Diffuse hyperplasia of the thyroid gland (Graves' disease).

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PATHOLOGY CLINIC

Widely known by its eponym *Graves' disease,* diffuse hyperplasia of the thyroid gland is an autoimmune condition in which excess thyroid hormone production is unchecked by the normal feedback loop between the thyroid and the pituitary gland. The immune-system abnormality is mediated by antibodies to the thyrotropin receptor found on follicular epithelial cells. When the most specific antibody, known as *thyroid-stimulating immunoglobulin* (TSI), is bound to the thyrotropin receptor, the TSI mimics the action of pituitary thyrotropin and stimulates the follicular epithelium to produce hormone. The clinical effect of this autoimmune process is (1) thyrotoxicosis accompanied by diffuse thyroid enlargement and an infiltrative ophthalmopathy and (2) a spectrum of the systemic effects of excessive thyroid hormone production.

Graves' disease is the most common cause of spontaneous hyperthyroidism, representing up to 80% of all cases in the United States. Patients usually present in the third and fourth decades of life. Graves' disease is much more common in women than men (10:1). The wide spectrum of symptoms includes weight loss, heat intolerance, fatigue, weakness, palpitations, dyspnea on exertion, stridor secondary to tracheal compression, hoarseness, chest pain, dysphagia, oligomenorrhea, hair loss or a change in hair texture, a gritty sensation in the eyes, proptosis, conjunctivitis, memory loss, poor attention span, emotional lability, muscle weakness, and irritability or agitation. In addition to hair loss and a wide-eyed stare or proptotic appearance, physical findings may include localized myxedema (particularly pretibial), irritative keratoconjunctivitis, lid lag, diplopia, tachycardia, hyperactive reflexes, and smooth, warm, and velvety skin. The thyroid is diffusely enlarged, although nodules may be seen in longstanding or treated disease. Laboratory evaluation will show an elevated serum free thyroxine (T4) or triiodothyronine (T3) level and a markedly suppressed thyroid-stimulating hormone level.

The appearance of the thyroid on low-power magnification in Graves' disease is remarkable for the accentuation of its normal lobular pattern (figure 1). This change in appearance is attributable to an increase in the amount of fibrous tissue in the interlobular septa. A patchy lymphocytic infiltrate is often present. Moreover, the entire gland is affected by papillary hyperplasia, with the cell growth showing both hyperplasia and hypertrophy. The thyroid follicles are lined with columnar epithelial cells with basally located round nuclei and relatively dense chromatin; the cytoplasm is granular and eosinophilic (figure 2). The nuclei are not irregular. The hyperplastic follicular epithelium forms infoldings into the lumen of the follicle, producing a stellate outline. Vacuoles are noted along the apical aspect of the follicular cells, giving the colloid a scalloped appearance. Sometimes Graves' disease is mistaken for papillary carcinoma or Hashimoto's thyroiditis, but other histologic features will help make the distinction.

Figure 1. Low-power view shows marked lobularity and a diffuse hyperplasia and hypertrophy of the gland.

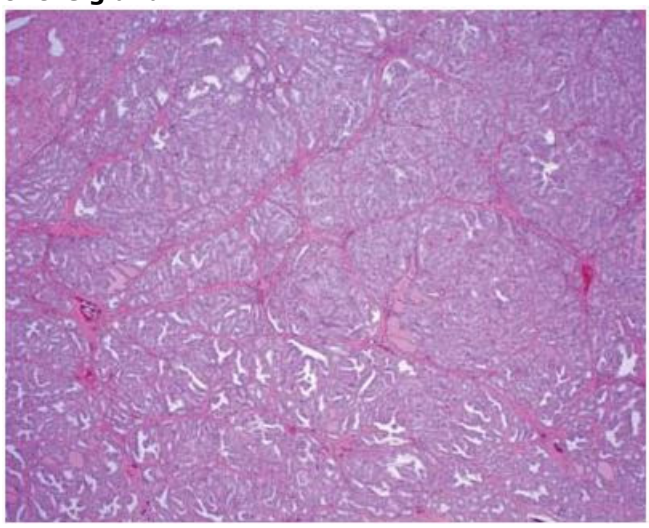
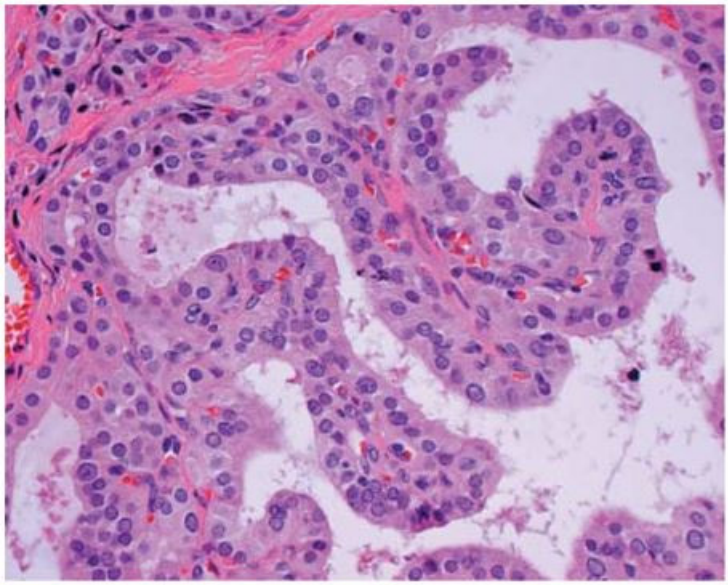


Figure 2. Slide shows simple papillary projections with round nuclei in columnar cells. Colloid is thin. The nuclear features of papillary carcinoma are not present.



Most cases of Graves' disease show treatment effect, specifically related to medical management or radioactive iodine. Potassium iodide causes involution, as follicular cells revert to their normal cuboidal or flattened appearance, alternating with areas that have retained some of the features of hyperplasia (figure 3, A). However, the failure rate with medical therapy is 40%, so most patients are forced to consider radioactive iodine or surgery. Radioactive iodine may produce a nodular gland; the nodules are often quite cellular and may exhibit striking nuclear atypia (figure 3, B). Beta blockers are used to ameliorate symptoms before surgery.

Figure 3A. Slides show the effects of different types of therapy. Medical therapy results in involution with abundant colloid and flattened papillary structures.

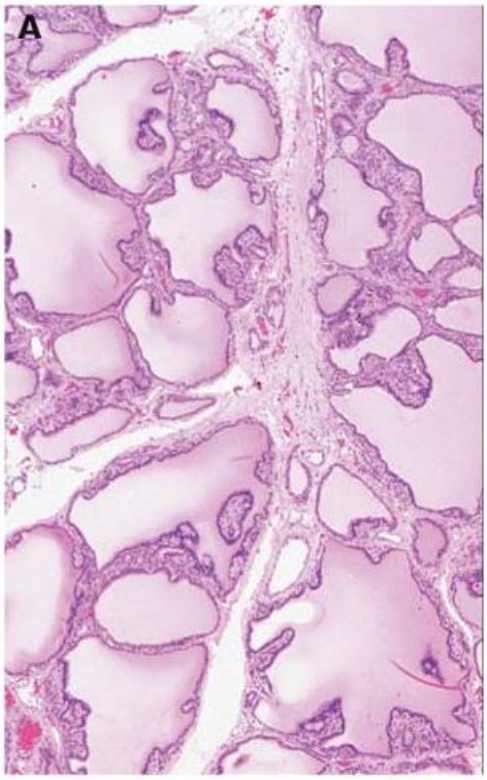
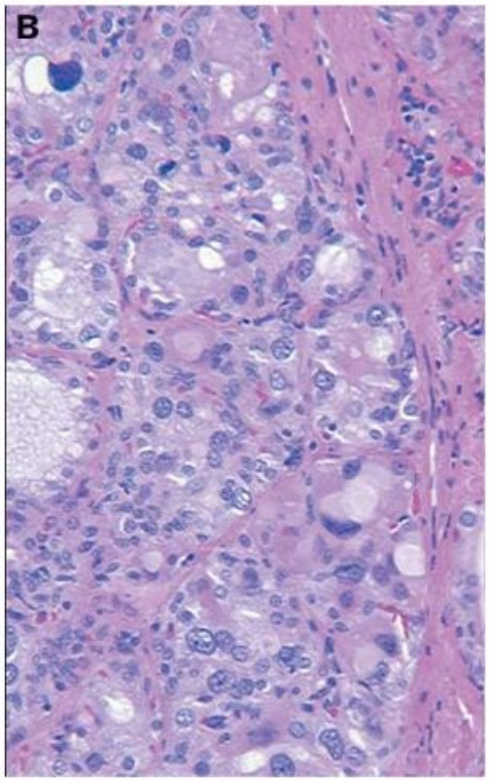


Figure 3B. Slides show the effects of different types of therapy. Radioactive iodine therapy results in cellular nodules with nuclear atypia.



The overall prognosis for patients with Graves' disease is excellent. However, thyroid storm is a life-threatening exacerbation of thyrotoxicosis. Patients exhibit severe central nervous system and cardiac manifestations. Thyroid storm requires rapid treatment, usually with antithyroid drugs for initial control.

Suggested reading

1. Cooper DS. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. Endocrinol Metab Clin North Am 1998; 27 (1): 225–47.
2. Dabon- Almirante CL, Surks MI. Clinical and laboratory diagnosis of thyrotoxicosis. Endocrinol Metab Clin North Am 1998; 27 (1): 25–35.
3. Mc Iver B, Morris JC. The pathogenesis of Graves' disease. Endocrinol Metab Clin North Am 1998; 27 (1): 73–89.

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