ENDOCRINOLOGY

THYROID

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Thyroid development

- Arises from floor of primitive pharynx, descends into neck.
- Connected to tongue by thyroglossal duct. May persist as pyramidal lobe of thyroid (in 50% of patients).
- Foramen cecum (floor of mouth) is remnant of thyroglossal duct.
- Most common site of ectopic thyroid tissue is the tongue.

Thyroglossal duct cyst

- Most common clinically significant congenital anomaly of the thyroid.
- A sinus tract may persist as a vestige of the tubular development of
- the thyroid gland.
- Parts of this tube may be obliterated, leaving small segments to form cysts.
- These occur at any age..

Thyroglossal duct cyst

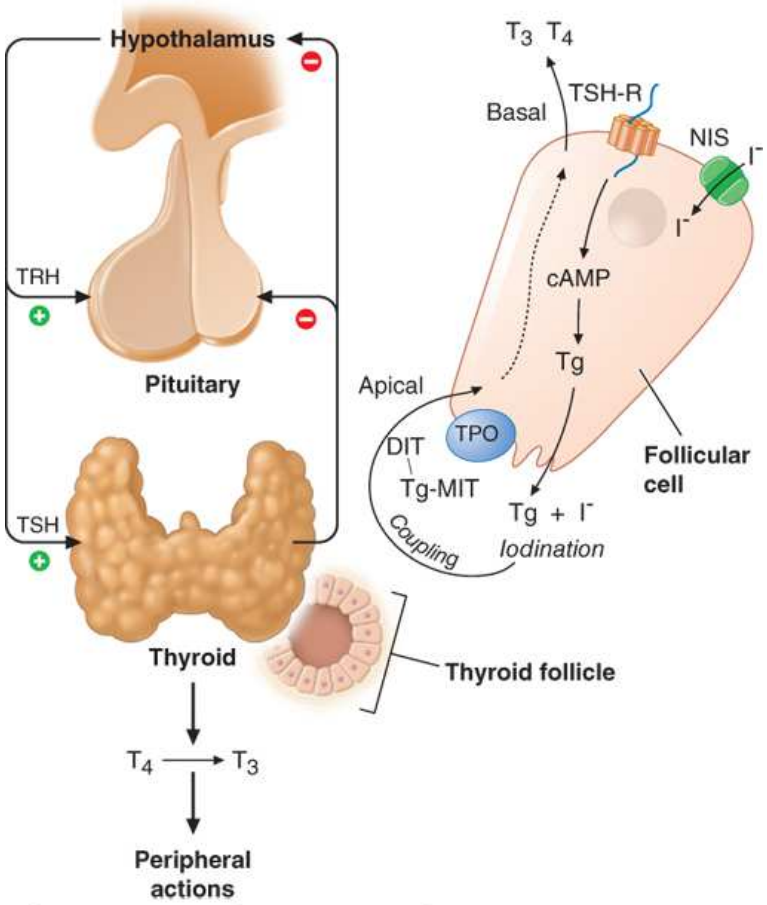
- Mucinous, clear secretions may collect within the cysts to form either spherical masses or fusiform swellings, rarely over 2 to 3 cm in diameter, that present in the midline of the neck anterior to the trachea.
- Segments of the duct and cysts that occur high in the neck are lined by stratified squamous epithelium resembling the covering of the posterior portion of the tongue in the region of the foramen cecum.

Thyroglossal duct cyst

- Anomalies that occur in the lower neck more proximal to the thyroid gland are lined by epithelium resembling the thyroidal acinar epithelium.
- Characteristically, subjacent to the lining epithelium, there is an intense lymphocytic infiltrate.

Thyroid function

- TRH (hypothalamus) stimulates pituitary to produce TSH, which stimulates follicular cells.
- Iodine transporter dependent upon Na^+-K^+ ATPase.
- Tyrosine iodinated, coupled in the cell.
- Joined to thyroglobulin in the follicular space.
- Taken back up by the cell where T_3 and T_4 produced.
- Released by hydrolysis.



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Regulation of thyroid hormone synthesis. Left. Thyroid hormones T_4 and T_3 feedback to inhibit hypothalamic production of thyrotropin-releasing hormone (TRH) and pituitary production of thyroid-stimulating hormone (TSH). TSH stimulates thyroid gland production of T_4 and T_3. Right. Thyroid follicles are formed by thyroid epithelial cells surrounding proteinaceous colloid, which contains thyroglobulin. Follicular cells, which are polarized, synthesize thyroglobulin and carry out thyroid hormone biosynthesis (see text for details). DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium iodide symporter; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH-R, thyroid-stimulating hormone receptor.

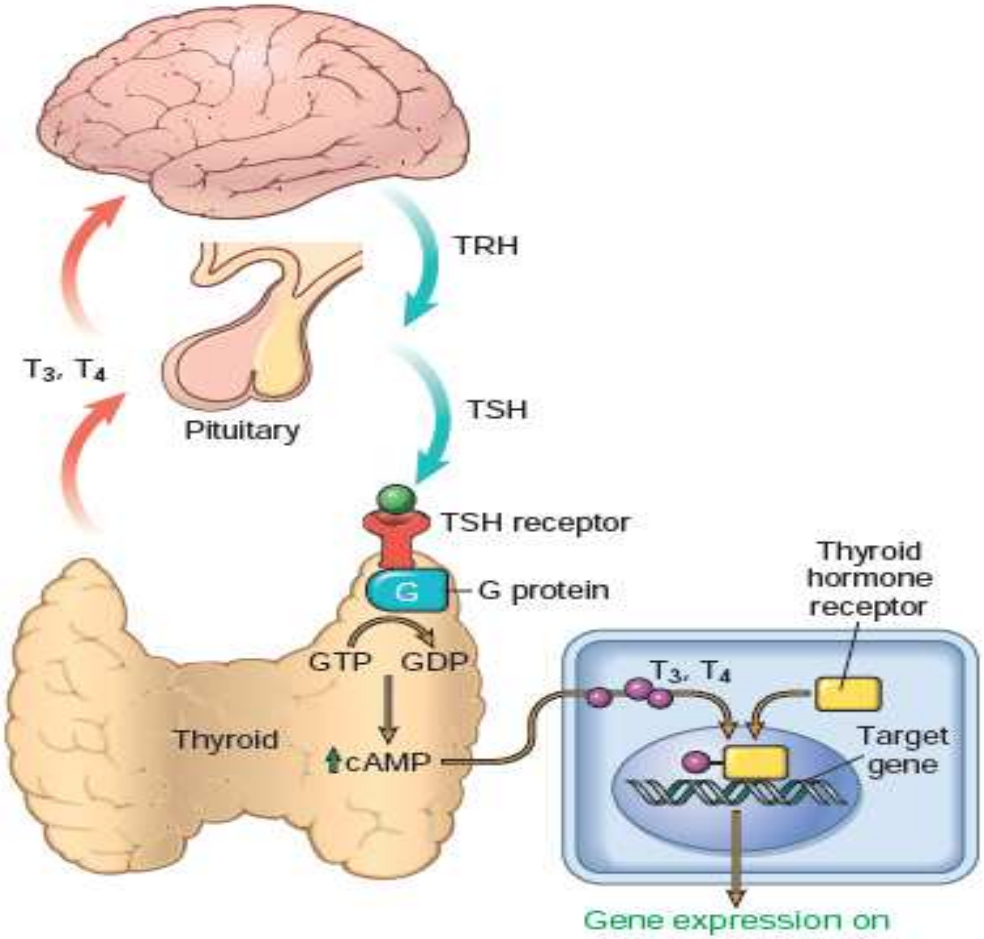


Figure 24-8 Homeostasis in the hypothalamus-pituitary-thyroid axis and mechanism of action of thyroid hormones. Secretion of thyroid hormones (T_3 and T_4) is controlled by trophic factors secreted by both the hypothalamus and the anterior pituitary. Decreased levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the anterior pituitary, causing T_3 and T_4 levels to rise. Elevated T_3 and T_4 levels, in turn, feed back to suppress the secretion of both TRH and TSH. TSH binds to the TSH receptor on the thyroid follicular epithelium, which causes activation of G proteins, and cAMP-mediated synthesis and release of thyroid hormones (T_3 and T_4). In the periphery, T_3 and T_4 interact with the thyroid hormone receptor (TR) to form a hormone-receptor complex that translocates to the nucleus and binds to so-called thyroid response elements (TREs) on target genes to initiate transcription.

Thyroid function

- Only free hormone acts on the cell
- 99% is protein bound, to thyroid binding globulin (TBG)
- 80% circulating thyroid hormone is T_4
- 80% of T_4 is converted to T_3 .
- T_3 binds to thyroid hormone nuclear receptors in target cells, upregulating transcription
- Negative feedback by T_3 to anterior pituitary.

Thyroid hormone

- The unoccupied thyroid hormone receptor (as well as the retinoid x receptor) is bound to DNA and represses transcription.
- It is part of the steroid receptor super-family.
- Binding of thyroid hormone to the receptor allows gene transcription to take place.
- Stimulates protein synthesis and degradation, contributing to bone growth and differentiation in synergy with GH.
- Affect CNS maturation (high density of TSH receptors).

Thyroid hormone

- Stimulates transcription of cell membrane Na^+/K^+-ATPase, leading to an increase in oxygen consumption
- Stimulates transcription of uncoupling protein, enhancing fatty acid oxidation and heat generation without production of ATP
- Stimulates epinephrine-induced glycogenolysis and gluconeogenesis, affecting insulin-induced glycogen synthesis and glucose utilization

Thyroid hormone

- Stimulates cholesterol synthesis and low-density lipoprotein receptor regulation.
- The induction of catecholamine-mediated lipolysis by thyroid hormones results from an increased β-adrenoceptor number and a decrease in phosphodiesterase activity resulting in an increase in cAMP level and hormone-sensitive lipase activity.
- Thyroid hormones are necessary for hepatic conversion of carotene to vitamin A.

Thyroid hormone

- T_3 is not formed from T_4 in myocytes.
- Circulating T_3 enters the myocytes and enhances the genes for -myosin heavy chain, sarcoplasmic reticulum Ca^{2+}-ATPase, adrenergic receptors, G proteins, Na^+/K^+-ATPase, and certain K^+ channels.
- Circulating T_3 inhibits the genes for β-myosin heavy chain, phospholamban, two types of adenylyl cyclase, T_3 nuclear receptors, and the Na^+–Ca^{2+} exchanger.
- The net result is increased heart rate and force of contraction.

Thyroid hormone

- Thyroid gland follicles also contain a population of parafollicular cells, or C cells, which synthesize and secrete calcitonin.
- This hormone promotes the absorption of calcium by the skeletal system and inhibits the resorption of bone by osteoclasts
- Goitrogens inhibit thyroid function
- Propylthiouracil inhibits the oxidation of iodide as well as the conversion of T_4 to T_3 in the periphery.

Symptoms of thyroid hormone excess

- Typical complaints include nervousness, irritability, excessive sweating, emotional lability, increased appetite, insomnia, headache, diarrhea, and weight loss.
- Amenorrhea may be seen in women.
- In children, performance is typically affected by a shortened attention span, restlessness, and deterioration in penmanship such as in ADD.
- In the elderly, weight loss, diarrhea, or atrial fibrillation may be the only signs.

Signs of thyroid hormone excess

- (1) An increase in the basal metabolic rate.
- The skin of thyrotoxic patients tends to be soft, warm, and flushed because of increased blood flow and peripheral vasodilation
- Adaptations that serve to increase heat loss.
- Heat intolerance is common.
- Sweating is increased because of higher levels of calorigenesis.
- Heightened catabolic metabolism results in weight loss despite increased appetite.

Signs of thyroid hormone excess

- (2) Increased β-adrenergic tone (peripheral amination of thyroid hormone).
- Cardiac manifestations are among the earliest and most consistent features.
- Cardiac contractility and cardiac output elevated in response to increased peripheral oxygen requirements.
- Tachycardia, palpitations common.
- May develop low-output cardiac failure (hyperthyroid cardiomyopathy)
- Atrial fibrillation common in older patients.

Signs of thyroid hormone excess

- (3) Overactivity of the sympathetic nervous system
- Tremor, hyperactivity, emotional lability, anxiety, inability to concentrate, and insomnia.
- Proximal muscle weakness and decreased muscle mass are common (thyroid myopathy).
- In the gastrointestinal system, sympathetic hyperstimulation of the gut results in hypermotility, diarrhea, and malabsorption.

Signs of thyroid hormone excess

- A wide, staring gaze and lid lag are present because of sympathetic overstimulation of the superior tarsal muscle (also known as Müller's muscle), which functions alongside the levator palpebrae superioris muscle to raise the upper eyelid
- Osteoporosis as thyroid hormone stimulates bone resorption, increasing porosity of cortical bone and reducing the volume of trabecular bone.
- Apathetic hyperthyroidism may be seen in older adults whose comorbidities blunt effect of hormone.

Causes of thyroid hormone excess

- Graves' disease (diffuse hyperplasia, infiltrative dermatopathy, ophthalmopathy),
- 85% of cases
- 3% of US cases in women; in men, 0.5%.
- Thyrotoxicosis in children is almost always secondary to Graves' disease.
- Neonatal thyrotoxicosis associated with maternal Graves’ disease
- Multinodular toxic goiter
- 15% of cases
- Hyperfunctional thyroid adenoma

Causes of thyroid hormone excess

- Multinodular toxic goiter
- 15% of cases
- Hyperfunctional thyroid adenoma
- Excessive TSH secretion (pituitary adenoma).
- A thyroid with both lobes larger than the patient's distal thumb is considered probably enlarged (positive likelihood ratio, LR+, 4.7; LR-, 0.1).

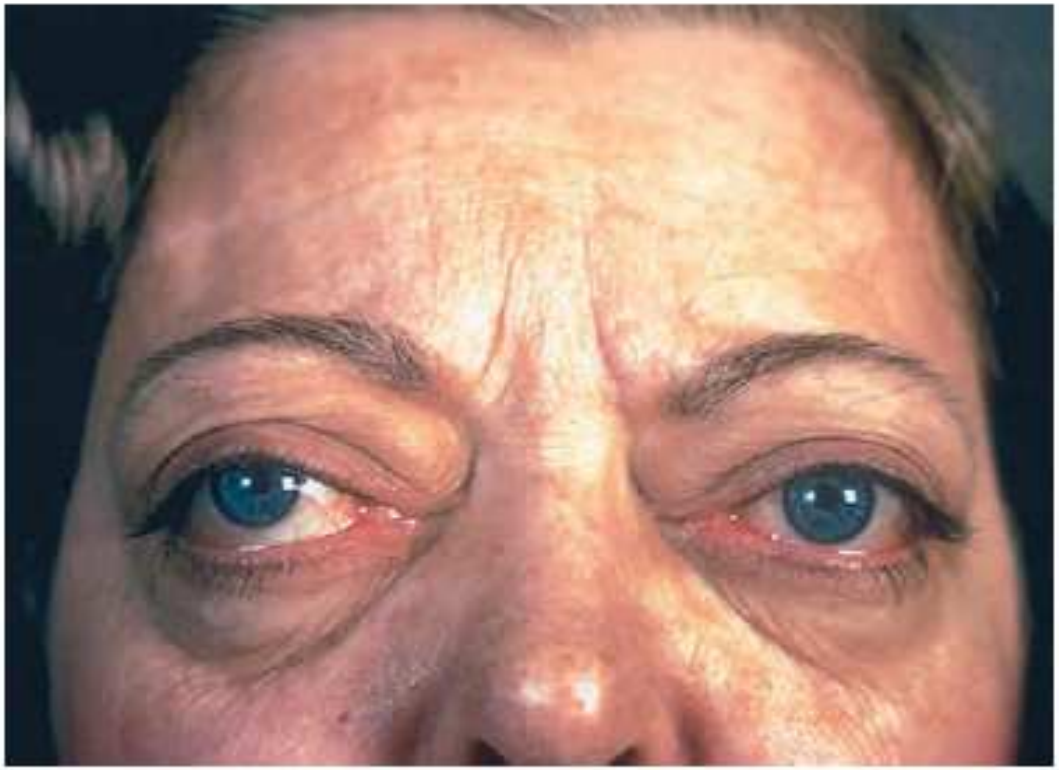


Figure 24-9 A person with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system, is one of the features of this disorder. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue behind the eyeballs, also adds to the protuberant appearance of the eyes.

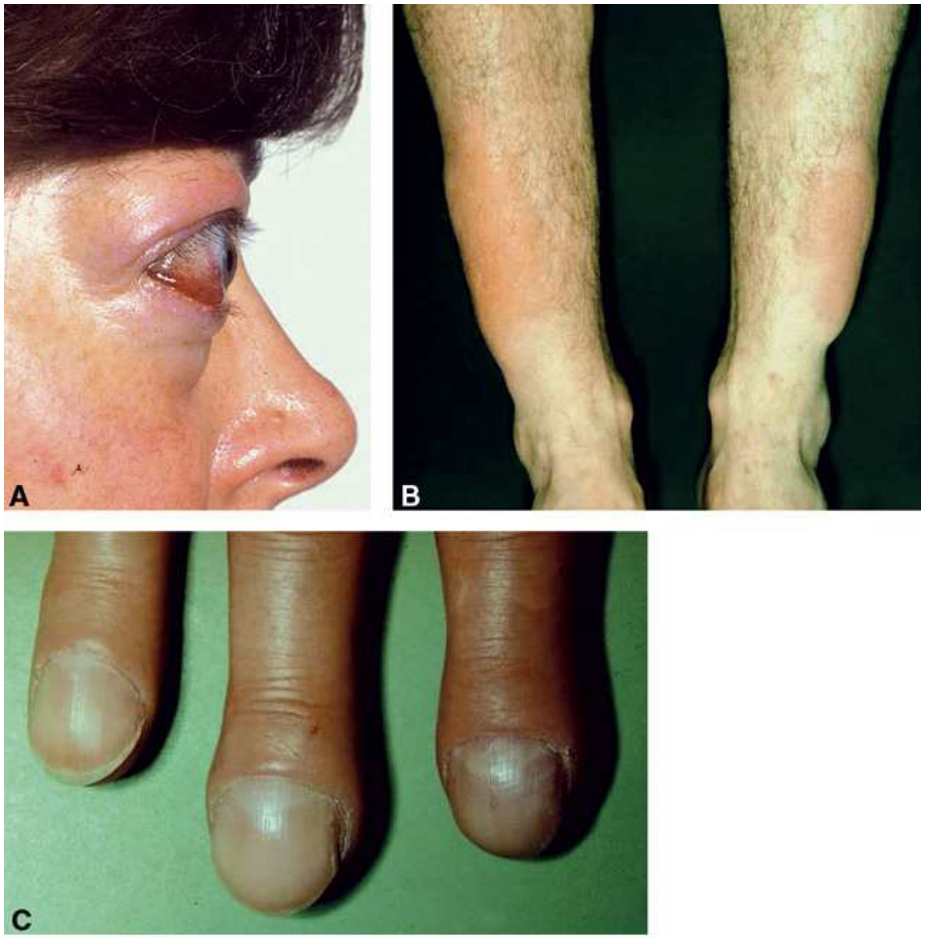
Signs of thyroid hormone excess

- Persistent tachycardia, systolic hypertension with a wide pulse pressure, eyelid retraction, tremulousness of outstretched hands, and smooth, moist, warm skin
- Reflexes are increased; fine straight hair
- Diffusely enlarged gland
- Mild itching of the lids, lacrimation, mild proptosis
- Ophthalmopathy not common in children

Grave's disease

- Triad of clinical findings
- Hyperthyroidism associated with diffuse enlargement of the gland
- Infiltrative ophthalmopathy with resultant exophthalmos
- Localized, infiltrative dermopathy (pretibial myxedema) which is present in a minority of patients
- 20-40 years of age
- Women 10:1
- CTLA4 or PTPN22 polymorphisms as well as polymorphisms in HLA-DR3 allele
- Concordance rate in monozygotic twins is 40%

Features of Grave's disease



A. Ophthalmopathy in Graves' disease: lid retraction, periorbital edema, conjunctival injection, and proptosis are marked.
B. Thyroid dermopathy (scaly thickening and induration) over the lateral aspects of the shins, the usual site.
C. Thyroid acropathy.

Fig. 335-7 Accessed 02/01/2010

Grave's disease

- Ophthalmopathy
- (1) marked infiltration of the retro-orbital space by mononuclear cells, predominantly T cells
- (2) inflammation with edema and swelling of extraocular muscles
- (3) accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate
- (4) increased numbers of adipocytes (fatty infiltration).
- The eyeball is displaced forward; may interfere with the function of the extraocular muscles.

Grave's disease

- Thyroid stimulating immunoglobulin (TSI) binds to the TSH receptor and mimics its actions, stimulating adenyl cyclase and increasing the release of thyroid hormones.
- Orbital preadipocyte fibroblasts express TSH receptors
- Ophthalmopathy a result of such stimulus
- Activated CD4+ helper T cells secrete cytokines that stimulate fibroblast proliferation and synthesis of extracellular matrix proteins (glycosaminoglycans)

Grave's disease

- Some patients also have TSH receptor blocking antibodies
- In a minority of patients these may lead to hypothyroidism.
- Dermatopathy is an accumulation of extracellular matrix components, specifically hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate
- Scaling thickening and induration

Pathologic criteria of Grave's disease

- The thyroid gland is usually symmetrically enlarged due to diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells
- The follicles are lined by crowded columnar cells, which may pile up and form projections into the lumen
- Papillae without a fibrovascular core.
- Scalloped colloid.
- Mononuclear cell infiltrate.
- Germinal center formation may be seen.
- Avid Iodine uptake on isotope scan

Pathologic change with treatment

- Administration of iodine causes involution of the epithelium and the accumulation of colloid by blocking thyroglobulin secretion.
- Treatment with the antithyroid drug propylthiouracil exaggerates the epithelial hypertrophy and hyperplasia by stimulating TSH secretion.

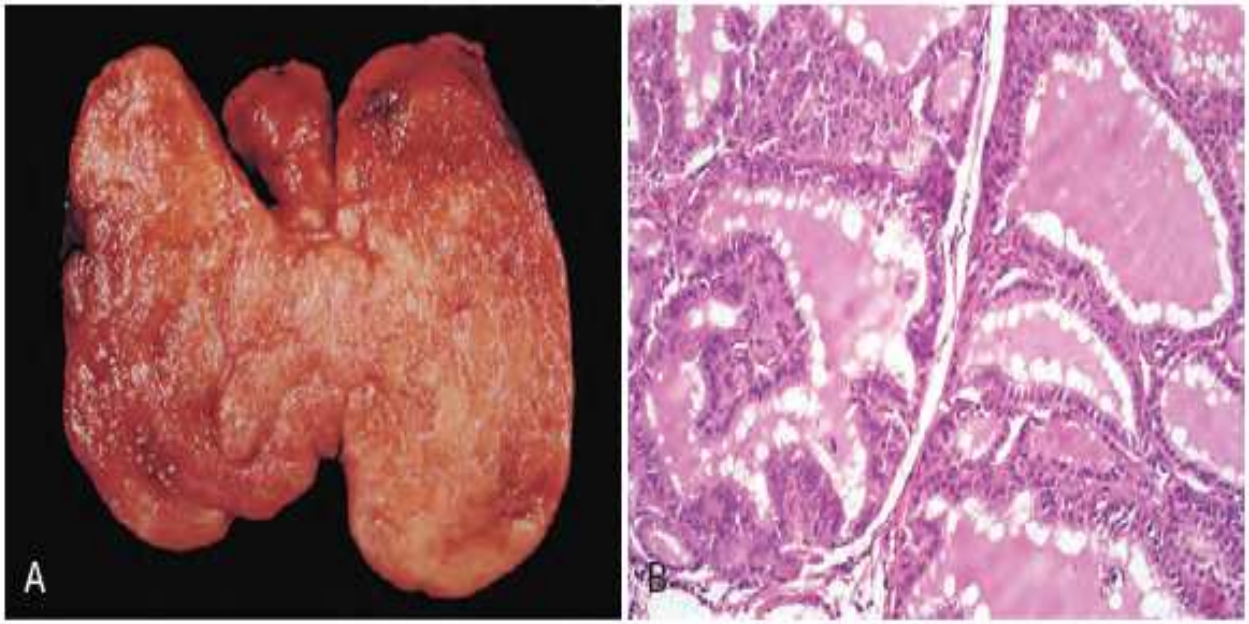


Figure 24-13 Graves disease. **A,** There is diffuse symmetric enlargement of the gland and a beefy deep red parenchyma. Compare with gross photograph of multinodular goiter in Figure 24-15. **B,** Diffusely hyperplastic thyroid in a case of Graves disease. The follicles are lined by tall, columnar epithelium. The crowded, enlarged epithelial cells project into the lumens of the follicles. These cells actively resorb the colloid in the centers of the follicles, resulting in the scalloped appearance of the edges of the colloid. (**A,** Reproduced with permission from Lloyd RV, et al (eds): Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)

Goiter

- Impaired synthesis of thyroid hormone
- Leads to a compensatory rise in TSH, which, in turn, causes hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, gross enlargement of the thyroid gland.
- The compensatory increase in functional mass of the gland overcomes the hormone deficiency.
- If response is inadequate, goitrous hypothyroidism

Diffuse nontoxic (simple) goiter

- Causes enlargement of the entire gland without producing nodularity.
- The enlarged follicles are filled with colloid (colloid goiter)
- Endemic in areas where little iodide is present in the soil
- Goitrogens that may contribute to development include cabbage, cauliflower, Brussels sprouts, turnips, and cassava
- Cassava contains a thiocyanate that interferes with intracellular transport of iodine

Diffuse nontoxic (simple) goiter

- The thyroid gland is diffusely and symmetrically enlarged.
- The follicles are lined by crowded columnar cells, which may pile up and form projections into the lumen
- Some follicles are hugely distended, whereas others remain small.

Diffuse nontoxic (simple) goiter

- If dietary iodine subsequently increases or if the demand for thyroid hormone decreases, the stimulated follicular epithelium involutes to form an enlarged, colloid-rich gland.
- The cut surface of the thyroid is usually brown, somewhat glassy, and translucent.
- Histologically the follicular epithelium is flattened and cuboidal, and colloid is
- abundant during periods of involution.

Multinodular goiter

- Virtually all longstanding simple goiters convert into multinodular goiters.
- Both polyclonal and monoclonal nodules coexist within the same multinodular goiter, the latter presumably having arisen because of the acquisition of a genetic abnormality favoring growth.
- Patchy uptake on radioiodine scan

Multinodular goiter

- Activating mutations affecting proteins of the TSH-signaling pathway have been identified in a subset of autonomous thyroid nodules in multinodular goiter
- 10% of cases
- Plummer syndrome is hyperthyroidism without infiltrative ophthalmopathy and dermatopathy (toxic multinodular goiter)

Multinodular goiter

- Due to size, may exert mass effects on trachea or esophagous. May grow into retrosternal space.
- Atrophic follicles alternate with hyperplastic follicles. No capsule separates hyperplastic areas from the remainder of the gland.
- Hürthle cells are prominent.
- Heavy mononuclear cell inflammatory infiltrate. Germinal centers prominent.
- Fibrosis.

Table 25.2 Contrasting features of simple and nodular goitre.

FEATURE	DIFFUSE GOITRE	NODULAR GOITRE
1. Nomenclature	Simple goitre, hyperplastic goitre, nontoxic goitre	Multinodular, adenomatous goitre
2. Etiology	Graves' disease, thyroiditis, puberty	Endemic thyroiditis, cancer
3. Pathogenesis	Hyperplasia-involution	Repeated cycles of hyperplasia with growth and involution with fibrosis
4. Composition	Cellular-rich	Colloid-rich
5. Gross	Moderate, symmetric, diffuse enlargement, colloid-filled follicles, gelatinous	Nodular asymmetric, haemorrhages, scarring, cystic change, calcification
6. Microscopy	Hyperplastic phase: papillary infoldings, Involution stage: large colloid filled follicles with flat epithelium	Incomplete encapsulation, nodularity, variable-sized follicles, fibrous scarring, haemorrhages, calcification, cyst formation
7. Functional status	Hyperthyroidism, euthyroid	Hypothyroidism, euthyroid

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

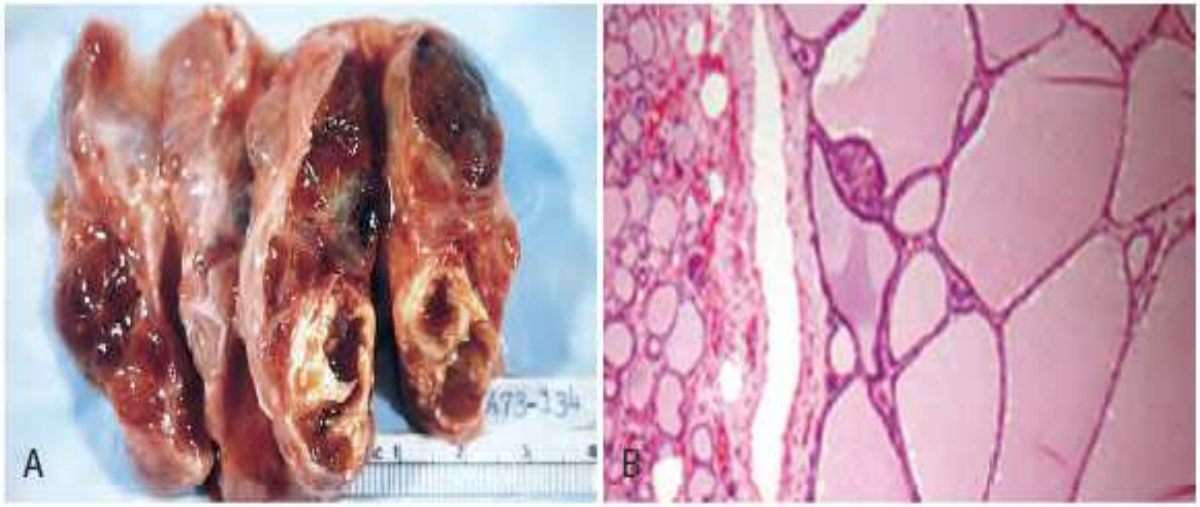
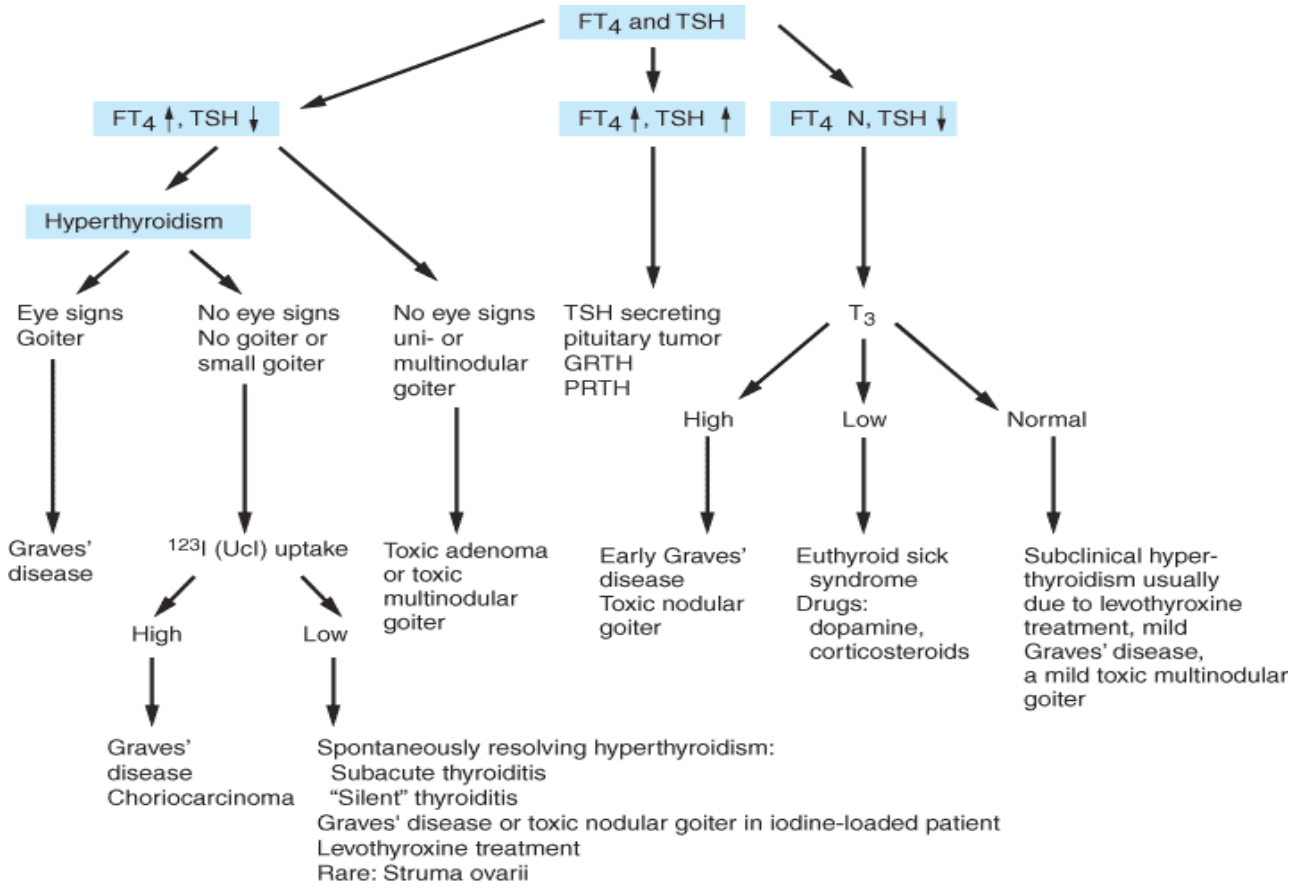


Figure 24-15 Multinodular goiter. **A,** Gross morphology demonstrating a coarsely nodular gland, containing areas of fibrosis and cystic change. **B,** Photomicrograph of a hyperplastic nodule, with compressed residual thyroid parenchyma on the periphery. Note absence of a prominent capsule, a distinguishing feature from follicular neoplasms. (**B,** Courtesy Dr. William Westra, Department of Pathology, Johns Hopkins University, Baltimore, Md.)

Diagnostic strategy



TSH is secreted in a pulsatile fashion with highest levels at midnight.

Fig. 8-37 Accessed 02/01/2010

Routine thyroid testing

- Patients with a family history of thyroid disease
- Asymptomatic patients older than 60
- Perimenopausal women
- Pregnant women older than 35 as well as those post-partum
- Diabetics
- Patients with autoimmune disease

Routine thyroid testing

- Patients with new onset of dementia or psychiatric disease
- Patients with new onset of heart disease
- Patients with obstructive sleep apnea
- Patients on Lithium therapy [ion uncouples receptor from its G-protein]

Enlarged thyroid gland

- If TSH elevated but fT_4 normal or low, and thyroid gland is diffusely enlarged, and there is no evidence of obstruction, a trial of thyroxine suppression of the pituitary is warranted. (Thyroxine is a T_4 analogue, binds to nuclear receptors.)
- If TSH and fT_4 normal, and thyroid gland is diffusely enlarged, and there is no evidence of obstruction, a trial of thyroxine suppression of the thyroid is warranted.
- If TSH is suppressed and fT_4 normal, exogenous hormone suppression not indicated as this may lead to escape by autonomous nodule.

Medical therapy

- PTU (propylthiouracil) is the drug of choice, particularly in those under 18 years of age. PTU blocks intrathyroidal synthesis of thyroxine and peripheral conversion of T_4 to T_3. (The other thionamide, methimazole, inhibits synthesis only.)
- 4-6 weeks of therapy before euthyroid; goiter may shrink in 50% of patients. Glands greater than three times normal size do not respond well.
- Medications needed for 18-24 months.
- Ophthalmopathy may not resolve. May require radiation to orbit.

Surgical therapy

- It is best to treat the thyroid gland when it is still small.
- As the gland enlarges, the risk of damage to the recurrent laryngeal nerve also increases if thyroidectomy is undertaken.
- Surgery in second trimester optimal for pregnant patient.
- Thyroid replacement will be required.

Radio-iodine therapy

- Radioiodine (^{131}I) is the preferred treatment for multinodular goiter. Concentrated in the gland. ^{131}I is a β-emitter with an 8 day half-life. Leads to gland necrosis. Two possible complications are thyroid storm and late hypothyroidism.
- Block Iodine uptake in salivary glands (via Na^{+}-I^{-} symporter) with perchlorate administration.
- Laxatives to protect intestinal mucosa.
- β-blocker for symptom control; also blocks intrathyroidal coversion of T_4 to T_3.

Thyroid storm

- Thyroid storm is a medical emergency.
- Thyroid storm is due to a pulsed release of thyroid hormone secondary to gland destruction, often following radioiodine ablation.
- Tachycardia and systolic hypertension predominate. Myocardial Oxygen demand increases.
- β-blocker for symptom control; also blocks intrathyroidal conversion of T_4 to T_3.

Thyroid storm

- May also administer iopanoic acid as it binds circulating hormone, blocks intrathyroidal conversion of T_4 to T_3, and reduces iodine uptake by the gland.
- Dexamethasone impairs peripheral generation of T_4 to T_3.

Thyroid hormone deficiency

- Congenital hypothyroidism is most often the result of endemic iodine deficiency in the diet (severe maternal iodine deficiency).
- Most common endocrine disorder in childhood.
- Decreased to absent T3 / T4 and high TSH)
- Neurological form is characterized by mental retardation, deaf mutism, squint, spastic diplegia, and disorders of stance and gait.
- Myxedematous form is less common and characterized by mild mental retardation, dwarfism, and hypothyroidism

Thyroid hormone deficiency

- Dyshormongenetic goiter.
- Second most common cause in children (10%)
- Females 2:1
- 80% occur by age 25
- Genetic autosomal recessive enzymatic defects in one of 7 genes that regulate the steps of thyroid hormone synthesis
- Deficiency of thyroid peroxidase (TPO) is the most common cause worldwide

Table 1

Known Gene Defects Causing Dyshormonogenesis

Affected Process	Substance/Gene	Gene Symbol	Chromo-somal Location	Characteristic Features	Diagnostic Test
iodide trapping	sodium iodide symporter	*SLC5A5* (NIS)	19p13	• reduced thyroidal iodide or pertechnetate uptake	• saliva/plasma RAI ratio <10
iodide efflux into follicular lumen	pendrin	*SLC26A4* (PDS)	7q31	• sensorineural deafness • enlarged vestibular aqueduct • PIOD and goiter	• MRI/CT of temporal bones
matrix protein for hormone synthesis	thyroglobulin	*TG*	8q24	• hypothyroidism • goiter • absent or very low serum TG level	• serum TG level
iodide organification/coupling reaction	thyroid peroxidase	*TPO*	2p25	• TIOD or PIOD	• CLO_4^- discharge test
H_2O_2 generation (co-substrate for TPO)	dual oxidase 2	*DUOX2* (THOX2)	15q15.3	• permanent or transient CH • PIOD	• CLO_4^- discharge test
H_2O_2 generation (co-substrate for TPO)	DUOX maturation factor 2	*DUOXA2*	15q15.3	• mild CH • PIOD	• CLO_4^- discharge test
Intrathyroidal iodide recycling	iodotyrosine deiodinase	*IYD* (*DEHAL1*)		• negative CH screen • goiter, hypothyroidism (after neonatal period)	• iodotyrosines in urine • rapid thyroidal loss of iodine

IOD, Iodide organification defect; **PIOD**, Partial IOD; **TIOD**, Total IOD.

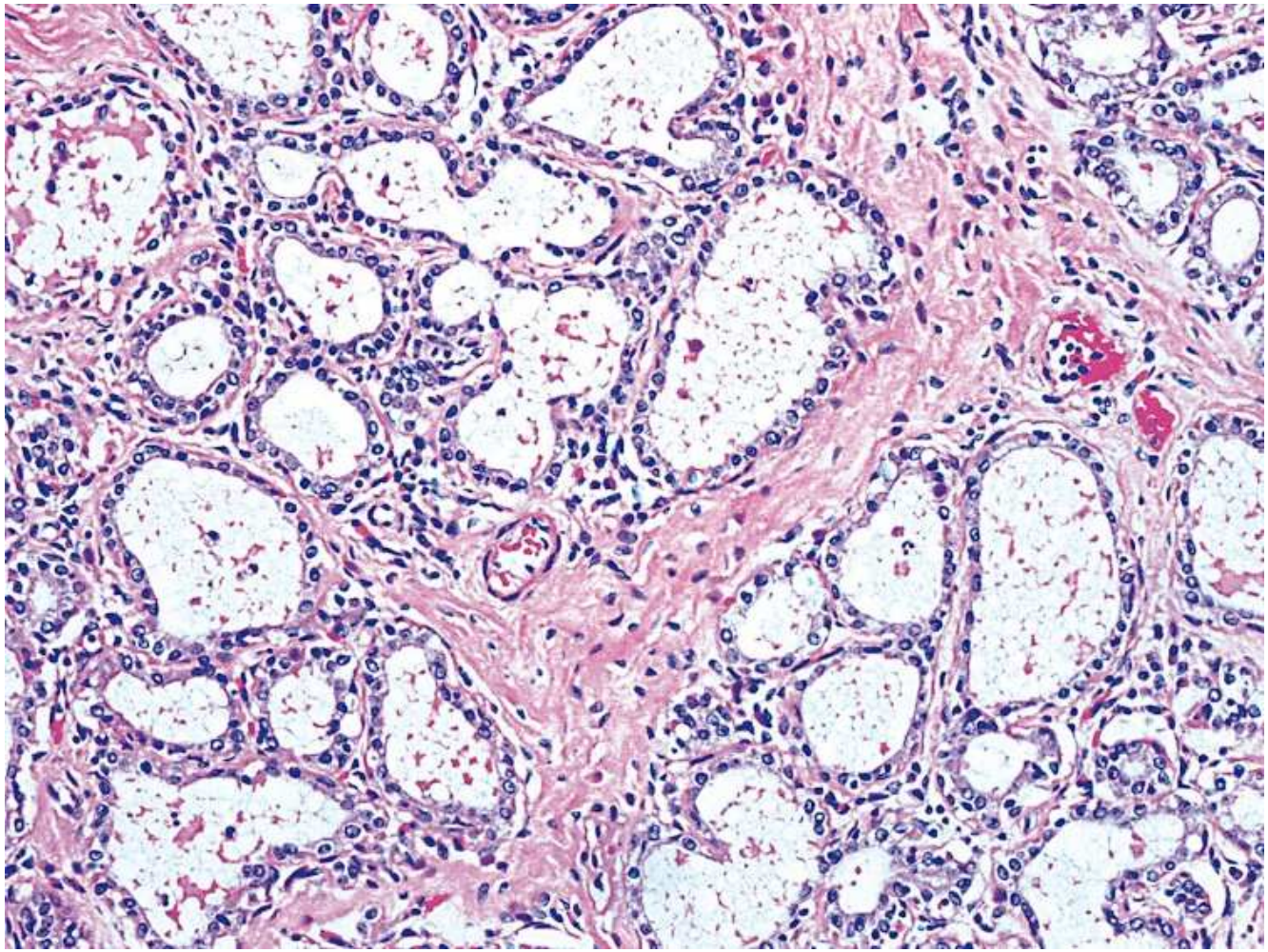
RAI, radioactive iodide

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3263319/table/T1/

Thyroid hormone deficiency

- Diffuse asymmetric enlargement of thyroid gland with prominent nodularity
- Histologic hallmarks are markedly hypercellular nodules with papillary hyperplasia, absence of colloid, frequent internodular bizarre cells and bridging fibrosis

Dysmorphogenetic goiter



http://www.pathologyoutlines.com/wick/thyroid%20dyshormonogenetic%20goiter%20micro2.jpeg

Thyroid hormone deficiency

- Full blown myxedema rare in adults
- Hair loss, cold intolerance, weight gain noted.
- Hair loss may be the presenting sign in women.
- Fatigue, apathy, and slowing of mental function.
- If TSH>7, increased risk of cardiovascular disease.
- Disease prevalence in women is 10%; 0.5%, men.
- 0.25% incidence in neonates (European ancestry); 0.03% (Sub-Saharan ancestry).
- In adults, sequel of Hashimoto's.
- Associated with diabetes mellitus in 35%.

Hypothyroidism

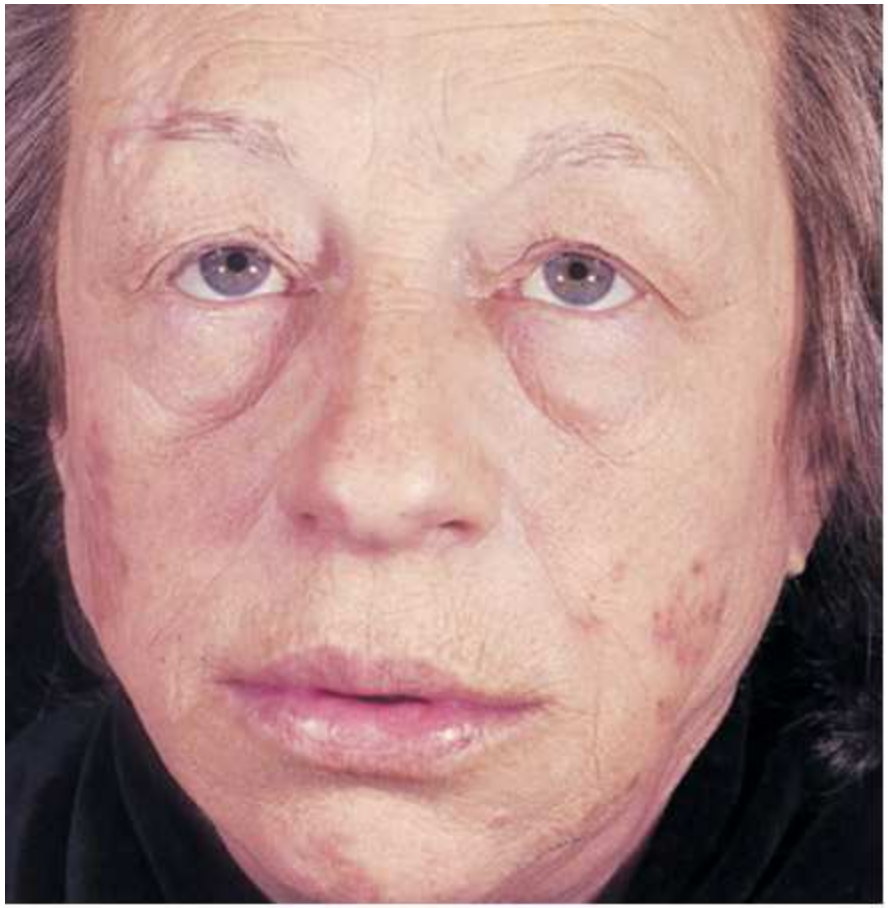


Fig. 152-12 Accessed 02/01/2010

Thyroid hormone deficiency

- Thyroid hormones regulate the transcription of several sarcolemmal genes, such as calcium ATPases and the β adrenergic receptor
- Lowered expression of these genes results in a decrease in cardiac output.
- Non-pitting edema, a broadening and coarsening of facial features, enlargement of the tongue, and deepening of the voice may be noted as a result of accumulation of matrix substances, such as glycosaminoglycans and hyaluronic acid, in skin, subcutaneous tissue, and a number of visceral sites.

Table 24-4 Causes of Hypothyroidism

Primary
Genetic defects in thyroid development (*PAX8*, *FOXE1*, TSH receptor mutations) (rare)
Thyroid hormone resistance syndrome (*THRB* mutations) (rare)
Postablative
Surgery, radioiodine therapy, or external irradiation
Autoimmune hypothyroidism
Hashimoto thyroiditis*
Iodine deficiency*
Drugs (lithium, iodides, *p*-aminosalicylic acid)*
Congenital biosynthetic defect (dyshormonogenetic goiter) (rare) *
Secondary (Central)
Pituitary failure (rare)
Hypothalamic failure (rare)

*Associated with enlargement of thyroid ("goitrous hypothyroidism"). Hashimoto thyroiditis and postablative hypothyroidism account for the majority of cases of hypothyroidism in developed countries. *FOXE1*, forkhead box E1; *PAX8*, paired box 8; *THRB*, thyroid hormone receptor β.

Autoimmune thyroiditis

- Hashimoto's thyroiditis or lymphocytic thyroiditis
- This is the major cause of hypothyroidism in patients with adequate Iodine intake.
- 45-60 years of age
- Women 10-20:1
- May occur in children
- Autoimmune hypothyroidism can occur in isolation or in conjunction with autoimmune polyglandular syndrome (APS), types 1 and 2
- 40% of patients with autoimmune gastritis

Autoimmune thyroiditis

- Presents as painless gland enlargement
- Initially, patients may have bouts of hyperthyroid symptoms, as the initial destruction of thyroid cells may lead to the increased release of thyroid hormone into the bloodstream.
- Eventually, when enough destruction has been caused by the antibody response, patients exhibit symptoms of hypothyroidism
- Poor uptake of iodine on radioisotope scan

Autoimmune thyroiditis

- There is a diffuse, symmetric enlargement of the thyroid. The capsule is often intact with a prominent pyramidal lobe.
- The cut surface has a pale brown to yellow color. Interlobular fibrosis may or may not be present.
- Atrophy may also occur and in some patients, the gland may become nodular or asymmetric.
- However, necrosis or calcification does not occur.

Autoimmune thyroiditis

- Anti-thyroid peroxidase (anti-TPO) is common
- Antithyroglobulin (anti-TBG) and TSH receptor-blocking antibodies (TBII) may also be found
- Anti-TPO antibodies can fix complement and kill thyrocytes.
- CD8+ cytotoxic T-cells as well as activated CD4+ T cells with their inflammatory cytokines may also lead to thyrocyte death.
- Positive serum TPO antibody is associated with active disease.
- 10% of patients may be TPO negative.

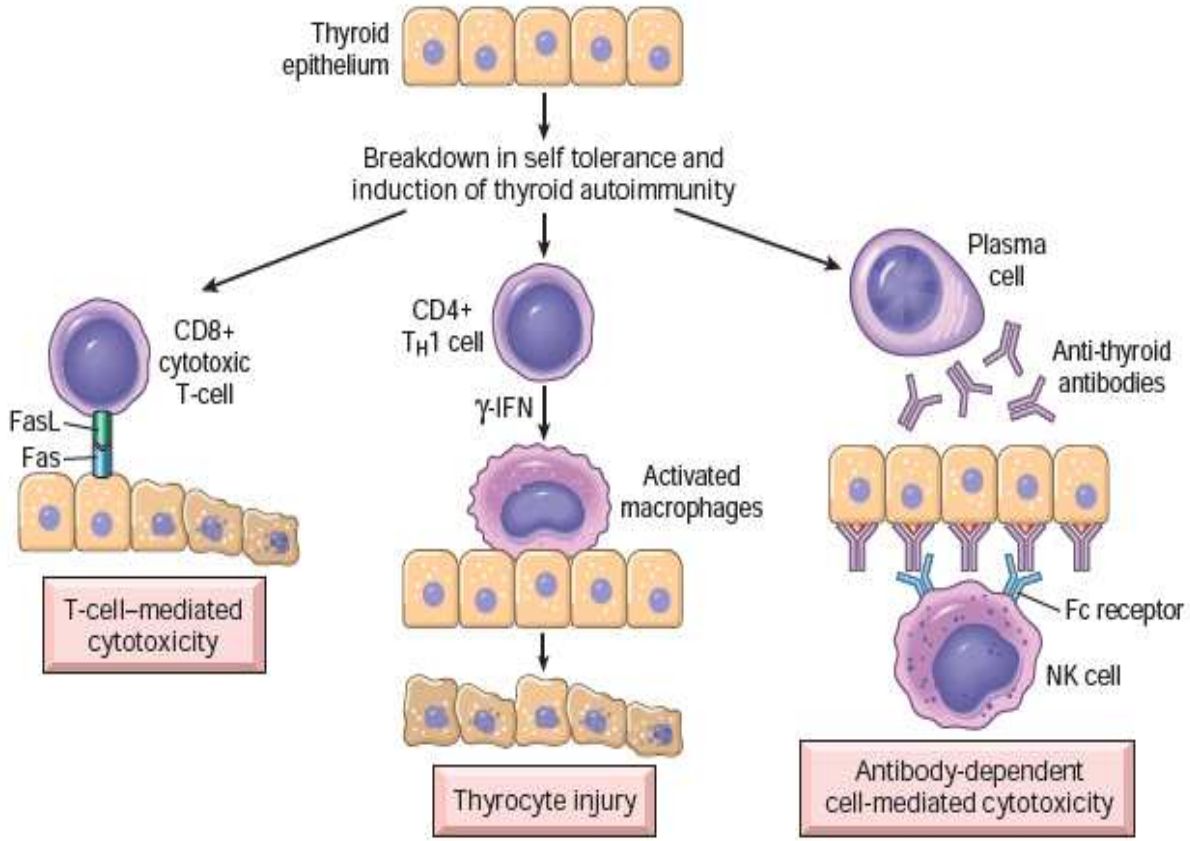


Figure 24-10 Pathogenesis of Hashimoto thyroiditis. Breakdown of peripheral tolerance to thyroid autoantigens, results in progressive autoimmune destruction of thyroid cells by infiltrating cytotoxic T cells, locally released cytokines, or by antibody-dependent cytotoxicity.

Autoimmune thyroiditis

- There is extensive infiltration of the parenchyma by a mononuclear inflammatory infiltrate containing small lymphocytes, plasma cells, and well-developed germinal centers.
- The thyroid follicles are atrophic and are lined in many areas by epithelial cells distinguished by the presence of abundant eosinophilic, granular cytoplasm (Hürthle cells).
- Interstitial connective tissue is increased.
- Fibrosis does not extend outside the capsule.

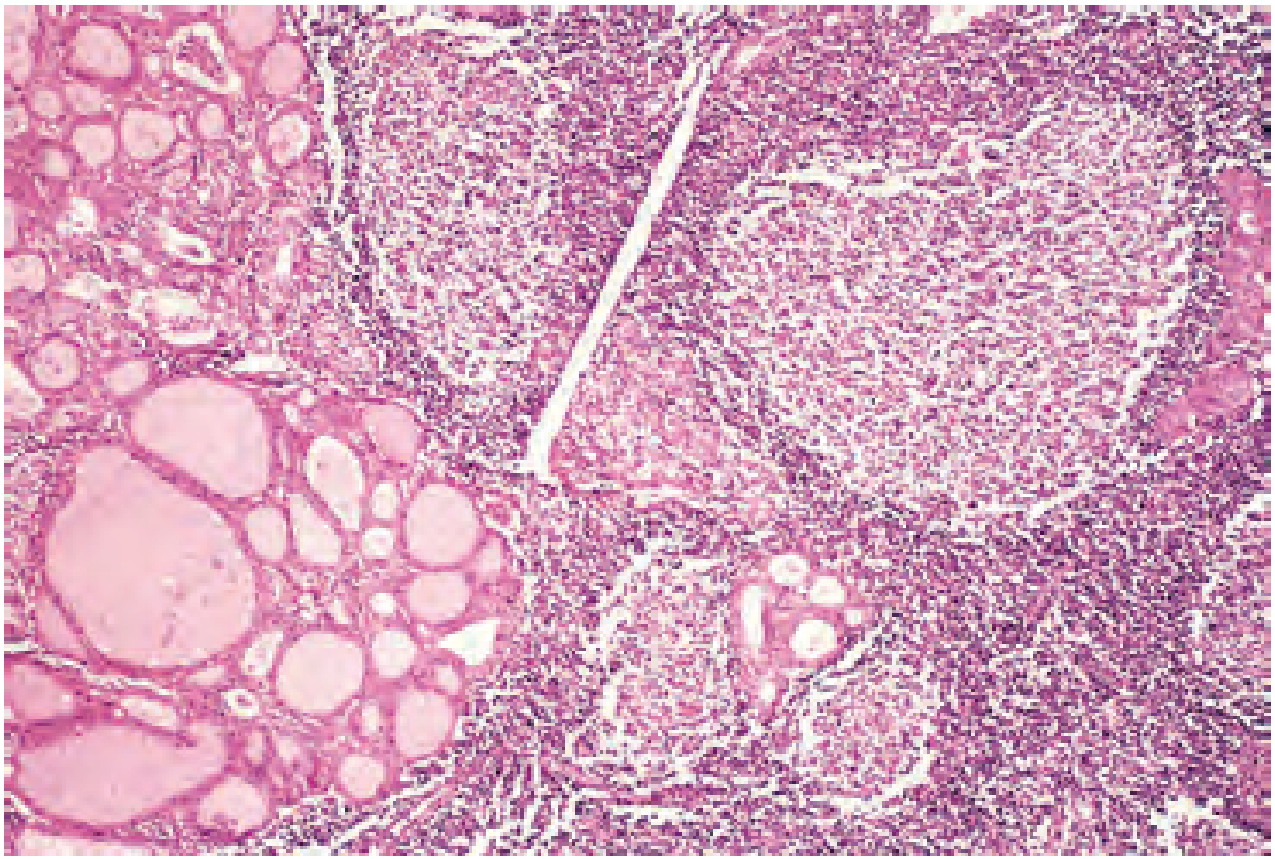


Figure 24-11 Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells are also seen.

Subacute lymphocyte thyroiditis

- Painless gland enlargement
- May have mild hyperthyroid symptoms
- Middle aged adults, principally women
- A variant is seen in 5% of women in the postpartum (postpartum thyroiditis)
- May progress to Hashimoto's thyroiditis
- Fibrosis and Hürthle cells are not seen

Granulomatous thyroiditis

- DeQuervain's (subacute thyroiditis)
- Probably triggered by virus infection.
- May present with sore throat.
- Most common cause of thyroid pain.
- Thyroid is tender.
- Women 4:1
- 40-50 years old
- Transient hyperthyroidism.
- May rest the gland by administering thyroid hormone; treat pain with anti-inflammatory agents.
- Resolves in 6 weeks.

Granulomatous thyroiditis

- The gland may be unilaterally or bilaterally enlarged and firm, with an intact capsule that may adhere to surrounding structures.
- On cut section, the involved areas are firm and yellow-white
- Histologic changes are patchy and depend on the stage of the disease.
- Early in the active inflammatory phase, scattered follicles may be disrupted and replaced by neutrophils forming microabscesses.

Granulomatous thyroiditis

- Later, more characteristic features appear in the form of aggregates of lymphocytes, activated macrophages, and plasma cells associated with collapsed and damaged thyroid follicles.
- Multinucleate giant cells enclose naked pools or fragments of colloid
- Fibrosis as late development at focus of injury.

Autoimmune polyglandular syndrome

- APS1
- Muco-cutaneous candidiasis, hypoparathyroidism, Addison's disease
- Present by age 5
- 75% present with non-endocrine features
- If endocrine feature presents first, it is usually hypoparathyroidism
- 60% will develop Addison's disease
- If Addison's disease presents first, 33% will develop hypothyroidism
- Ovarian failure will develop in 60%

Autoimmune polyglandular syndrome

- APS 2 (Schmidt syndrome)
- Diabetes mellitus type 1, Addison's disease, Hashimoto's thyroiditis
- 20-40 years of age
- Women predominate
- Associated with specific HLA DR3 and DR4 haplotypes and with the class II HLA alleles DQ2 and DQ8, also strongly linked to celiac disease
- ASP3 (Carpenter syndrome)
- Diabetes mellitus type 1 and Hashimoto's thyroidtis

Autoimmune polyglandular syndrome

- Immunotherapy
- Associated with the use of inhibitors of CTLA4 (cytotoxic T-lymphocyte-associated protein 4), and immune checkpoint blockade of programmed death 1(PD-1) and its ligands PDL1 and PDL2
- May also cause hypophysitis
- PTPN22 gene polymorphisms may also cause these syndromes

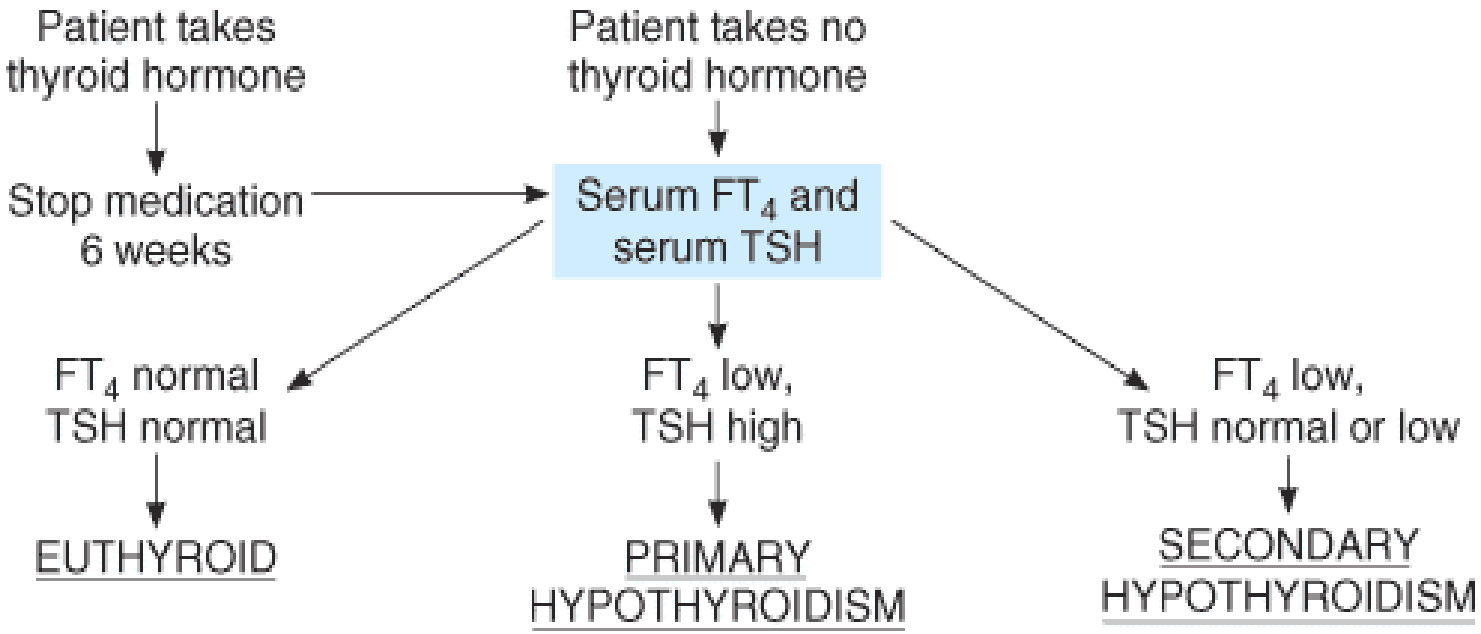
Reidel thyroiditis

- Characterized by extensive fibrosis involving the thyroid and contiguous neck structures.
- Hard and fixed thyroid mass clinically
- May be associated with fibrosis in other sites in the body, such as the retroperitoneum.
- IgG_4-related disease

Medical therapy

- Theoretical replacement dose is 100mcg/qd of thyroxine.
- In patients with ischemic heart disease, begin replacement at 25% of dose and titer slowly (following TSH response) to reach appropriate replacement dose.
- Full replacement dose appropriate to begin in patients post thyroidectomy or radioiodine therapy.

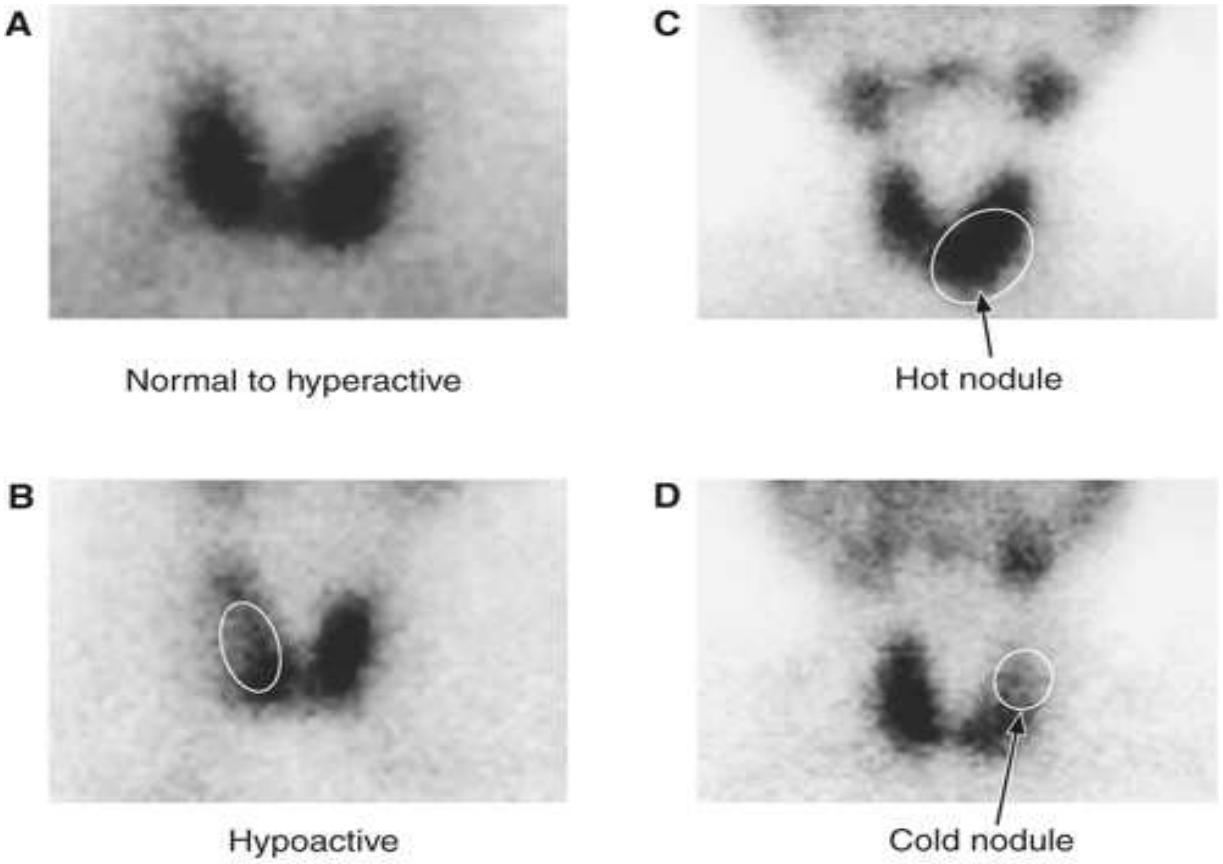
Evaluation of a patient on thyroid hormone replacement therapy



Source: Gardner DG, Shoback D: *Greenspan's Basic and Clinical Endocrinology*, 8th Edition: http://www.accessmedicine.com

Fig. 8-29 Accessed 02/01/2010

Thyroid nodules



Source: Molina PE: *Endocrine Physiology*, 2nd Edition:
http://www.accessmedicine.com

Images courtesy of Dr. Luis Linares, Memorial Medical Center, New Orleans, LA

Fig. 8-29 Accessed 02/01/2010

The solitary nodule

- Usually painless
- May represent the only thyroid gland present
- May also represent the portion of intra-thoracic thyroid in the neck.
- Solitary nodule present in 1-10% of population.
- Four times more common in women
- 1% malignant
- BUT, 10% of “cold” nodules are malignant
- Nodules <1 cm in size are generally benign
- Nodules >4 cm in size are generally malignant

The solitary nodule

- Younger patients, men, and history of radiation to the head and neck are factors associated with increased incidence of thyroid malignancy (up to 35%).
- Malignancy more frequent in Chinese.
- Thyroid suppression to induce resolution of nodule is not particularly useful.
- Fine needle aspiration accuracy 70-97%. CT scan more sensitive if medullary carcinoma.
- Isotope scanning may identify autonomously functioning nodule.

Diagnostic strategy

- Fine needle aspiration is the first step.
- If the aspirate is benign, measure TSH.
- If TSH elevated, measure anti-TPO and follow observed nodule serially.
- If TSH normal, follow observed nodule serially.
- If TSH low, perform radioisotope scan.
- If the nodule is hot and not the only tissue present, proceed to radioiodine ablation.
- If the nodule is cold, follow serially.
- Nodules <1cm diameter may be followed with yearly ultrasonography.

Diagnostic strategy

- If the fine needle aspiration is inadequate or non-diagnostic, it must be repeated.
- If the fine needle aspiration is diagnostic of medullary thyroid carcinoma, obtain RET genetic testing.
- If no RET mutation and no suspicion of multiple endocrine neoplasia (MEN), proceed to surgery.
- If RET mutated or there is suspicion of MEN, measure VMA, metanephrine, PTH, and test RET in kindred.
- Proceed to surgery.

Diagnostic strategy

- If the fine needle aspiration is suspicious or diagnostic for thyroid carcinoma, proceed to surgery.
- Measure iCa^{2+} (ionized) preoperatively.
- Total thyroidectomy is the preferred approach in the US.
- Patients with papillary carcinoma frequently have involvement of lateral neck regions IV, III, V, and II.
- Parathyroid glands should be preserved in the dissection.

Adenoma

- Discrete, solitary mass derived from follicular epithelium
- Vast majority of adenomas are nonfunctional
- 20% of non-functioning adenomas have RAS or PIK3CA mutations or bear a PAX-PPARG fusion gene (t(2;3)(q13;p25)).
- A small subset cause clinically apparent thyrotoxicosis ("toxic adenoma")
- Hormone production in functional adenomas is independent of TSH stimulation.
- TSHR and the α-subunit of G_S (GNAS) gain of function mutations are found in toxic adenomas

Adenoma

- Well-defined capsule separates the solitary adenoma from surrounding thyroid parenchyma
- Bulges from the cut surface and compresses the adjacent thyroid. The color ranges from gray-white to red-brown
- The constituent cells often form uniform appearing follicles that contain colloid.
- Growth pattern differs from adjacent normal thyroid
- Abnormal nuclei do not necessarily indicate malignancy.

Adenoma

- Hürthle cell or oxyphil change may be present.
- Hüthle cell adenoma behaves as does a follicular adenoma.
- The integrity of the capsule distinguishes this from carcinoma.
- Extensive mitotic activity, necrosis, or cellularity is unusual in an adenoma and may suggest the follicular variant of papillary carcinoma
- Fusion partners rare

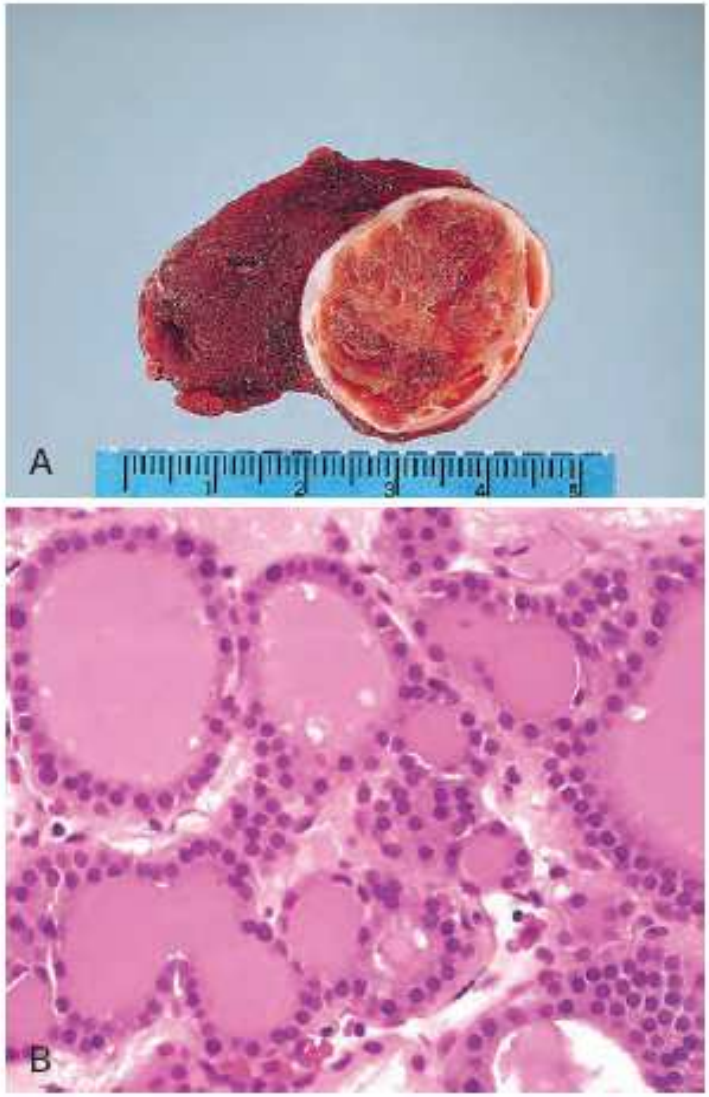
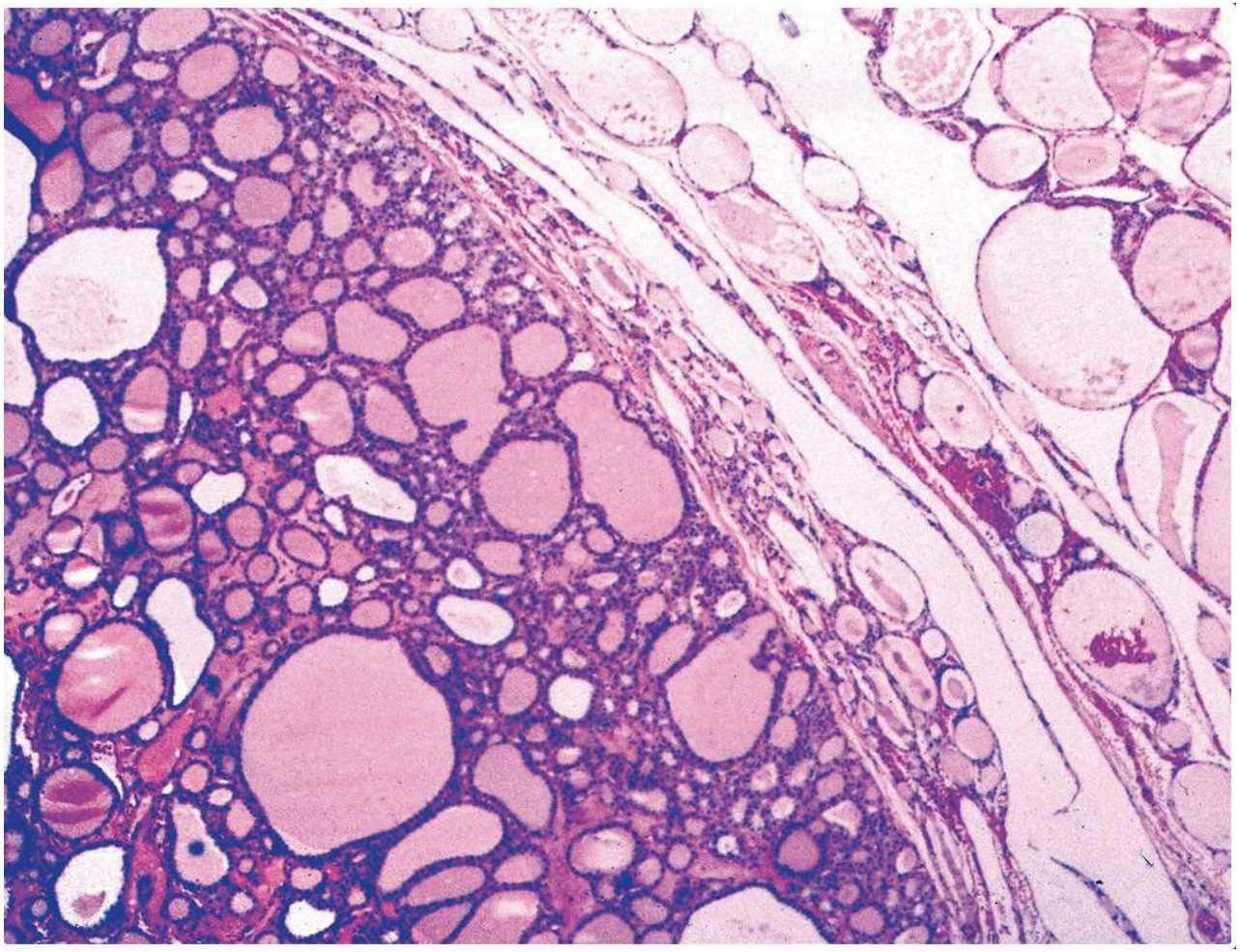


Figure 24-16 Follicular adenoma of the thyroid. **A,** A solitary, well-circumscribed nodule is seen. **B,** The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.

Follicular adenoma



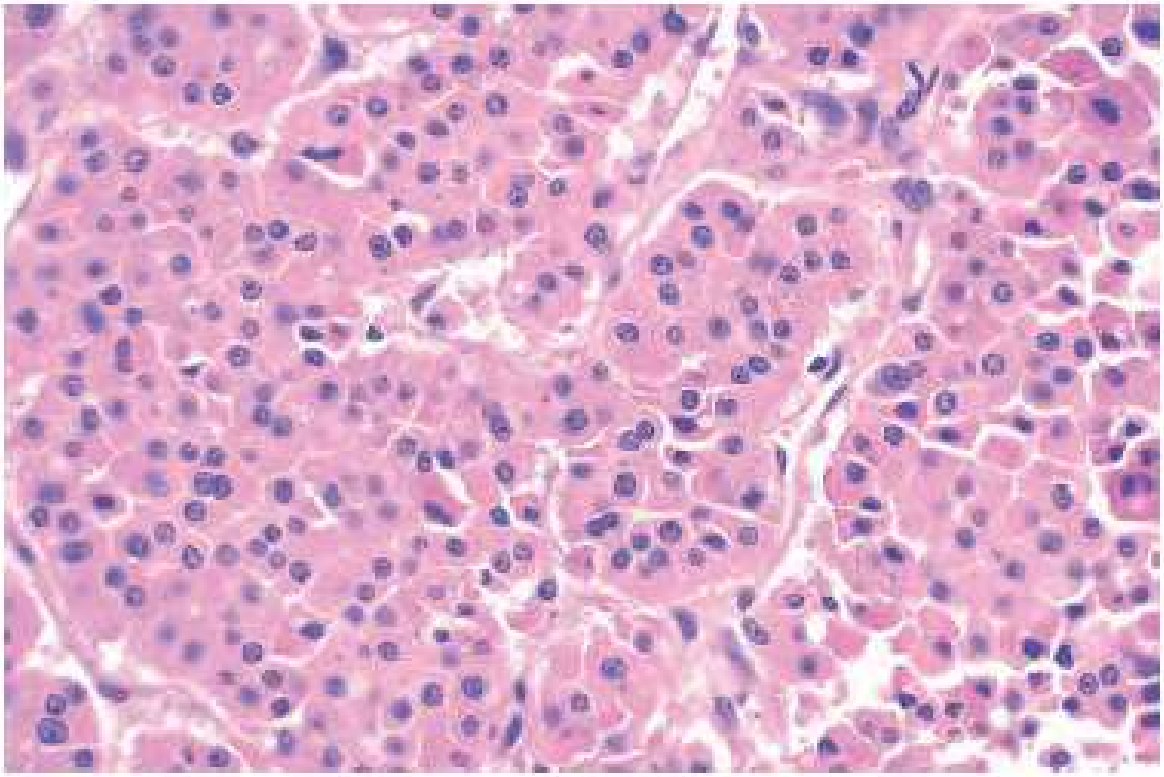


Figure 24-17 Hürthle cell (oxyphil) adenoma. A high-power view showing that the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei. (Courtesy Dr. Mary Sunday, Duke University, Durham, N.C.)

Adenocarcinoma

- Patients <20 years old have a higher expression of proteins involved in iodine metabolism.
- Proliferative rates of normal thyroid tissue decrease with age.
- Relative to normal thyroid, thyroid cancer is characterized by reduced Na^{+}-I^{-} transporter expression.
- Iodine deficiency may predispose to follicular carcinoma
- Female predominance if thyroid cancer occurs in early and mid-adult years

Adenocarcinoma

- Genetic alterations in the three follicular cell–derived malignancies are in growth factor receptor signaling pathways
- Somatic testing is recommended for patients with differentiated thyroid carcinoma that is locally recurrent, advanced, or metastatic
- OR is not amenable to radioactive iodine therapy
- AS WELL as patients with anaplastic thyroid carcinoma
- RET/PEC rearrangement (disrupt TSH action) more common in young
- BRAF mutation more common in adults
- Associated with invasion, extension, metastasis.

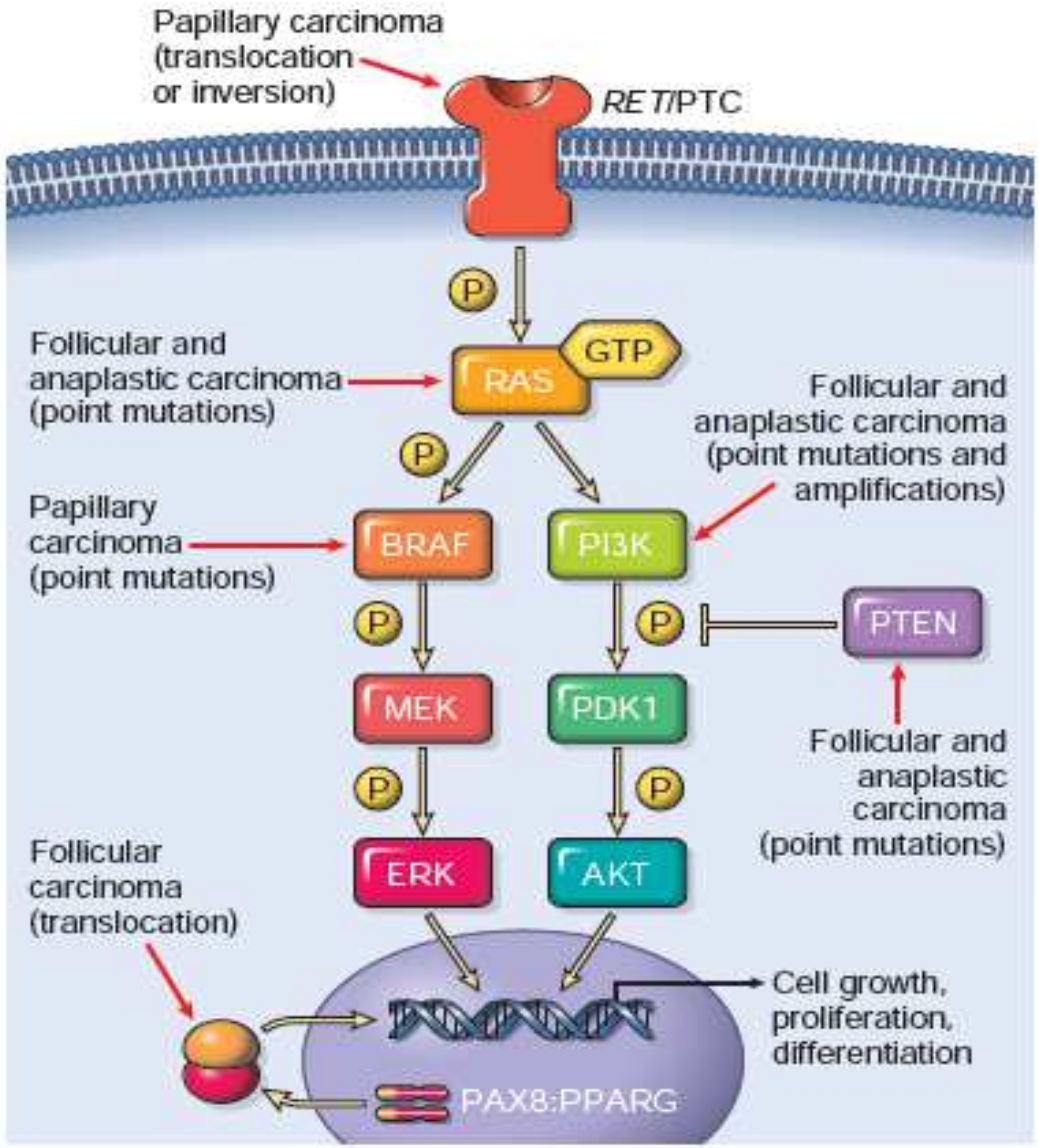


Figure 24-18 Genetic alterations in follicular cell-derived malignancies of the thyroid gland.

Papillary carcinoma

- >85% of thyroid cancers.
- 25-50 years of age
- Single nodules that move freely with the thyroid gland during swallowing
- First manifestation may be a mass in a cervical lymph node.
- Hoarseness, dysphagia, cough, or dyspnea suggests advanced disease
- 4% of patients present with metastases.
- 10% RET mutation
- Fusion partners common

Papillary carcinoma

- May be solitary or multifocal.
- Some tumors are well circumscribed and even encapsulated
- Others infiltrate the adjacent parenchyma and have ill-defined margins.
- The tumors may contain areas of fibrosis and calcification and are often cystic.
- The cut surface sometimes reveals papillary foci.

Papillary carcinoma

- Contain complex branching papillae having a dense fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells.
- Generally, the epithelium covering the papillae consists of well-differentiated, uniform, orderly cuboidal cells

Papillary carcinoma

- Pathognomonic are groundglass or Orphan Annie eye nuclei,
- With invaginations of the cytoplasm that give the appearance of intranuclear inclusions (“pseudo-inclusions”) or intranuclear grooves.
- Psammoma bodies are concentrically calcified bodies within the core of the papillae.
- Rarely found in other thyroid neoplasms

Papillary carcinoma

- The follicular variant of papillary carcinoma is the most common
- Has the characteristic nuclear features of papillary carcinoma and an almost totally follicular architecture.
- A lower frequency of RET/PTC rearrangements; a lower frequency and different spectrum of BRAF mutations; and a significantly higher frequency of RAS mutations
- If well encapsulated, behaves as does a follicular carcinoma

Papillary carcinoma

- The tall-cell variant
- Occur in older individuals
- Higher frequencies of vascular invasion, extrathyroidal extension, and cervical and distant metastases
- Tall columnar cells with intensely eosinophilic cytoplasm lining the papillary structures.
- Up to 100% have BRAF mutations
- Often have RET/PTC translocations as well.
- Aggressive

Papillary carcinoma

- The diffuse sclerosing variant of papillary carcinoma occurs in younger individuals, including children.
- The tumor has a prominent papillary growth pattern intermixed with solid areas containing nests of squamous metaplasia.
- Fibrosis is extensive.
- Lymphocytic infiltrates are prominent.
- Lymph node metastases common.
- Lack BRAF mutation
- 50% have RET/PTC translocation
- Aggressive

Papillary carcinoma

- Columnar variant
- Columnar cells with nuclear pseudostratification, scant cytoplasm and absent or minimal nuclear features of papillary thyroid carcinoma
- Up to 70% in women
- 55% with lymph node metastases
- 33% with BRAF mutation
- Aggressive
- Papillary microcarcinoma
- Papillary carcinoma less <1 cm
- Usually incidental
- May be precursors of typical papillary carcinoma

Papillary carcinoma

- If encapsulated, 80-95% survival rate.
- 5-20% may recur
- Thyroidectomy followed by ^{131}Iodine ablation of residual tissue.
- Thyroxine administration improves survival.
- Follow with measurement of serum thyroglobulin to detect disease recurrence.

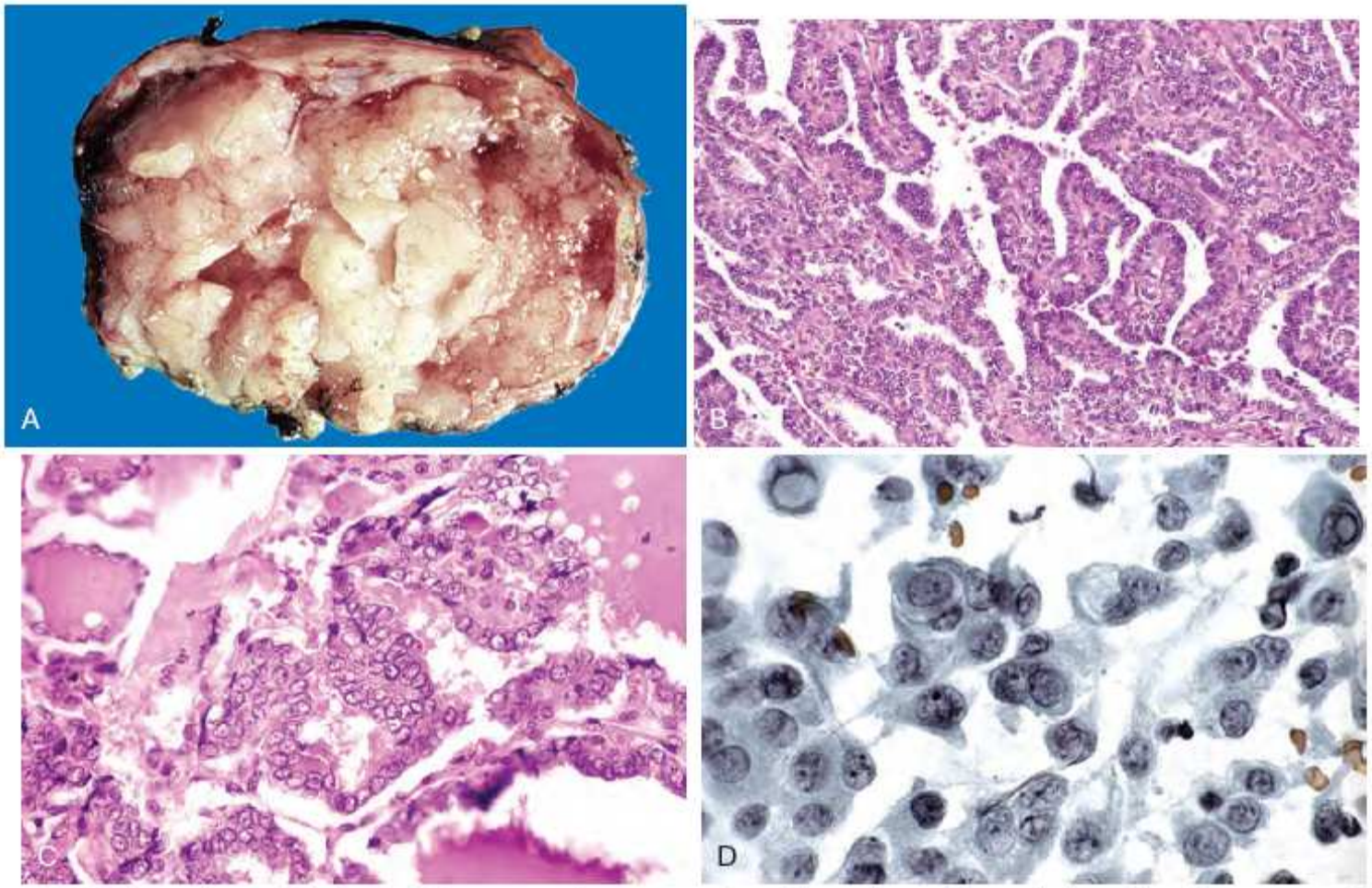


Figure 24-19 Papillary carcinoma of the thyroid. **A,** The macroscopic appearance of a papillary carcinoma with grossly discernible papillary structures. **B,** This particular example contains well-formed papillae. **C,** High power shows cells with characteristic empty-appearing nuclei, sometimes called "Orphan Annie eye" nucle. **D,** Cells obtained by fine-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells.

Papillary carcinoma

Branching papillae with fibrovascular core. Nuclei show ground-glass appearance. Psammoma body is characteristic. If one sees a psammoma body in what otherwise appears to be a follicular or medullary carcinoma, reconsider the diagnosis.

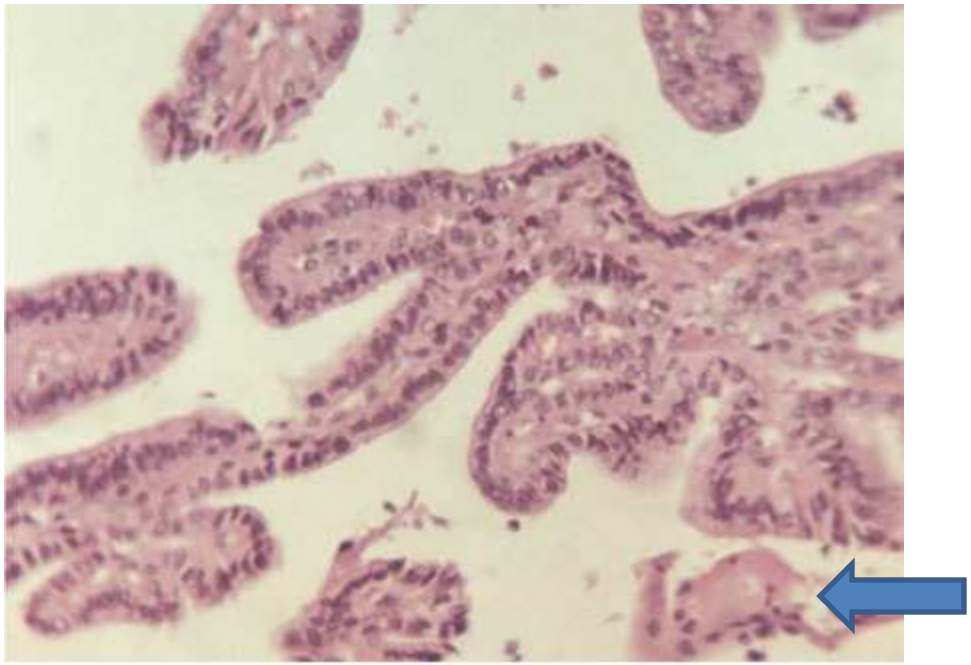


Fig. 31-2 Accessed 08/01/2010

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Follicular carcinoma

- 5-10% of thyroid malignancies.
- Women 3:1
- 40-60 years old
- Up to 50% have RAS or PI_3K/AKT pathway mutations.
- Up to 50% have t(2;3)(q13;p25)
- Fusion gene of PAX8 and the peroxisome proliferator-activated receptor gene (PPARG),
- Noted in 10% of follicular adenomas

Follicular carcinoma

- Single nodule
- May be sharply demarcated from surrounding tissue
- Gray to tan to pink on cut section and may be somewhat translucent due to the presence of large, colloid-filled follicles.
- Fairly uniform cells forming small follicles containing colloid with back to back apposition of glands.
- Abnormal nuclei
- Extension beyond capsule
- Lymph node metastases are uncommon
- .

Follicular carcinoma

- Vascular dissemination common.
- From 16-33% of patients present with metastases.
- 80-95% survival rates if treated while confined to gland.
- Thyroidectomy followed by ^{131}Iodine ablation of residual tissue has replaced neck dissection.
- Thyroxine administration improves survival.
- Follow with measurement of serum thyroglobulin to detect disease recurrence.

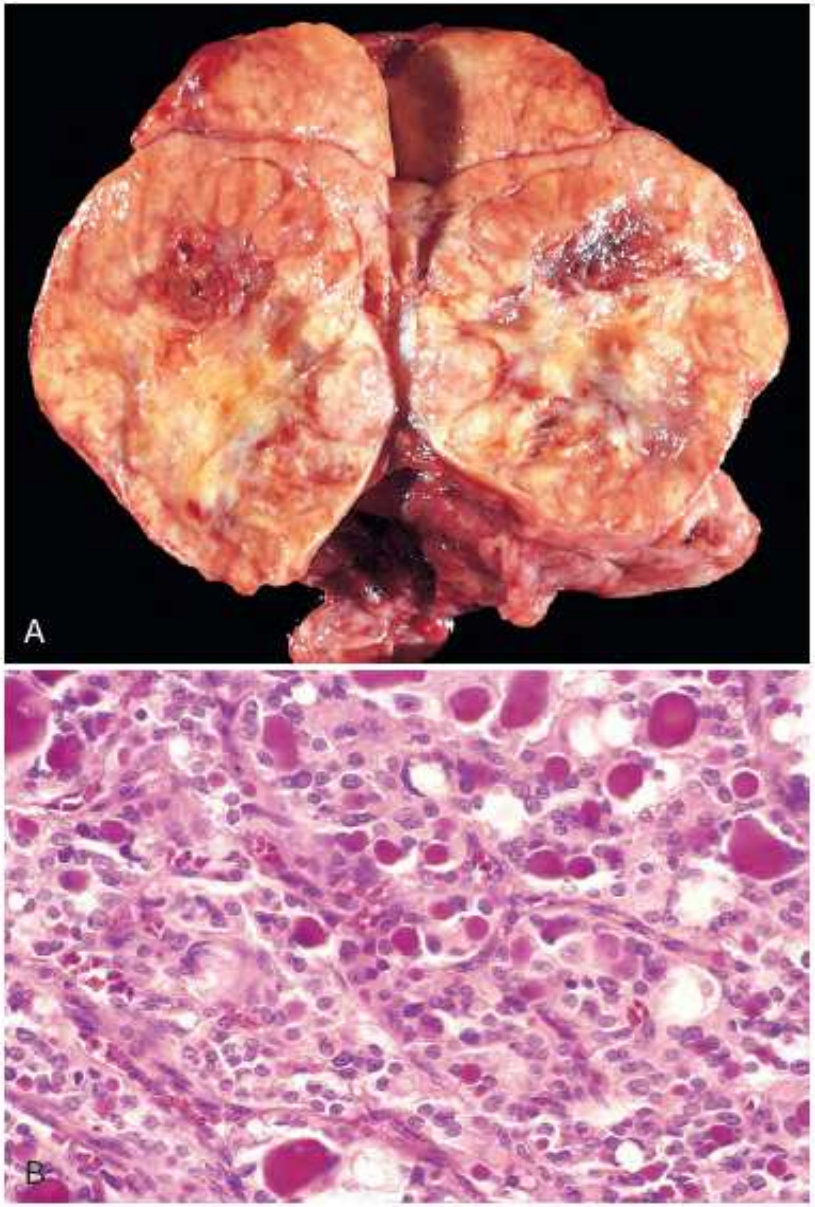


Figure 24-20 Follicular carcinoma. **A,** Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage. **B,** A few of the glandular lumens contain recognizable colloid.

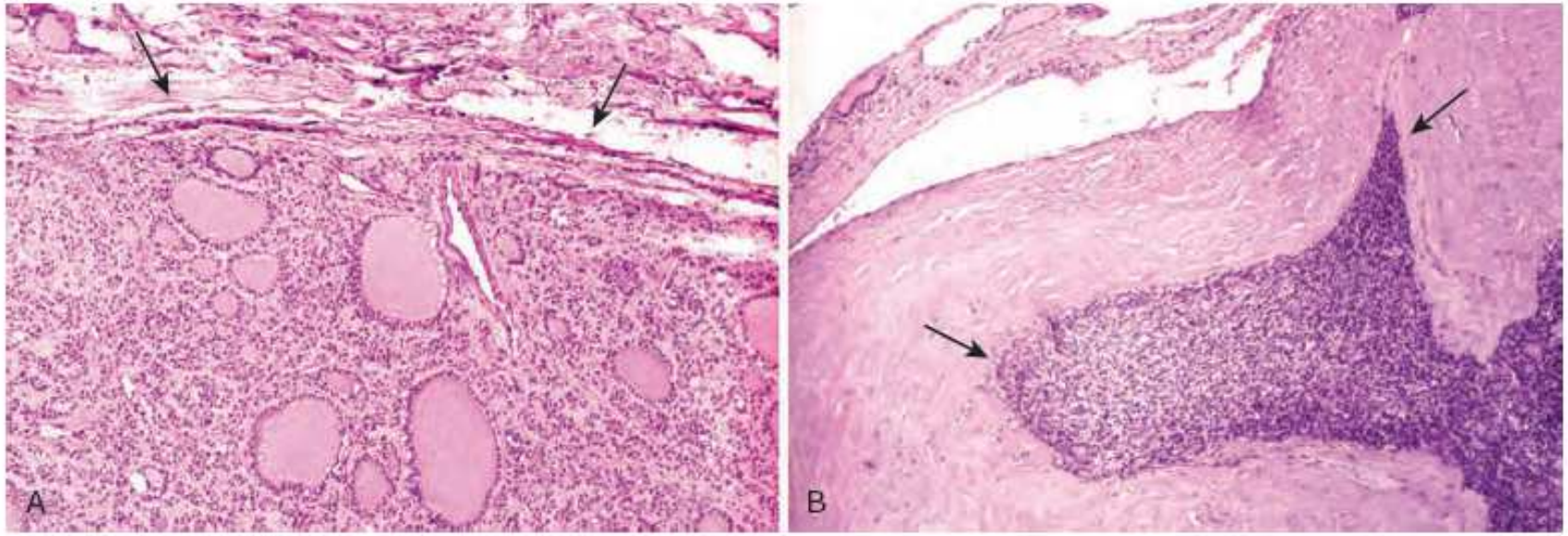
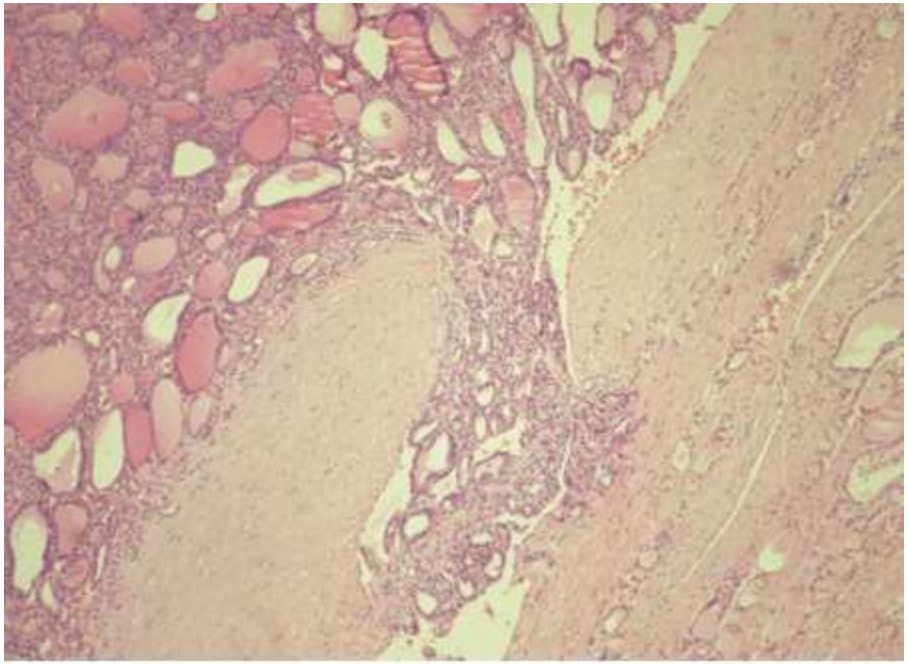


Figure 24-21 Capsular integrity in follicular neoplasms. In adenomas (**A**), a fibrous capsule, usually thin but occasionally more prominent, circumferentially surrounds the neoplastic follicles and no capsular invasion is seen *(arrows)*; compressed normal thyroid parenchyma is usually present external to the capsule *(top of the panel)*. In contrast, follicular carcinomas demonstrate capsular invasion (**B,** *arrows*) that may be minimal, as in this case, or widespread. The presence of vascular invasion is another feature of follicular carcinomas.

Follicular carcinoma



Histology of follicular carcinoma at the site at which the cancer invades the capsule of the nodule. Capsular and vascular invasion of nodules in a lesion that contains cells with the features of follicular neoplasm is follicular carcinoma by definition.

Fig. 31-3 Accessed 08/01/2010

Anaplastic carcinoma

- Present as rapidly enlarging bulky mass with involvement of surrounding structures and with lung metastases
- May represent dedifferentiation of papillary or follicular carcinoma
- 40% have BRAF mutations
- Additional mutations are of TP53 and β-catenin
- 65 years of age
- Highly aggressive (up to 100% mortality within 1 year)

Anaplastic carcinoma

- Histopathology
- Anaplastic cells:
- Pleomorphic giant cells and occasional osteoclast-like multinucleate giant cells;
- Spindle cells with a sarcomatous appearance;
- Mixed spindle and giant cells.
- Cytokeratin positive staining
- Thyroglobulin negative staining

Medullary carcinoma

- 3-5% of all thyroid carcinomas.
- Neuroendocrine tumor of parafollicular C cells.
- 30% associated with MEN 2A and 2B.
- Bilateral or multicentric
- Germline RET mutations
- Sporadic cancers occur at 40-50 years of age
- Single nodules
- 50% present with regional lymphadenopathy.
- Somatic testing including TMB or somatic RET fusions is also recommended for patients who are RET germline wild-type or germline unknown with recurrent, persistent locoregional, or distant metastatic disease

Medullary carcinoma

- Usually presents as neck mass.
- The tumor tissue is firm, pale gray to tan, and infiltrative.
- Polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles.
- More anaplastic cells may be found.
- Acellular amyloid deposits derived from calcitonin polypeptides are present in the stroma in many cases

Medullary carcinoma

- Presence of multicentric C-cell hyperplasia in the surrounding thyroid parenchyma in familial cases.
- Stain positively for calcitonin.
- Neurosecretory granules demonstrable on electron microscopy

Medullary carcinoma

- In some instances, the initial manifestations are those of a paraneoplastic syndrome caused by the secretion of vasoactive intestinal peptide (VIP) or Cushing syndrome due to ACTH
- Hypocalcemia is not a prominent feature
- Median survival 3-4 months if metastatic.

Medullary carcinoma

- Thyroidectomy and central node dissection treatment of choice.
- ETV6 common fusion partners
- NTREK3 common fusion partners
- Iodine refractory tumors and symptomatic, use VEGFR inhibitor (Selpercatinib)
- TKI (Cabozantanib) prolongs survival in metastatic disease.
- Blocks MET, VEGFR2, RET and KIT

Medullary carcinoma

- Calcitonin produced in parafollicular cells.
- Diminshes bone resorption of Calcium.
- Secreted in response to rising serum Calcium level.
- Calcitonin (>100 pg/ml)and CEA elevated in serum.
- Calcitonin >1000 pg/ml associated with distant metastases.

Table 25.3 Contrasting features of main histologic types of thyroid carcinoma.

	FEATURE	PAPILLARY CARCINOMA	FOLLICULAR CARCINOMA	MEDULLARY CARCINOMA	ANAPLASTIC CARCINOMA
1.	*Frequency*	75-80%	10-20%	5%	5%
2.	*Age*	All ages	Middle to old age	Middle to old age; familial too	Old age
3.	*Female/male ratio*	3:1	2.5:1	1:1	1.5:1
4.	*Relation to radiation*	Maximum	Present	None	Present
5.	*Genetic alterations*	*RET* gene over-expression, *NTRK* gene rearrangement	*RAS* mutation, *PAX-PPAR γ1* fusion	*RET* point mutation	*p53* loss, β-catenin mutation
6.	*Cell of origin*	Follicular	Follicular	Parafollicular	Follicular
7.	*Gross*	Small, multifocal	Moderate size, nodular	Moderate size	Invasive growth
8.	*Pathognomonic* microscopy	Nuclear features, papillary pattern	Vascular and capsular invasion	Solid nests, amyloid stroma	Undifferentiated, spindle-shaped, giant cells
9.	*Regional metastases*	Common	Rare	Common	Common
10.	*Distant metastases*	Rare	Common	Rare	Common
11.	*10-year survival*	80-95%	50-70%	60-70%	5-10% (median survival about 2 months)

Mohan, H, Textbook of Pathology, 7th ed., Health Science Publishers. New Delhi. 2015.

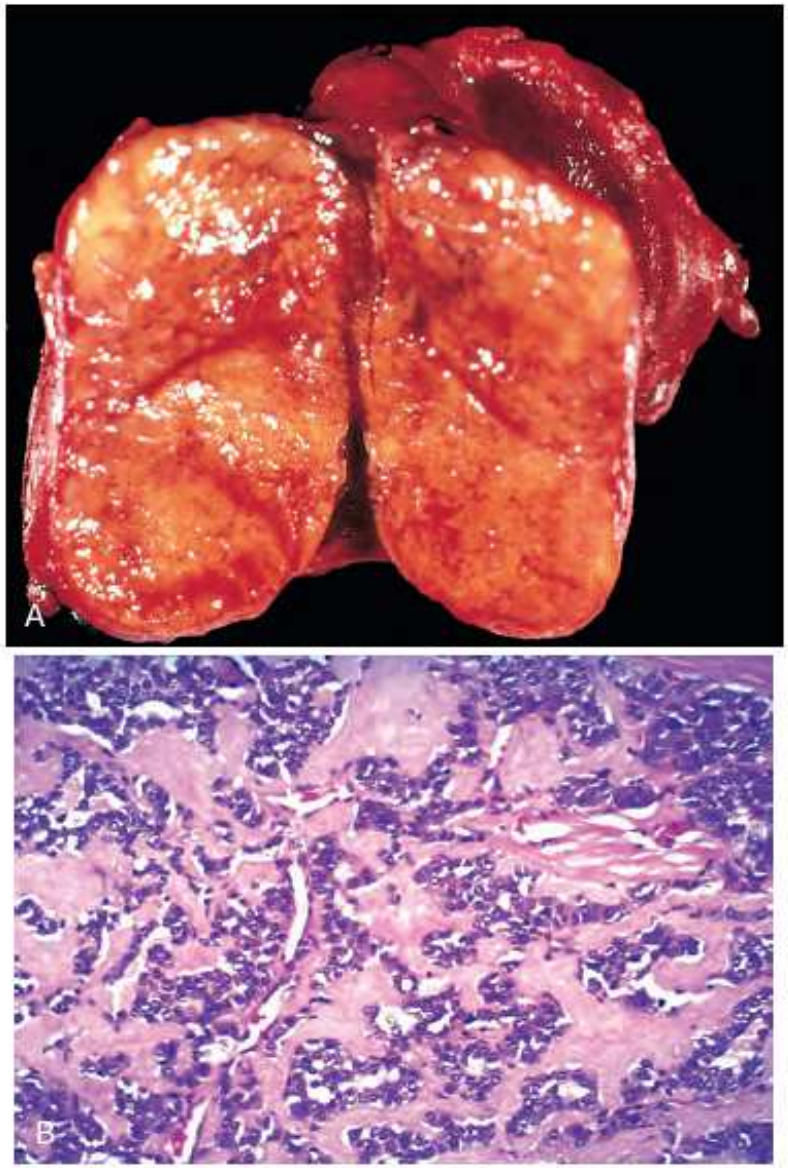
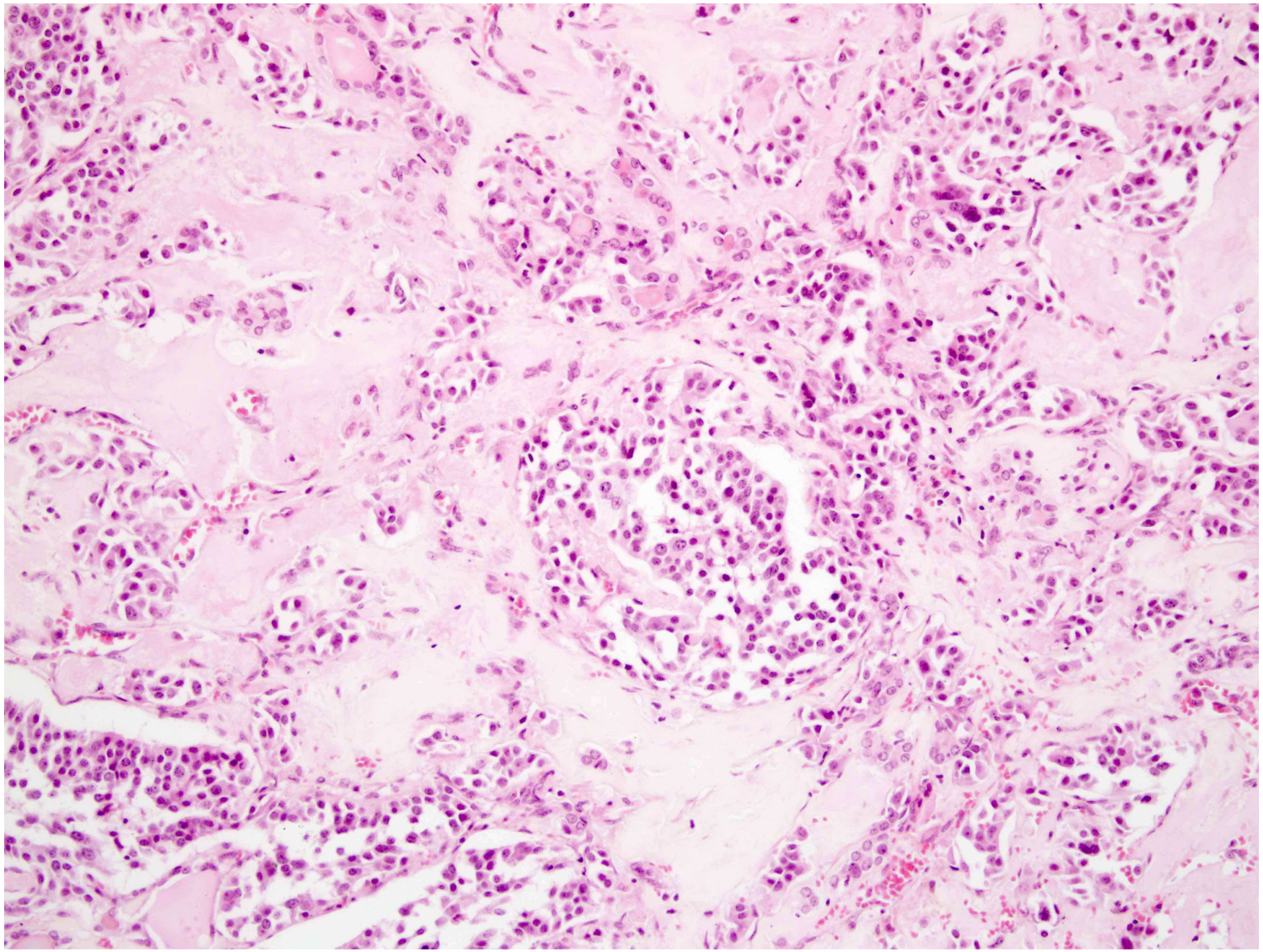


Figure 24-22 Medullary carcinoma of thyroid. **A,** These tumors typically show a solid pattern of growth and do not have connective tissue capsules. **B,** Histology demonstrates abundant deposition of amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells. (**A,** Courtesy Dr. Joseph Corson, Brigham and Women's Hospital, Boston, Mass.)

Medullary carcinoma



Background of amyloid (x200)

Therapy

- Thyroidectomy with removal of lymph nodes adjacent to thyroid (central compartment neck dissection)
- Thyroid hormone replacement initiated prior to surgery
- Radioiodine therapy (I^{131}) is administered following thyroidectomy for T3 and T4 tumors
- For spread to lymph nodes or distant sites

Therapy

- Unresectable or borderline resectable anaplastic thyroid carcinoma
- Attempt to shrink the tumor to permit resection
- Dabrafenib and trametinib for BRAF V600E mutations
- Addition of pembrolizumab associated with 11 median month survival
- Selpercatinib or pralsetinib for RET gene fusion–positive tumors
- Larotrectinib or entrectinib for patients with NTRK gene fusion–positive tumors
- In resectable disease, neoadjuvant trametinib and dabrafenib associated with median 63 month