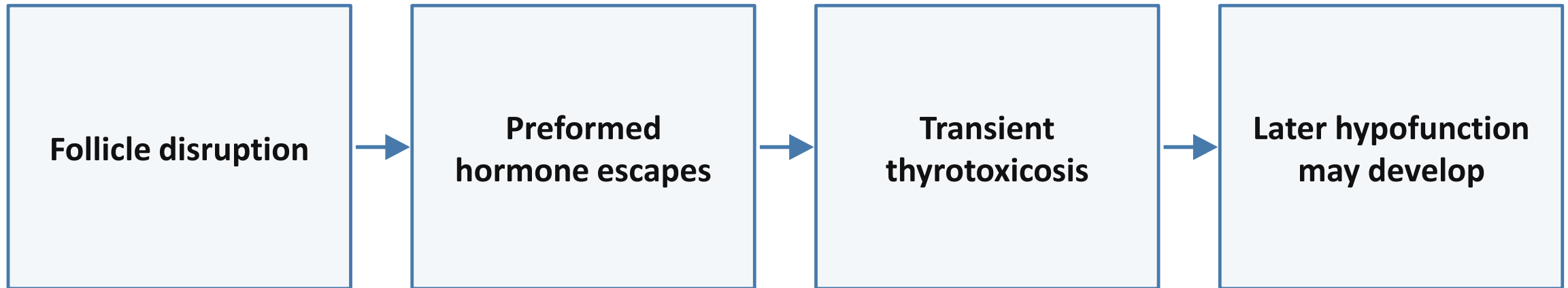
Compensation

TSH responds as hormone synthesis becomes limited

Overt failure

Thyroid hormone levels decline as tissue loss progresses

Hashitoxicosis: Release, not stimulation



Transient thyrotoxicosis can precede the more characteristic hypothyroid phase.

Destructive versus stimulatory thyrotoxicosis

Hashitoxicosis

Leakage from injured follicles

Transient phase may precede failure

Autoimmune destruction of gland

Graves disease

TSH-receptor antibody stimulation

Sustained hormone overproduction

Diffuse epithelial hypertrophy / hyperplasia

An elevated thyroid-hormone level does not automatically imply increased synthesis.

Primary thyroid feedback during failure

Thyroid follicle loss

T₄ and T₃ output falls



Anterior pituitary response

TSH secretion increases

**Primary hypothyroidism: Low thyroid output with compensatory
TSH elevation**

Directional physiology only; Hormone concentrations vary with stage.

Laboratory pattern evolves with disease stage

Stage or physiology	Expected direction of markers
Progressive primary thyroid failure	TSH increases as feedback weakens
Established hypothyroidism	T ₄ and T ₃ decline; TSH becomes elevated
Transient destructive thyrotoxicosis	Released thyroid hormone may temporarily rise

These are directional patterns, not diagnostic cutoffs or substitute reference intervals.

Autoimmune disorders may coexist

Endocrine

Type 1 diabetes; Autoimmune adrenalitis.

Nonendocrine

Systemic lupus erythematosus; Myasthenia gravis; Sjögren syndrome.

Implication

The thyroid disorder may be one manifestation of broader immune dysregulation.

Endocrine comorbidity: Diagnostic context

- Type 1 diabetes and autoimmune adrenalitis are specifically associated conditions.
- Autoimmune hypothyroidism may occur in the setting of autoimmune polyendocrine syndromes.
- An existing autoimmune disease increases clinical suspicion but does not by itself establish thyroiditis.

Nonendocrine autoimmune comorbidity

- Systemic lupus erythematosus, myasthenia gravis and Sjögren syndrome are recognized associations.
- Coexistence supports an autoimmune tendency across tissue systems.
- The thyroid diagnosis still requires direct clinical, functional or pathologic evidence.

Rare lymphoma association

- Hashimoto thyroiditis confers an increased risk of extranodal marginal zone B-cell lymphoma in the thyroid.
- The complication is rare, despite chronic lymphoid infiltration being common.
- Distinguish reactive thyroid-associated lymphoid tissue from true lymphoma when morphology raises concern.

Thyroid epithelial cancer: Preserve uncertainty

Established in Robbins

Increased risk of thyroid extranodal marginal zone B-cell lymphoma

Coexistence of autoimmunity and thyroid lesions can occur

Not firmly established

Causal predisposition to thyroid epithelial carcinoma

Whether papillary carcinoma risk is increased remains controversial

Do not treat a disputed epithelial cancer link as settled.

Clinicopathologic diagnostic synthesis

Presentation



Painless diffuse goiter or evolving dysfunction

Immune evidence



Anti-TPO and/or anti-Tg antibodies

Microscopy



Lymphoid germinal centers, oncocytes and atrophy

Function



Progressive primary hypothyroidism; Sometimes
hashitoxicosis

Serology: What the test establishes

Anti-TPO / anti-Tg finding

Interpretation

Present

Evidence of autoimmune response to thyroid antigens

Absent or unavailable

Assess the total clinical and pathologic picture

High antibody result

Not a direct quantitative measure of tissue destruction

These autoantibodies in the great majority, not in every patient.

Differential: Hashimoto versus painless thyroiditis

Hashimoto

Gradually progressive hypothyroidism is typical

Oncocytic metaplasia and fibrosis prominent

Painless goiter possible

Painless (silent) thyroiditis

Often transient thyrotoxicosis followed by recovery

Oncocytic change and fibrosis not prominent

Painless goiter common; postpartum cases recognized

Both may display lymphocytic infiltration and germinal centers.

Differential: Hashimoto versus subacute thyroiditis

Hashimoto

Usually painless

Lymphoid infiltrates, oncocytes, follicular atrophy

Usually progressive thyroid failure

Subacute granulomatous (de Quervain)

Painful thyroid is characteristic

Granulomatous inflammation with giant cells and colloid

Often transient, self-limited thyroiditis

Pain and tissue reaction pattern strongly shift the differential.

Differential: Hashimoto versus Graves

Hashimoto

Autoimmune follicular destruction

Atrophic follicles and oncocytic change

Hypothyroidism dominates later course

Graves disease

TSH-receptor stimulation is the principal mechanism

Tall, crowded hyperplastic epithelium

Hyperthyroidism dominates usual presentation

Lymphoid infiltrates can be present in both: Their existence alone does not discriminate.

Thyroiditis differential: A morphology map

Hashimoto

Painless · oncocytes · intrathyroidal fibrosis

Silent thyroiditis

Painless · transient · minimal oncocytes / fibrosis

De Quervain

Painful · giant-cell reaction to colloid

Riedel

Hard fixed gland · fibrosis beyond thyroid

Case 1: Painless goiter and rising TSH

Clinical vignette

- A 52-year-old woman presents with a gradually enlarging, painless thyroid gland.
- Serum TSH has increased over serial testing and thyroid hormone output is declining.
- What unifying disease process and microscopic triad should be considered?

Use the mechanism and tissue pattern to answer; Discussion follows.

Case 1: Mechanistic resolution

Immune phase



Lost tolerance to thyroid antigens

Tissue phase



T-cell / cytokine injury and follicular atrophy

Functional phase



Declining T₄ / T₃ and compensatory TSH rise

Pattern



Painless goitrous chronic autoimmune thyroiditis

Case 2: Initial thyrotoxicosis

Clinical vignette

- A patient with autoimmune thyroiditis develops transient clinical thyrotoxicosis.
- The gland subsequently shows declining functional reserve.
- Does the initial hormone excess prove a Graves-type stimulatory mechanism?

Use the mechanism and tissue pattern to answer; Discussion follows.

Case 2: Distinguish the mechanism

Destructive release

Follicular rupture liberates stored hormones

May be transient before thyroid failure

Underlying morphology: injury / atrophy

Active synthesis

TSH receptor stimulation increases ongoing production

Sustained stimulation is typical of Graves disease

Underlying morphology: hyperplasia

Mechanism, not the isolated word “thyrotoxicosis,” determines the differential.

Case 3: Hard thyroid and fibrosis

Clinical vignette

- A firm thyroid enlargement is investigated for possible neoplasia.
- Histology shows extensive lymphoplasmacytic inflammation and fibrosis.
- Which anatomic observation best helps distinguish classic Hashimoto from Riedel thyroiditis?

Use the mechanism and tissue pattern to answer; Discussion follows.

Case 3: The importance of boundaries

Intrathyroidal fibrosis

Compatible with classic Hashimoto

Thyroid border remains discernible

Evaluate oncocytes and germinal centers

Extrathyroidal fibrosis

Suggests Riedel-type invasive fibrosclerosis

Contiguous surrounding neck tissue becomes involved

Hard fixed mass may resemble a carcinoma

The gross-anatomic pattern is an etiologically useful morphologic sign.

Four high-yield diagnostic anchors

Mechanism

Autoimmune loss of thyrocytes.

Morphology

Germinal centers, atrophy, oncocytes, variable fibrosis.

Functional evolution

Often gradual primary hypothyroidism;
Possible hashitoxicosis.

Complication

Rare extranodal marginal zone B-cell lymphoma.

Common interpretation errors

- Calling thyroid autoantibodies proven causes of follicular injury; Their role remains uncertain.
- Mistaking a transient destructive hormone leak for sustained synthesis-driven hyperthyroidism.
- Interpreting oncocytes alone as evidence of a thyroid epithelial neoplasm.
- Overstating papillary carcinoma risk when the literature remains controversial.

Essential reading and image provenance

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. 2026. Chapter 24, pp. 980–985.

Hashimoto thyroiditis: textbook pp. 982–983; pathogenesis Fig. 24.10 and morphology Fig. 24.11.

Thyroiditis key concepts and the Graves disease comparison: pp. 983–985.

All explanatory tissue illustrations in this lecture are original editable schematics; no photomicrographs are reproduced.