

Thymic Hyperplasia

Architecture • Germinal centers • Autoimmunity • Differential diagnosis

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Learning objectives

- Distinguish follicular hyperplasia from an enlarged but architecturally normal thymus.
- Recognize normal thymic compartments and the significance of ectopic germinal centers.
- Explain the clinicopathologic link with myasthenia gravis and central tolerance.
- Differentiate benign thymic changes from key mediastinal neoplastic lesions.

“Hyperplasia” describes two different findings

Follicular hyperplasia

- Increased intrathymic B-cell follicles.
- Germinal centers are the defining tissue clue.
- The whole gland need not be larger.

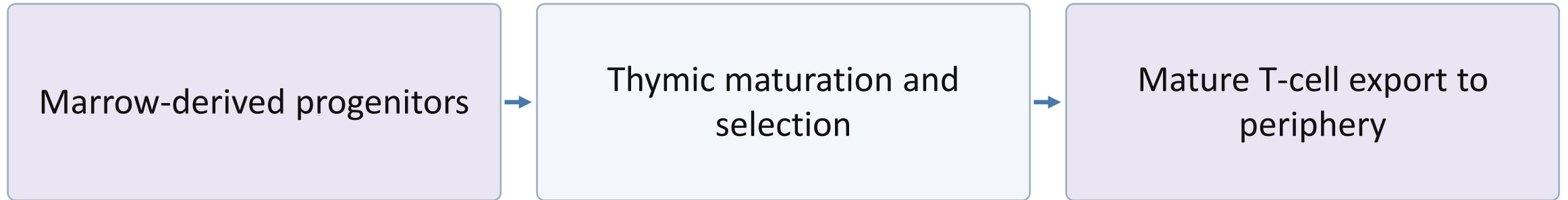
Age-relative enlargement

- Thymus is large for the patient’s age.
- Histologic architecture may remain normal.
- May imitate a thymic mass on imaging.

Why terminology matters

- The same clinical label may describe different histologic processes.
- Organ enlargement is not required to diagnose follicular hyperplasia.
- An enlarged thymus does not automatically imply follicular hyperplasia.
- The distinction determines what pathologists and radiologists are describing.

The thymus is a primary T-cell organ



Embryologic origin

- The thymus derives mainly from the third pair of pharyngeal pouches.
- A contribution from the fourth pouch pair is described as inconsistent.
- Developmental abnormalities can affect both anatomy and immune function.

Thymus size changes with age

Birth: 10–35 g



Growth to puberty: 20–50 g



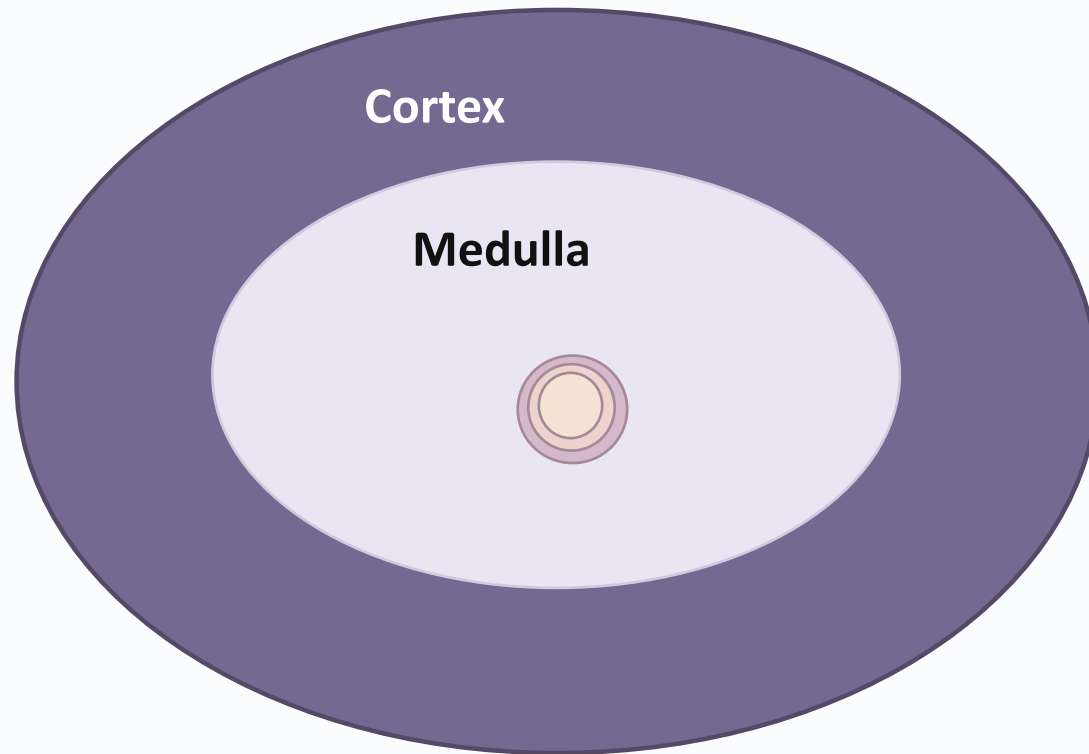
Involution in older adults: 5–
15 g

Size must be interpreted in context

- Thymic size varies widely between individuals.
- The organ grows before puberty and progressively involutes thereafter.
- Severe illness or HIV infection may accelerate involution in younger persons.
- A seemingly prominent thymus is not sufficient evidence of neoplasia.

Normal thymic lobules: Cortex and medulla

Original schematic — not a photomicrograph



Central whorl: Hassall corpuscle

How to read the diagram

- Fibrous septa divide the gland into lobules.
- Each lobule has an outer cortex and central medulla.
- Lobulation and compartment relationships organize interpretation.

The thymic cortex

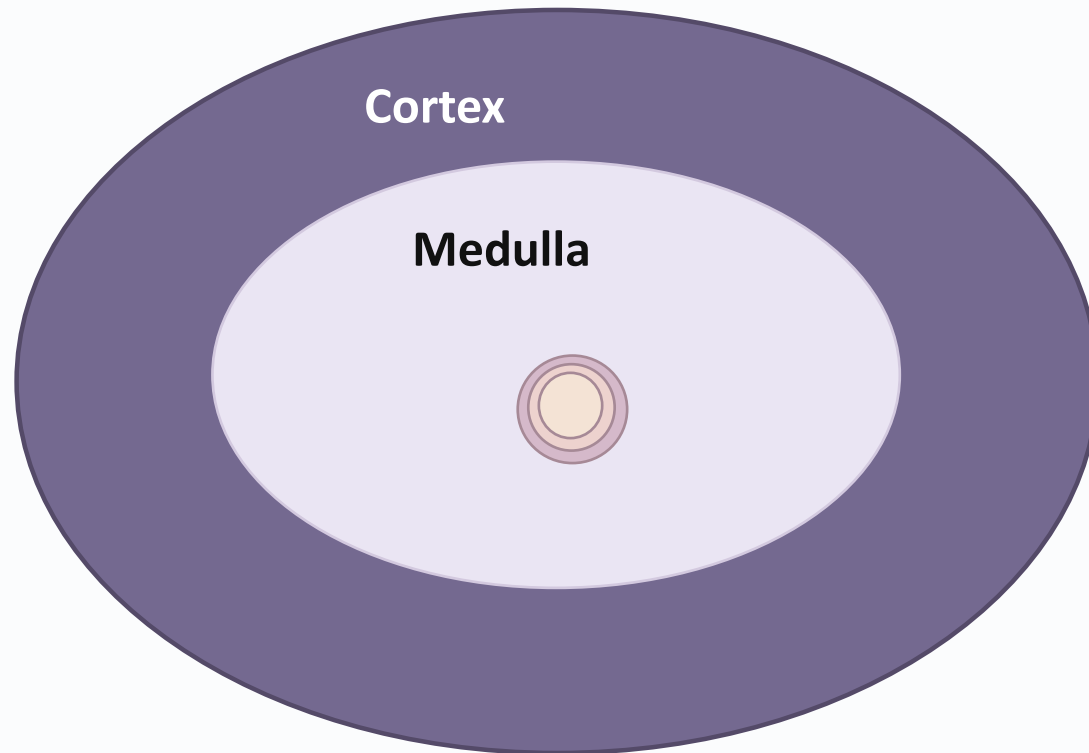
- Cortical thymic epithelial cells are polygonal with abundant cytoplasm.
- Dendritic epithelial extensions connect with adjacent cells.
- Immature thymocytes are a dominant cellular component.
- Cortex and medulla are histologically distinct compartments.

The thymic medulla

- Medullary epithelial cells are densely packed and often spindle-shaped.
- They have relatively scant cytoplasm and lack prominent interconnecting processes.
- Degenerated epithelial whorls create Hassall corpuscles.

Hassall corpuscles identify medullary differentiation

Original schematic — not a photomicrograph



Central whorl: Hassall corpuscle

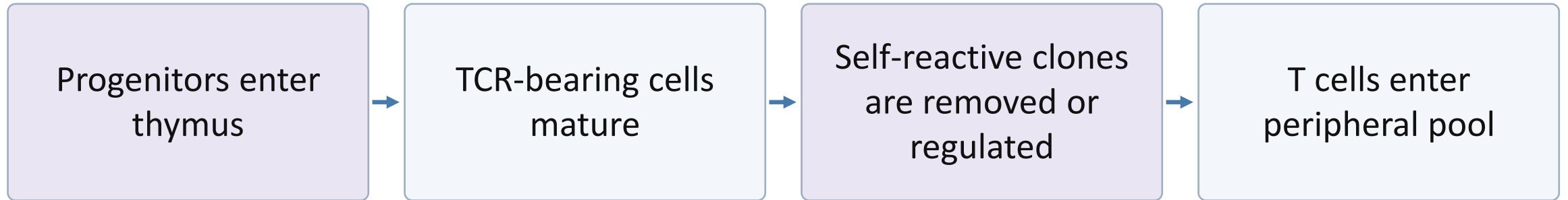
How to read the diagram

- Hassall corpuscles are whorls of epithelial cells.
- Their central material is characteristically keratinized.
- They help orient the observer within the medullary compartment.

Thymic residents beyond epithelial cells

- Immature T cells are the principal lymphoid population.
- Macrophages and dendritic cells also populate the tissue.
- B lymphocytes are normally a minor population.
- Myoid cells with muscle-like features are scattered in the gland.

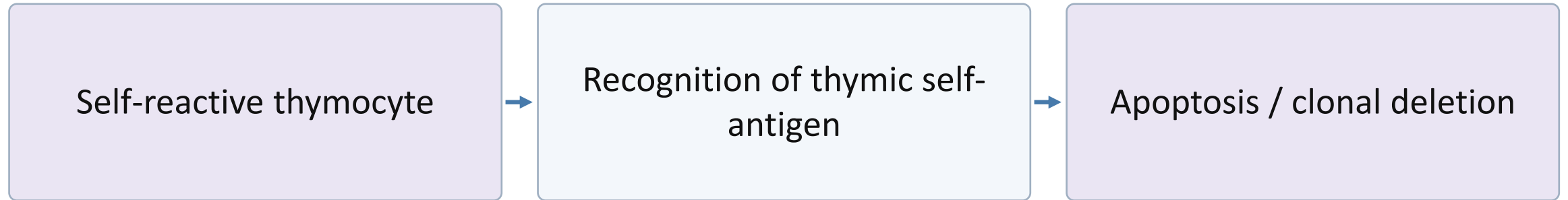
From thymocyte arrival to immune competence



Central tolerance operates in the thymus

- Immature T cells develop receptors through somatic gene rearrangement.
- Some receptors happen to recognize self-antigens strongly.
- Selection mechanisms prevent many potentially harmful clones from entering the mature pool.

Negative selection removes dangerous T cells



AIRE and tissue-restricted self-antigens

- Thymic antigen-presenting cells display many self-proteins.
- AIRE facilitates expression of selected peripheral tissue–restricted antigens.
- This supports deletion of developing T cells reactive to those antigens.
- Failure of this pathway illustrates why thymic tolerance is clinically important.

Central tolerance is not absolute

- Not every self-antigen is represented in central lymphoid organs.
- Some autoreactive lymphocytes escape thymic deletion.
- Peripheral tolerance is then necessary to prevent tissue injury.
- Autoimmunity need not imply a visible structural thymic lesion.

A thymic route to regulatory T cells

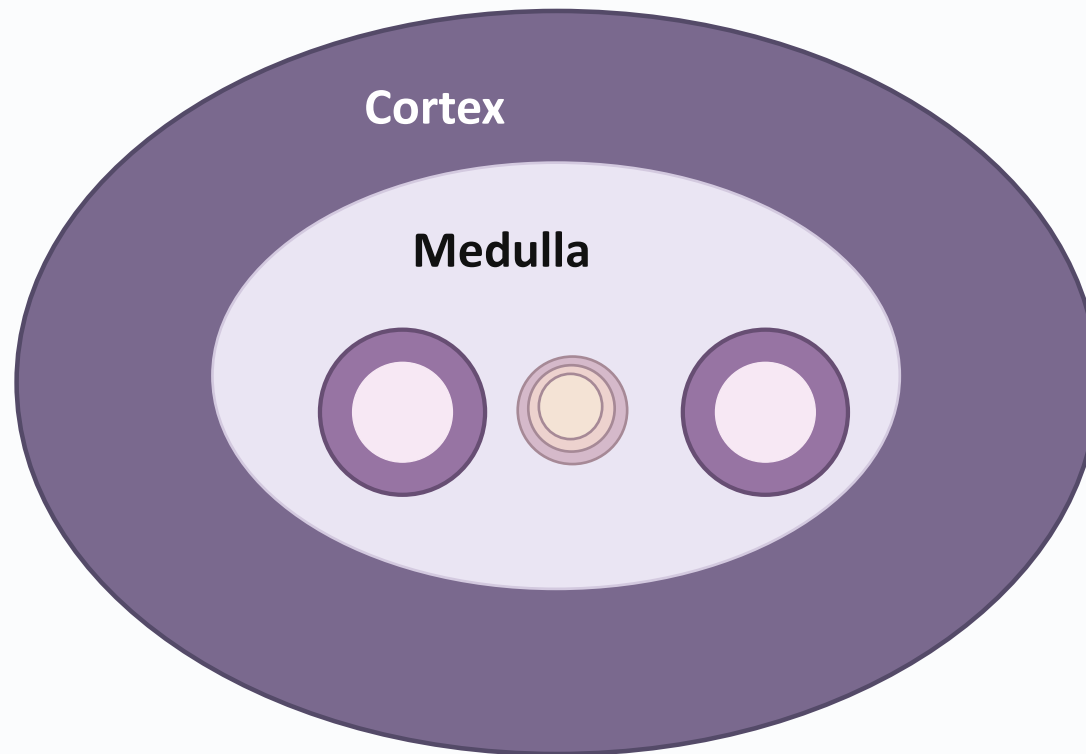
- A subset of developing CD4-lineage T cells becomes regulatory T cells.
- The balance between deletion and regulatory differentiation is incompletely understood.
- Central tolerance therefore includes more than simple destruction of lymphocytes.

B cells are normally sparse in the thymus

- The thymus is primarily a site of T-cell differentiation.
- B-cell follicles are usually present in only small numbers.
- Conspicuous germinal centers therefore change the normal architectural expectation.

Follicular hyperplasia: The microscopic concept

Original schematic — not a photomicrograph



Central whorl: Hassall corpuscle Large circles: B-cell follicles

How to read the diagram

- The defining change is an increase in B-cell follicles.
- Some follicles develop germinal centers.
- Background lobular thymic tissue may still be recognizable.

Why the name can be misleading

- “Hyperplasia” suggests growth of an organ or one of its structural cell populations.
- Here the term usually emphasizes germinal-center formation.
- The tissue finding and total thymic size should be reported as separate observations.

Architecture: Normal versus follicular change

Expected normal thymus

- Cortex and medulla remain identifiable.
- B cells are a minor component.
- Few small follicles may be present.

Follicular hyperplasia

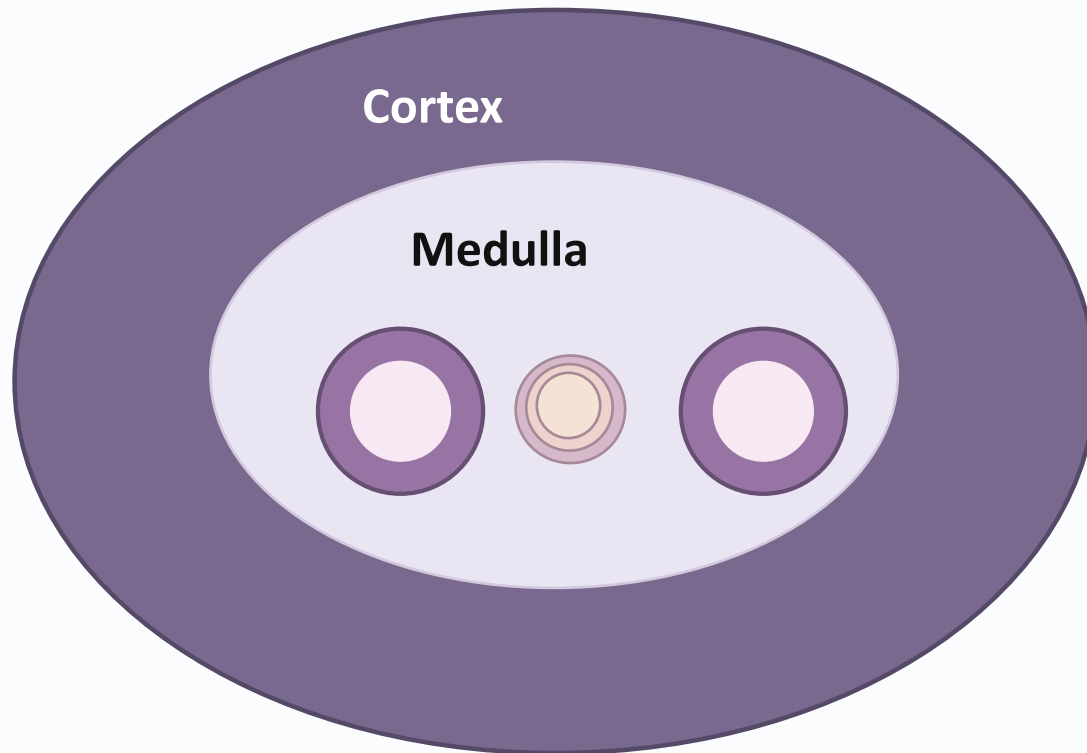
- B-cell follicles become conspicuous.
- Germinal-center formation is evident.
- The appearance reflects a prominent immune response.

What a germinal center signifies

- A germinal center is a specialized structure within a B-cell follicle.
- Its recognition locates an organized B-cell immune response inside the thymus.
- The key diagnostic observation is the follicular pattern, not merely scattered B cells.

Thymic follicular hyperplasia: Spatial map

Original schematic — not a photomicrograph



Central whorl: Hassall corpuscle

Large circles: B-cell follicles

How to read the diagram

- Schematic dark outer cortex and pale medulla orient the viewer.
- Round B-cell follicles with paler centers represent germinal centers.
- Real diagnosis requires genuine microscopy and architectural context.

Describe follicles without overinterpretation

- Record the presence and prominence of intrathymic lymphoid follicles.
- Describe germinal centers when they are actually visible.
- Relate the lymphoid change to preserved or altered thymic compartments.
- Do not label an epithelial tumor solely because lymphoid tissue is dense.

Organ weight and follicle burden answer different questions

Anatomic size

- How large is the gland for this age?
- May fluctuate with physiologic or clinical context.
- Main differential issue can be an apparent mediastinal mass.

Follicular architecture

- Are B-cell follicles conspicuous microscopically?
- Requires tissue-based assessment.
- Links most strongly to autoimmune clinicopathologic settings.

Age-relative thymic enlargement

- Some morphologically normal thymuses are large for the patient's age.
- True hyperplasia versus normal variation is not always clear.
- The principal clinical hazard is radiologic confusion with thymoma.

Two benign patterns should not be conflated

Follicular phenotype

- Defined microscopically by germinal-center proliferation.
- Linked to myasthenia gravis and other autoimmune conditions.
- Large organ volume is not essential.

Morphologically normal enlargement

- Maintains ordinary histology.
- May represent age-related variation rather than a distinct lesion.
- Potentially triggers unnecessary surgery if misidentified as tumor.

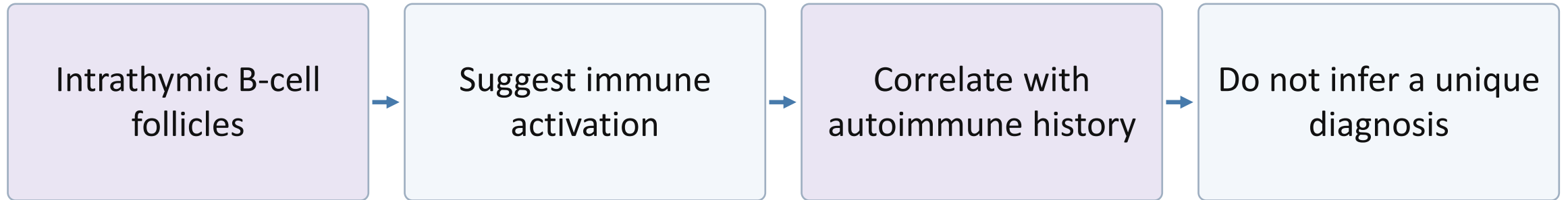
Immunologic diseases linked to follicular change

- Myasthenia gravis is the emphasized association.
- Similar thymic changes also appear with several other immune disorders.
- The histologic pattern does not, by itself, identify the specific autoimmune disease.

Autoimmune associations beyond myasthenia gravis

- Graves disease.
- Systemic lupus erythematosus.
- Systemic sclerosis (scleroderma).
- Rheumatoid arthritis and other autoimmune disorders.

A cautious clinicopathologic interpretation



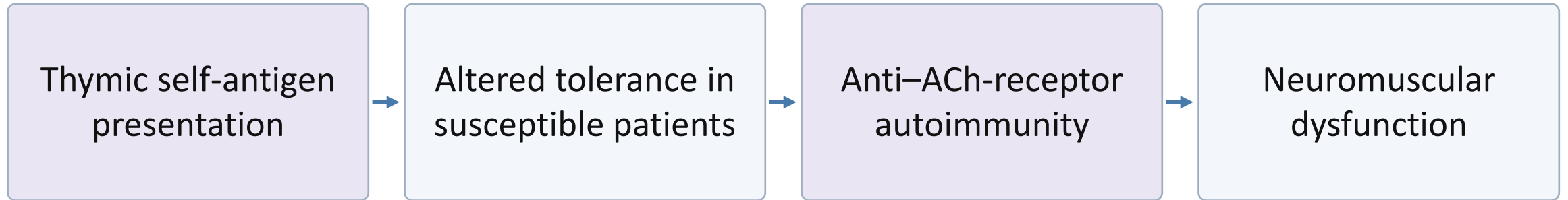
Myasthenia gravis: The central association

- Myasthenia gravis is usually an autoantibody-mediated disorder of the neuromuscular junction.
- Thymic follicular hyperplasia is particularly encountered in the associated thymic pathology.
- A thymoma is a separate thymic abnormality associated with some patients.

Patient age modifies thymic findings

- The myasthenia gravis chapter emphasizes hyperplasia in younger patients.
- Older-onset myasthenia gravis often lacks a detectable thymic abnormality.
- Age and autoimmune phenotype therefore matter when interpreting a thymic specimen.

The proposed thymus–autoimmunity link



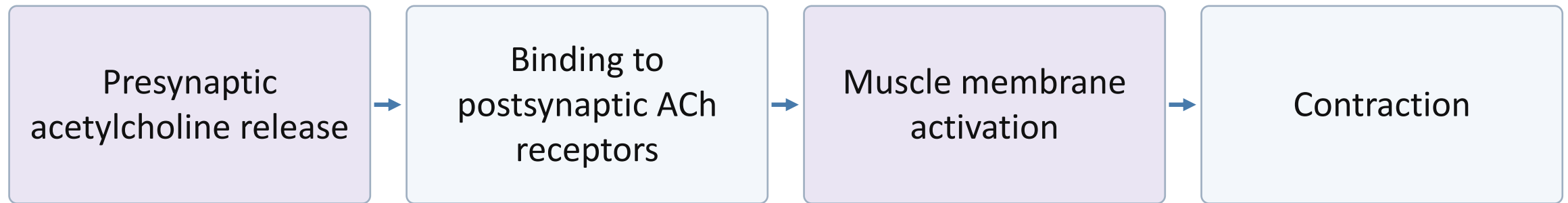
Myoid cells provide relevant tissue context

- The thymus contains scattered muscle-like myoid cells.
- Their possible importance in myasthenia gravis.
- The proposed link is biologically plausible but does not establish causation in an individual patient.

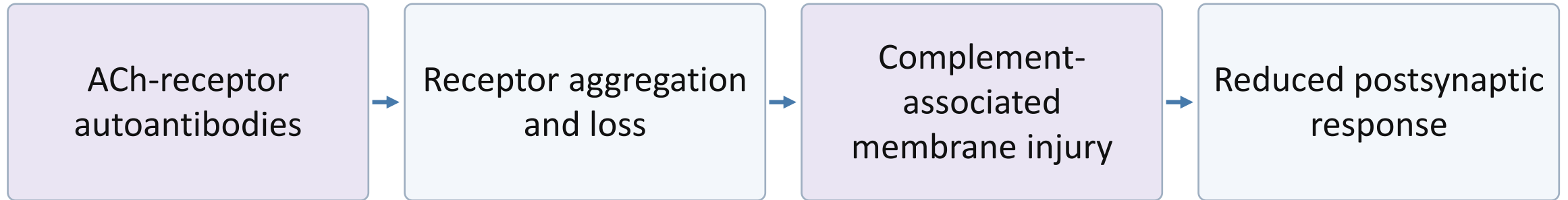
What remains mechanistically uncertain

- The chapter frames disruption of thymic self-antigen expression as a hypothesis.
- Follicular hyperplasia does not prove that a thymic lesion initiated autoimmunity.
- Anti-ACh-receptor autoimmunity can occur without visible thymic abnormalities.

Neuromuscular transmission under normal conditions



Anti-ACh-receptor antibodies impair transmission



Complement damage is mechanistically important

- Anti-ACh-receptor antibodies can activate complement.
- The postsynaptic membrane becomes structurally and functionally impaired.
- The reduction in effective ACh-receptor function produces fatigable weakness.

Not all myasthenia gravis antibodies act alike

Anti-ACh-receptor MG

- Autoantibodies target postsynaptic receptors.
- Receptor depletion and complement-mediated injury are important.
- Strongly linked to characteristic thymic changes.

Anti-MuSK MG

- Targets muscle-specific receptor tyrosine kinase.
- Interferes with ACh-receptor trafficking and clustering.
- Does not rely on the same complement-fixing mechanism.

Why weakness fluctuates in myasthenia gravis

- Impaired transmission reduces the functional safety margin of the neuromuscular junction.
- Clinical weakness commonly worsens with repeated use.
- Symptoms may worsen later in the day and improve with rest.

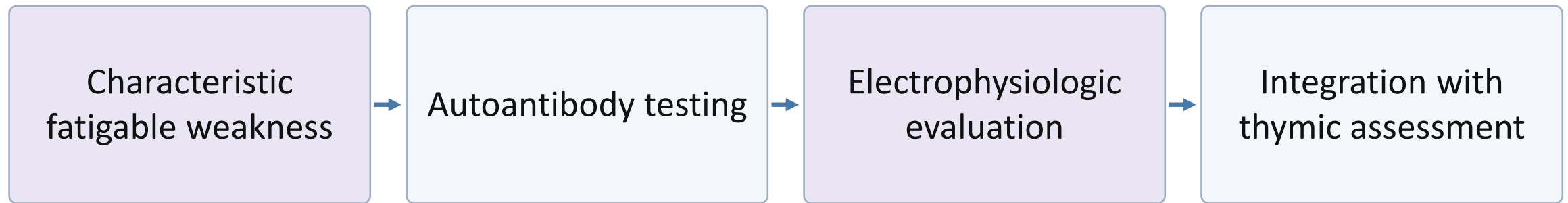
Ocular findings offer a clinical clue

- Diplopia and ptosis are common presentations.
- Extraocular muscle involvement is less typical in many primary myopathies.
- An ocular presentation can precede or accompany generalized weakness.

Generalized disease has clinical consequences

- Patients may develop bulbar, limb, or respiratory muscle weakness.
- Severe involvement may require mechanical ventilatory support.
- Thymic histology should be interpreted in the context of the full clinical phenotype.

Assessing suspected myasthenia gravis



Electrophysiology tests neuromuscular function

- Repeated stimulation can produce a decremental muscle response.
- This result supports a disorder of neuromuscular transmission in the appropriate setting.
- It diagnoses physiological dysfunction, not the microscopic type of thymic change.

The thymic finding does not replace MG diagnosis

- Follicular hyperplasia is a tissue association, not an independent MG diagnostic test.
- Clinical features, autoantibodies, and electrophysiology remain central.
- Likewise, normal-appearing thymic tissue does not exclude myasthenia gravis.

Thymic histology does not determine MG therapy

- A thymoma and non-neoplastic hyperplasia are different pathologic entities.
- Microscopic follicular hyperplasia is not, by itself, a treatment algorithm.
- Clinical subtype, severity, imaging, and contemporary evidence are needed for management.
- Robbins provides a pathology framework rather than a current treatment guideline.

Thymoma is a thymic epithelial neoplasm

- The word thymoma is restricted to tumors of thymic epithelial cells.
- Benign immature thymocytes can be present within thymomas.
- A lymphocyte-rich field is therefore not sufficient to classify a lesion.

Reactive follicles versus epithelial neoplasia

Follicular hyperplasia

- Prominent B-cell follicles with germinal centers.
- Non-neoplastic reactive thymic pattern.
- Autoimmune association is common.

Thymoma

- Neoplastic proliferation of thymic epithelial cells.
- Often accompanied by non-neoplastic immature T cells.
- Invasion and epithelial cytology matter clinically.

The thymoma differential has an anatomic setting

- Thymomas most often arise in the anterior superior mediastinum.
- Other thymic-region neoplasms include lymphomas and germ cell tumors.
- An apparently enlarged thymus requires consideration of non-neoplastic and neoplastic causes.

Invasion is not a feature of ordinary hyperplasia

- The chapter distinguishes thymomas by epithelial cytology and invasive behavior.
- Invasive thymoma extends beyond the capsule to adjacent tissues.
- A benign-appearing thymic gland must not be conflated with locally invasive epithelial tumor.

Three pathologic categories encountered at the thymus

Finding	Primary feature	Clinical implication
Follicular hyperplasia	Intrathymic B-cell germinal centers	Seek compatible autoimmune setting
Large normal-appearing thymus	Age-relative enlargement, preserved architecture	Risk of radiologic tumor mimicry
Thymoma	Neoplastic thymic epithelial population	Assess epithelial tumor and invasion

Cystic findings require a different question

- Isolated thymic cysts are uncommon and usually clinically insignificant.
- Neoplastic masses may compress normal thymus and cause cyst formation.
- A symptomatic cystic thymic lesion warrants evaluation for an underlying neoplasm.

Hypoplasia and hyperplasia are opposite thymic problems

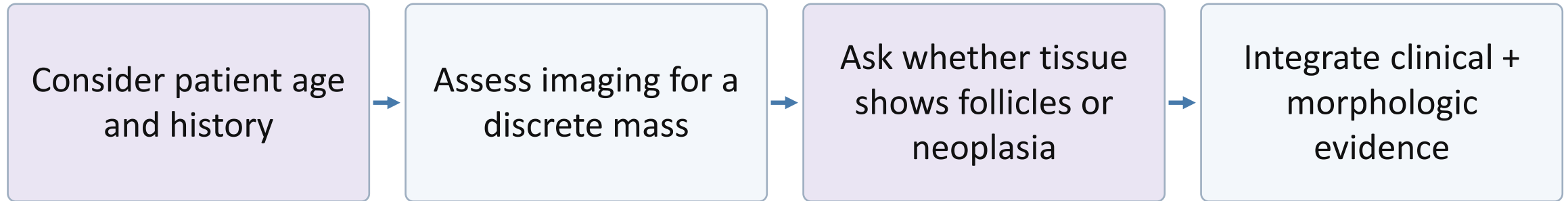
Developmental hypoplasia/aplasia

- Associated with DiGeorge syndrome.
- Severe deficiency of cell-mediated immunity.
- Often part of 22q11 deletion syndrome.

Hyperplastic patterns

- Preserved thymus with B-cell follicles or relative enlargement.
- May be associated with autoimmune disease.
- Does not imply a primary absence of T-cell development.

A structured approach to a prominent thymus



Diagnostic pitfalls in small or partial samples

- Sampled tissue may fail to represent the overall thymic architecture.
- Scattered lymphocytes must not be mistaken for a thymoma without epithelial evidence.
- The presence of follicles alone does not diagnose a particular autoimmune disorder.
- Morphology, age and clinical data should be considered together.

Case 1 — fatigable ocular weakness

A young adult reports fluctuating ptosis and diplopia. A resected thymus shows preserved thymic compartments with numerous B-cell follicles and germinal centers.

Interpretation question

What is the best morphologic designation?

Case 1 — interpretation

Thymic follicular hyperplasia

- Germinal-center-rich B-cell follicles are the central tissue finding.
- Myasthenia gravis is the classic clinical association.
- The finding does not require a grossly enlarged thymus.

Case 2 — a prominent anterior mediastinal gland

An adolescent has a prominent thymic contour on imaging. Histology, if obtained, shows ordinary lobular cortex–medulla organization without excess follicles or an epithelial tumor.

Interpretation question

Is the term follicular hyperplasia justified?

Case 2 — interpretation

No: Prominence of size is not follicular hyperplasia

- Age-relative normal size is variable.
- Normal architecture argues against a follicular lesion.
- Robbins warns that this situation may be mistaken radiologically for thymoma.

Case 3 — a symptomatic cystic lesion

A symptomatic patient has an anterior mediastinal cystic lesion. Adjacent thymic tissue appears distorted and compressed.

Interpretation question

What pathologic possibility must be actively considered?

Case 3 — interpretation

Search for an associated neoplasm

- Cystic change can be secondary to a thymic-region neoplasm.
- Thymoma and lymphoma are specific considerations.
- Cystic appearance alone does not establish a harmless thymic cyst.

Synthesis: Tissue observation versus diagnosis

Observation in the thymus

- Germinal centers → follicular process.
- Normal architecture with prominence → age-relative size question.
- Epithelial proliferation/invasion → consider thymoma.

Required interpretation

- Correlate follicles with autoimmune context.
- Correlate size with age and radiology.
- Classify tumors through epithelial morphology and behavior.

What students should retain

- Follicular hyperplasia means prominent B-cell germinal centers—not necessarily a large gland.
- Myasthenia gravis is a key association, but causality should not be overstated.
- Age-relative thymic enlargement is a recognized mimic of thymoma.
- When a mass is suspected, separate reactive thymus from epithelial neoplasia.

Selected source material

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026).

- Chapter 13: Thymus — normal architecture, developmental disorders, thymic hyperplasia, and thymoma.
- Chapter 6: Central tolerance, clonal deletion, AIRE, and regulatory T-cell differentiation.
- Chapter 27: Myasthenia gravis — autoantibodies, neuromuscular pathogenesis, and thymic associations.