[Thyrotoxicosis of other Etiologies](#)

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INTRODUCTION

Thyrotoxicosis is defined as the clinical syndrome of hypermetabolism resulting from increased free thyroxine (T4) and/or free triiodothyronine (T3) serum levels (1). The term thyrotoxicosis is not synonymous with hyperthyroidism, the elevation in thyroid hormone levels caused by an increase in their biosynthesis and secretion by the thyroid gland (Table 1) (2). For example, thyrotoxicosis can result from the destruction of thyroid follicles and thyrocytes in the various forms of thyroiditis, or it can be caused by an excessive intake of exogenous thyroid hormone. It should also be noted that the elevation of free thyroid hormone levels does not always result in thyrotoxicosis in all tissues. In the syndrome of Resistance to Thyroid Hormone (RTH), dominant negative mutations in the thyroid hormone receptor ⨳ (TR⨳) result in decreased thyroid hormone action in tissues where TR⨳ is the predominant receptor, for example in the liver and the pituitary, whereas other tissues such as the heart, which express mainly TR◇, show signs of increased thyroid hormone action (See Chapter 16 D). The most common form of thyrotoxicosis is Graves' disease, which is discussed in Chapter 10. This chapter reviews other etiologies of thyrotoxicosis (Table 1). The determination of the etiology of thyrotoxicosis is of importance in order to establish a rational therapy.

Table 1. Etiologies of thyrotoxicosis
A) Thyrotoxicosis caused by hyperthyroidism

Entity	Pathogenesis
Graves' disease	TSH receptor-stimulating antibodies
Toxic adenoma	Somatic gain-of-function mutations in the TSH receptor or Gs◇
Toxic multinodular goiter	Somatic gain-of-function mutations in the TSH receptor or Gs◇
Hyperthyroid thyroid carcinoma	Somatic gain-of-function mutations in the TSH receptor
Familial non-autoimmune hyperthyroidism	Germline gain-of-function mutations in the TSH receptor
Sporadic non-autoimmune hyperthyroidism	Germline gain-of-function mutations in the TSH receptor
TSH secreting pituitary adenoma	Increased stimulation by inappropriate TSH secretion
hCG-induced gestational hyperthyroidism	Increased stimulation of the TSH receptor by hCG
Familial hypersensitivity to hCG	TSH receptor mutation with increased sensitivity to hCG
Trophoblast tumors (hydatiform	Increased stimulation of the TSH receptor by hCG

mole, choriocarcinoma)

Struma ovarii	Autonomous function of thyroid tissue in ovarian teratoma
Iodine-induced hyperthyroidism	Increased synthesis of thyroid hormone in autonomously functioning thyroid tissue after exposure to excessive amounts of iodide

B) Thyrotoxicosis without hyperthyroidism

Subacute thyroiditis	Release of stored thyroid hormone
Silent thyroiditis	Release of stored thyroid hormone
Drug-induced thyroiditis	Release of stored thyroid hormone
Exogenous thyroid hormone (iatrogenic, thyrotoxicosis factitia)	Thyroid hormone

TSH: Thyroid-stimulating hormone. Gs✧: stimulatory G protein subunit. hCG = human chorionic gonadotropin.

TOXIC ADENOMA

Definition and Epidemiology

A toxic adenoma is a monoclonal, autonomously functioning thyroid nodule (AFTN) that produces supraphysiological amounts of T4 and/or T3 resulting in suppression of serum TSH. The function of the surrounding normal thyroid tissue is often, but not always, suppressed. Approximately 1 in 10 to 20 solitary nodules present with hyperthyroidism. The prevalence of hyperthyroidism appears to be more common in Europe than in the USA, and it is more common in women than in men (3, 4). In a series of 349 patients with AFTNs, 287 were nontoxic and 62 were toxic (3). Toxic lesions were seen in 56.5% of patients over 60 years, but in only 12.5% of the younger patients. The female to male ratio was 14.9:1 for nontoxic AFTNs and 5.9:1 for toxic AFTN patients. T3 thyrotoxicosis was observed in 46% of the patients with hyperthyroidism. All but 4 of the toxic AFTN measured 3 cm in diameter or were larger. AFTNs 3 cm or larger were more than twice as common in patients 40 years or older than in younger patients. Of 159 untreated nontoxic AFTN patients, 14 became toxic within 1 to 6 years (3). In a study from Switzerland on 306 patients with toxic adenomas, the female to male ratio was 5: 1 (5). The frequency of toxic adenomas in patients referred for thyrotoxicosis varies considerably in different geographical areas and appears to be more common in countries with insufficient nutritional iodide intake; reported percentages vary between 1.5 and 44.5% (6). In a prospective European multicenter study (17 centers in 6 countries) 924 untreated hyperthyroid patients were investigated (2). 9.2% of the patients had an autonomous adenoma and 59.6% had Graves' disease. Among the 31.2% with unclassified hyperthyroidism, a majority probably also had Graves' disease. Autonomous adenomas were more frequent in iodine-deficient areas (10.1%) than in iodine-sufficient areas (3.2%) (2). In a Swedish study, the mean annual incidence of toxic adenomas (4.8 per 100,000) did not differ between 1988 and 1990 and between 1970 and 1974 (7).

Clinical presentation

Patients with toxic adenomas present with signs and symptoms of thyrotoxicosis and/or a thyroid nodule. The signs and symptoms of thyrotoxicosis do not differ from other etiologies. Features suggestive for Graves' disease such as endocrine ophthalmopathy, (pretibial) myxedema and acropachy are missing. The onset of thyrotoxicosis is often insidious and more common in older patients, who

typically have larger adenomas. However, a toxic adenoma has even been documented as a cause of neonatal hyperthyroidism (8). Mechanical symptoms such as dysphagia or hoarseness are uncommon. Autonomously functioning nodules may remain stable in size, grow, degenerate or become gradually toxic. In one series, 10% of patients followed for 6 years became thyrotoxic (3). Thyrotoxicosis may develop independent of age, but is much more common in nodules ov er 3 cm in diameter (up to 20%). By sonography, the critical volume at which hyperthyroidism occurs is about 16 ml (9). Changes in nodule size were followed in 159 patients during a period of 1 to 15 years (3). An increase in size was seen in only 10%, 4% of nodules decreased, and a loss of function due to degenerative changes was observed in 4 nodules. Eight percent developed overt thyrotoxicosis during a follow-up of 3 to 5 years, and 3% developed subclinical hyperthyroidism (3).
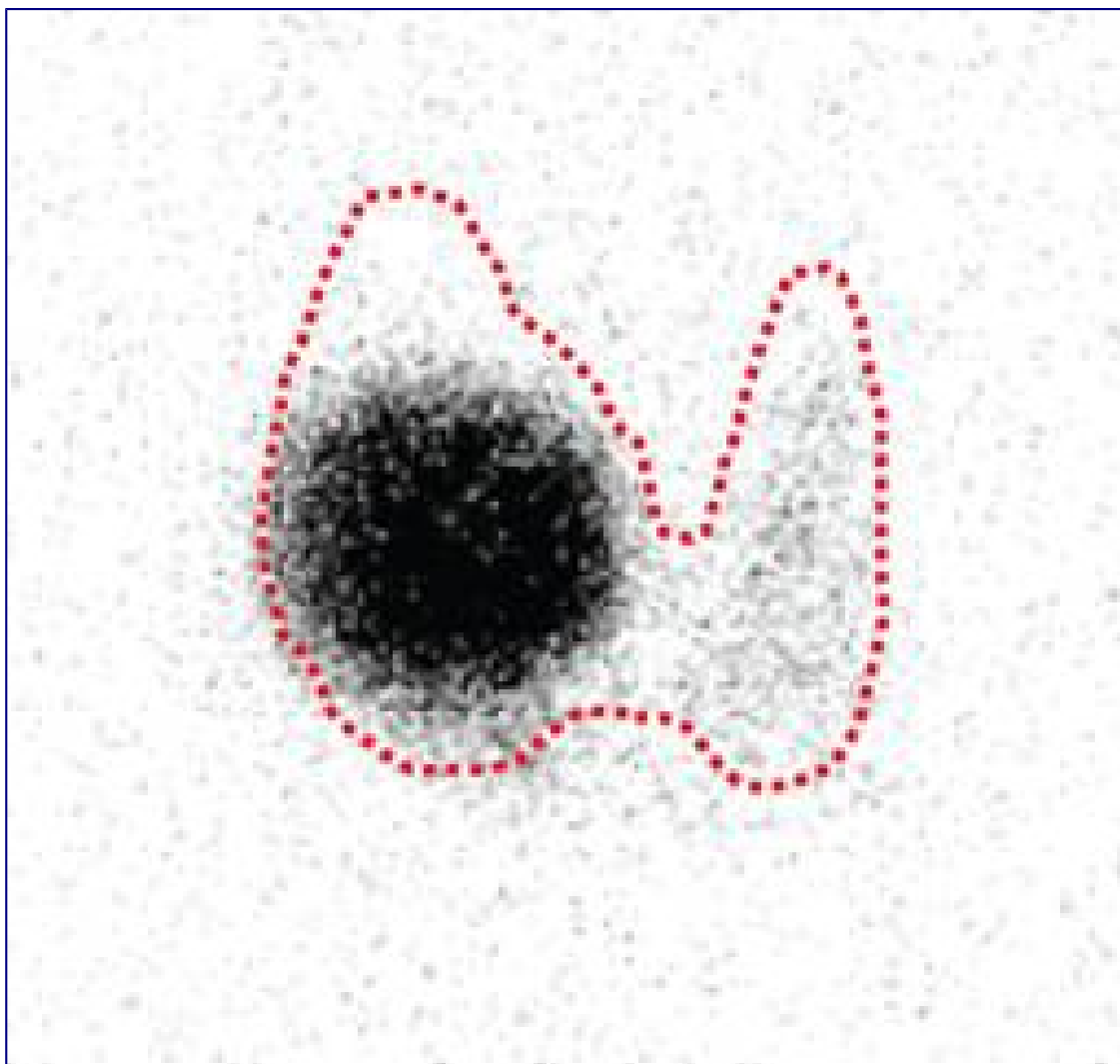
Diagnosis

Figure 1. Scintigraphy of a toxic adenoma in the right thyroid lobe.

The measurement of serum TSH with a sensitive third-generation assay represents the best biochemical marker to establish the diagnosis of thyrotoxicosis because TSH and FT4 have an inverse log-linear

relationship and a small decrease or increase in FT4 is thus associated with an exponential change in TSH levels (10). If the TSH is suppressed, measurement of serum (free) T4 and T3 permit to ascertain the severity of the thyroid overactivity. A thyroid scan can be performed with 123iodine, 131iodine, or 99technetium-labeled pertechnetate (11). Iodine isotopes, which are not only trapped but also organified in the thyroid, are preferred because 3-8% of nodules that appear functioning on pertechnetate scanning are nonfunctioning on radioiodine scanning. A scan will show uptake of the isotope that is either limited to the nodule, or preferential uptake in the adenoma compared to the surrounding tissue (Figure 1). Scintigraphically, an AFTN may be warm (uptake similar to surrounding tissue), hot (uptake increased without suppression of surrounding tissue), or toxic (uptake increased and suppression of the surrounding tissue). A toxic nodule is associated with overt or subclinical hyperthyroidism. A warm nodule may develop into a hot nodule and ultimately into a toxic adenoma. Toxic adenomas are usually larger in size and often more than 3 cm in size (3, 12). In the case of incomplete suppression of the surrounding tissue, autonomous function of the nodule can be established by a suppression test. After the administration of thyroid hormone (e.g. 75 ï¿½g of levothyroxine for 2 weeks, followed by 150 ï¿½g for 2 weeks), a repeat thyroid scan would fail to show remaining uptake in the non-autonomous tissue because of the suppression of serum TSH, thereby unmasking the autonomy of the nodule (13). However, this procedure has no practical consequences and is therefore unnecessary in clinical practice. Ultrasound will confirm the presence of a solitary nodule and may show a small contralateral thyroid lobe. There is no indication to perform fine needle aspiration in patients with toxic adenomas because the risk of a thyroid carcinoma is extremely low and cytological evaluation will not permit distinguishing between a follicular adenoma and a follicular carcinoma (14, 15).

Treatment

In patients with overt thyrotoxicosis, definitive forms of treatment include surgical excision of the nodule, treatment with radioactive iodine, or percutaneous ethanol injection (11, 16). Treatment with antithyroid drugs is used infrequently as it requires long-term therapy and a relapse will almost invariably occur after discontinuation of the medication. Surgical excision permits to achieve a rapid and permanent control of hyperthyroidism with a very low operative complication rate. The disadvantage of a surgical approach includes the risks of general anesthesia and the potential complications of thyroid surgery. Usually the patient is treated preoperatively with antithyroid drugs and beta-blockers. The incidence of hypothyroidism after operation is low, but may occur. In a series of 60 patients operated for AFTNs, 6.6% became hypothyroid after operation (17). Two of these patients had previously received therapeutic doses of 131iodine or long-term treatment with antithyroid drugs. In a series of 35 patients with a solitary toxic adenoma, lobectomy resulted in 30 euthyroid and 5 hypothyroid outcomes, although hypothyroidism was only temporary in 3 patients (4). It remains unclear why some of these patients remained permanently hypothyroid after lobectomy; information about the presence of autoantibodies and the morphology of the contralateral lobe is not provided in this study. Generally, it is believed that long-term suppression of the thyroid gland does not lead to permanent inactivation after suppression is relieved. Administration of 131iodine is a widely used therapeutic modality for patients with toxic adenomas. The main disadvantage consists in the possibility of permanent hypothyroidism in a subset of patients. In a study by Goldstein et al., 23 patients were followed for 4 to 16.5 years and 8/23 (35%) developed hypothyroidism (18). The incidence of hypothyroidism was not related to nodule size, the level of thyroid function, or the administered dose of 131iodine. In a similar study by Mariotti et al. on 126 patients, 5/126 (4%) developed overt hypothyroidism 1 to 10 years after 131iodine therapy (19). There was no relationship between the development of hypothyroidism, nodule size or the administered dose of 131iodine (19).

Hypothyroidism occurred in 9.7% of patients with an euthyroid hot nodule treated with 131iodine, and in only 1.5% of patients with a toxic adenoma. When antithyroglobulin and/or antithyroid microsomal antibodies were present, the prevalence of hypothyroidism after 10 years was 18% versus 1.4% in antibody-negative patients. In two studies, evaluating 48 and 45 patients 6 months after radioiodine therapy, hypothyroidism could not be documented in any of the patients (20, 21). In a more recent study by Bolusani et al. on 105 patients with solitary autonomous nodules, the cumulative incidence of hypothyroidism was 11% at 1 year, 33% at 5 years, and 49% at 10 years (22). The development of hypothyroidism was not associated with age, sex, radioiodine dose, radioiodine uptake, or degree of suppression of extranodal tissue on scintiscans. The predictors of occurrence of hypothyroidism were pretreatment with antithyroid medications and a positive thyroid antibody status. Antibody-positive patients showed an earlier progression towards hypothyroidism than did antibody-negative patients (22). In aggregate, these results suggest that longer follow-up periods may uncover hypothyroidism more frequently and that the development of hypothyroidism may often be related to the presence of thyroid autoantibodies, but less to the administered dose of 131iodine and nodule size. In patients treated with antithyroid drugs prior to radioiodine therapy, the increase in TSH may reactivate suppressed thyroid tissue and iodide uptake resulting in damage by 131iodine. Some clinicians administer levothyroxine for two weeks prior to therapy in order to assure that the tissue surrounding the toxic adenoma is suppressed. In some instances, high doses of 131iodine in the nodule may provide enough radiation to the surrounding tissue that its function is seriously damaged. It is noteworthy that therapy with 131iodine may trigger the development of humoral thyroid autoantibodies (23). For example, about 5% of patients treated with 131iodine for toxic or euthyroid multinodular goiter develop stimulating TSH receptor antibodies and Graves' disease (24). Hence, hypothyroidism may, in part, result from the development of humoral autoantibodies in patients with toxic adenomas treated with 131iodine. An alternative to surgery and 131iodine therapy for toxic adenomas consists in the use of percutaneous ethanol injection into the nodule under ultrasound guidance (11). The injection results in necrosis and thrombosis of small vessels. Side effects include local pain and, in rare cases, recurrent nerve damage. In studies evaluating the outcomes at 12 or 30 months, about 85% of patients were euthyroid (25, 26). Results of ethanol injection in relatively large AFTNs (diameter 3 to 4 cm) are also favorable, particularly in patients with subclinical hyperthyroidism (27, 28). Surpisingly, previous ethanol injection did not hinder histological assessment in 13 patients who ultimately underwent surgical excision of their nodule (29). Percutaneous laser thermal ablation (LTA) is a more recently introduced technique for the debulking of thyroid nodules and has also been used for the debulking of anaplastic thyroid cancer (30). In hyperfunctioning nodules, LTA induced a nearly 50% volume reduction with a variable frequency of normalization of thyroid-stimulating hormone levels (31, 32). Most patients become and remain euthyroid after treatment. However, serum TSH measurement at yearly intervals is necessary in order to detect those patients, especially with circulating thyroid autoantibodies, who will eventually develop hypothyroidism.

Pathogenesis

Chronic stimulation of the cAMP cascade results in enhanced proliferation and function of thyrocytes (33). Hence, any molecular alteration leading to constitutive activation of the cAMP pathway in a thyroid follicular cell is expected to result in clonal autonomous growth and function, and ultimately in a toxic adenoma (33). In line with this concept, somatic mutations were first discovered in the *GNAS1* gene encoding the stimulatory G s◇subunit in toxic adenomas (34-36). Stimulatory Gs◇mutations impair the hydrolysis of guanine triphosphate (GTP) to guanine diphosphate (GDP), resulting in persistent activation of adenylyl cyclase. Stimulatory Gs◇mutations are also found in 35ï¿½40% of somatotroph tumors in acromegalic patients (37), and mosaicism for Gs◇mutations with onset during

blastocyst development causes the McCune Albright syndrome (38). The observation that site-directed mutagenesis of a residue in the third intracellular loop of the ⋄1b-adrenergic receptor can lead to constitutive activation of this G protein-coupled receptor (GPCR) in the absence of ligand led to the search and detection of naturally occurring activating mutations in numerous GPCRs (39). Somatic mutations in the TSH receptor were first discovered in toxic adenomas (40). The initially characterized mutations were clustered in the third intracellular loop and the sixth transmembrane domain of the receptor, but a wide variety of activating somatic mutations have been found in subsequent studies (see Chapter 16 A) (41-44). Mutations conferring constitutive activity occur in the entire transmembrane domain, as well as in the carboxy-terminal region of the extracellular domain. All mutations increase basal cAMP levels, but only a few amino acid substitutions activate the phospholipase C (PLC) cascade in a constitutive manner. Inositoltriphosphate (IP3) accumulation in response to TSH is usually retained. The reported prevalence of TSH receptor mutations in toxic adenomas varies widely, but is as high as 80% (43, 45). For example, in a study on 33 toxic adenomas from 31 patients from Belgium, 27/33 of adenomas were positive for a somatic mutation in the TSH receptor (46). In contrast, in a Japanese study that analyzed the part of the gene encoding the third cytoplasmic loop and the sixth transmembrane segment, only 1/38 toxic adenomas harbored a functionally silent mutation (45). Differences in sampling technique and methodological approach, as well as variations in iodine intake, may contribute to the reported differences (47). It is now well established that somatic, constitutively activating TSH receptor mutations play a predominant role in the pathogenesis of AFTNs, while Gs⋄ mutations are less common (48). It is likely that other somatic mutations are involved in the pathogenesis of the monoclonal toxic adenomas that are negative for mutations in the TSH receptor and Gs⋄ (49). Functionally, some of the mutations may alter the positions of the transmembrane helices, thereby mimicking the conformational changes induced by binding of ligand. Alternatively, some mutations may alter the structure of domains that inhibit coupling of the receptor to G proteins in the absence of TSH (50, 51). Activating mutations in the extracellular domain appear to result in a relief of a negative constraint present in the unliganded carboxy-terminal part of the extracellular domain (8, 43, 52-54). It has been suggested that iodine deficiency may be a predisposing factor for the development of AFTNs (55). Based on the fact that autonomous (multi)nodular goiters develop also in iodine-sufficient regions and that there is often a hereditary predisposition, others propose that hereditary and acquired heterogeneity among the thyrocytes play a fundamental role in the pathogenesis of AFTNs and that iodine deficiency only serves as a modulating factor (56).

Pathology

On macroscopic examination, a solitary toxic nodule is surrounded by normal thyroid tissue that is functionally suppressed. Toxic adenomas are histologically classified as encapsulated follicular neoplasms or adenomatous nodules without a capsule (57). Hemorrhage, calcifications and cystic degeneration are commonly present. In a study on 51 solitary adenomas, functional and pathologic characteristics were determined and compared to normal surrounding tissue (58). The adenomas displayed a higher number of cycling cells in the periphery of the adenomas, a high level of iodide trapping because of a high level of sodium/iodide symporter (NIS) gene expression, a high thyroperoxidase (TPO) mRNA and protein content, and low H2O2 generation. The adenomas secreted higher amounts of thyroid hormone than the quiescent tissue (58). The proliferation index was determined in 20 toxic adenomas using labeling with proliferating cell nuclear antigen (PCNA) and Ki-67 epitope as markers (59). In line with the slow growth of these lesions, cell proliferation was found to be modestly increased compared to the surrounding tissue (59). Malignant AFTNs are uncommon. In a study of 306 patients presenting with AFTNs, Horst et al. did not find any thyroid malignancy (5). Sandler et al. concluded that most reported hyperfunctioning carcinomas resulted from the coexistence

of small malignancies in or adjacent to a benign hot lesion (14). Isolated cases of carcinomas in hot nodules have, however, been reported (4, 60-62). Smith et al. reported the occurrence of 3 carcinomas in 30 consecutive patients operated for solitary hot nodules (62). In a series of 164 patients, 3 of 29 patients treated surgically were diagnosed with thyroid cancer (63). It is an open question whether the diagnosis of cancer would be established in all these cases using modern histological criteria and molecular markers (64). In most instances, the presence of an AFTN argues against the presence of a malignant lesion.

TOXIC MULTINODULAR GOITER

Definition

Hyperthyroidism may occur due to AFTNs in a multinodular thyroid gland and this is discussed in detail in Chapter 17.

Clinical presentation

In addition to the signs and symptoms associated with hyperthyroidism, patients with large toxic multinodular goiters may also have dysphagia, shortness of breath, stridor, or hoarseness.

Diagnosis

The diagnostic approach is in general similar to patients with a solitary AFTN, but cross-sectional imaging with computer tomography and pulmonary function tests need to be considered in a subset of patients in whom compression by the goiter is evident or suspected.

Treatment

Therapeutically, surgery and radioiodine therapy are the most commonly used therapeutic modalities.

Pathogenesis

While the mechanisms underlying the development of nodules are of complex nature (65), it has become apparent that hyperfunctioning adenomas within multinodular goiters or autonomous areas within euthyroid goiters may also harbor somatic gain-of-function mutations in the TSH receptor (66-68). It is noteworthy that the mutations may differ among the adenomas within the same multinodular goiter (66). This observation is consistent with studies demonstrating distinct clonal origins of different thyroid adenomas within the same multinodular goiter (69). For example, in two adenomas from the same goiter, one neoplasm harbored a M453T mutation, the second adenoma a T632I substitution (66). In another study, L632I and F631L mutations were found in two distinct lesions within the same goiter, whereas another patient had two distinct toxic nodules with the same I630L mutation (67). These studies reveal that the pathogenesis of hyperfunctioning adenomas does not differ between solitary toxic adenomas and multinodular goiters. In a study analyzing hyperfunctioning and nonfunctioning areas from patients with toxic multinodular goiters, gain-of-function TSH receptor mutations were detected in 14 of 20 hyperfunctioning areas, whereas no mutation was identified in nonfunctioning nodules (70). On microscopic analysis, only two of the hyperfunctioning areas corresponded to classic

adenomas surrounded by a capsule, whereas the remainder had the characteristic features of hyperplastic lesions. The development of multinodular goiters had been associated with a D727E germline polymorphism in the TSH receptor (71), but this finding could not be corroborated in other studies (72, 73). Constitutively activating TSH receptor mutations have also been detected in autoradiographically hyperfunctioning areas of goiters from euthyroid patients (74). The observation that TSH receptor mutations are rare in nonfunctioning adenomas, even if of monoclonal origin (68, 75), indicate that distinct mechanisms must be implicated in the abnormal growth leading to nonfunctioning nodules (65).

HYPERTHYROID THYROID CARCINOMA

Definition and Epidemiology

As discussed above, hyperfunctioning nodules are most commonly benign. Rarely, follicular carcinoma is associated with thyrotoxicosis. Ehrenheim compiled 20 such cases in 1986 (76), and Salvatori et al. reviewed 54 similar cases reported in the literature (77). Age and sex distribution in these patients does not differ from that of patients with follicular carcinoma without thyrotoxicosis.

Clinical presentation

Most commonly, thyrotoxicosis and thyroid carcinoma are diagnosed at the same time because of signs of thyrotoxicosis and the finding of a thyroid nodule prompting fine needle aspiration.

Diagnosis

Patients with thyrotoxic thyroid cancer have predominantly T3 thyrotoxicosis (78). Thyroglobulin levels are elevated. Cytology reveals most commonly follicular thyroid cancer (79), but hyperfunctinoning papillary thyroid cancer has also been documented (80). In patients who are on levothyroxine substitution after total thyroidectomy, the presence of hyperfunctioning metastases may not be readily apparent. Gradual reduction or withdrawal of levothyroxine therapy is necessary in order to recognize whether the thyrotoxicosis is caused by excessive exogenous levothyroxine or hyperfunctioning metastases. Whole-body scanning with radioiodine is used for the localization of the hyperfunctioning metastases.

Treatment

Treatment of patients with functioning thyroid carcinomas does not differ from the therapy of thyroid cancer patients without thyrotoxicosis, but appropriate control of the hyperthyroid state with antithyroid drugs and beta-blockers is important before submitting a patient to thyroid surgery or 131iodine therapy. Exacerbation of the hypermetabolic state with precipitation of thyroid storm has been reported in a patient undergoing radioiodine therapy for metastatic thyroid carcinoma without prior control with antithyroid drugs (81).

Pathogenesis

In well-differentiated thyroid cancers, mutations in the Gs♦subunit and the TSH receptor genes occur

only very rarely (36, 80, 82-86). Although constitutive activation of the cAMP pathway results in enhanced growth, it is not thought to be sufficient for malignant transformation of otherwise normal thyrocytes. A few patients with hyperthyroidism due to autonomously functioning thyroid cancers harboring mutations in the TSH receptor have, however, been identified. For example, Russo et al. reported a patient who presented with hyperthyroidism and increased uptake in two nodules, but suppressed uptake in the remainder of the gland (80). After surgical removal of the right thyroid lobe, histological examination revealed the presence of an insular papillary carcinoma with lymph node and lung metastases. Mutational analysis of the TSH receptor gene documented a somatic mutation, D633H, in DNA isolated from the primary tumor and metastatic tissue. Another mutation that activates both the cAMP and the IP3 pathways, I486F, was found in a hyperfunctioning well-differentiated follicular carcinoma in a patient presenting with hyperthyroidism and increased radioiodine uptake within the thyroid mass (86). It is conceivable that concomitant activation of these two signaling casca des may promote transformation. In a patient with an Hï¿½rthle cell carcinoma, Russo et al. identified a L677V TSH receptor mutation (85). Basal cAMP levels were increased in transfected Chinese hamster ovary (CHO) cells, but IP3 accumulation has not been determined. A somatic M453T substitution has been identified in a 11-year-old girl with a hyperfunctioning nodule and a papillary carcinoma (87). The same mutation has been found in the germline of two patients with congenital hyperthyroidism, but there was no suggestion that it is oncogenic (88, 89). Interestingly, however, overexpression of the M453T TSH receptor mutation in the FRTL-5 rat cell line was sufficient to induce neoplastic transformation as assessed by growth in semisolid medium and athymic mice (90). Follicular carcinomas have also been reported in patients with Graves' disease (91-93). It has been suggested that long-standing stimulation through TSH receptor-stimulating antibodies may play a role in the pathogenesis of these neoplasias (94). Whether thyroid carcinomas affecting patients with underlying Graves' disease behave more aggressively, as suggested by some authors (95), remains uncertain (96).

FAMILIAL NON-AUTOIMMUNE HYPERTHYROIDISM WITH TSHR MUTATIONS

Definition and Epidemiology

Autosomal dominant familial hyperthyroidism without evidence of an autoimmune etiology has been first described by Thomas et al. in 1982 (Chapter 16 A) (97). Currently 27 families with a total of 152 affected individuals with non-autoimmune familial hyperthyroidism have been reported (For recent review see: (98)). The hyperthyroidism is caused by monoallelic gain-of-function germline mutations in the TSH receptor.

Clinical presentation

The typical signs associated with autoimmune hyperthyroidism, i.e. the presence of stimulatory TSH receptor antibodies, endocrine ophthalmopathy, myxedema, lymphocytic infiltration of the thyroid gland, are absent. The age of onset of hyperthyroidism is variable and depends, in part, on the activity of the mutated allele. The majority of patients has a goiter.

Diagnosis

Affected individuals have a suppressed TSH and elevated peripheral hormones in the absence of TSH receptor-stimulating antibodies and TPO antibodies. The family history is key in order to demonstrate familial clustering suggestive for an autosomal dominant disorder. Ultimately, the diagnosis requires sequence analysis of the *TSH receptor* gene in order to evaluate it for the presence of a monalllelic mutation. If the mutation is unknown, functional *in vitro* analyses are needed to demonstrate that the mutated allele confers constitutive activity to the receptor.

Treatment

In order to achieve permanent cure, it is necessary to destroy all thyroid tissue, either by thyroidectomy followed by radioiodine therapy, or radiotherapy alone (98). In younger patients, temporary therapy with thionamides can be considered. Because the condition may not be readily recognized and confused with Graves' disease, patients treated with thionamides or insufficient amounts of radioiodine have frequent relapses (98).

Pathogenesis

The molecular basis of hereditary non-autoimmune hyperthyroidism was elucidated by detecting activating germline mutations in the TSH receptor in the family reported by Thomas et al. (51). Gain-of-function mutations are by definition dominant, and alteration of one allele is thus sufficient for generating the phenotype. Interestingly, the onset of hyperthyroidism may vary in carriers of the same mutation in a given kindred. Hence, other factors, for example genetic background and/or iodine intake, appear to modulate the phenotypic expression (97, 99, 100).

SPORADIC NON-AUTOIMMUNE HYPERTHYROIDISM

Autoimmune neonatal hyperthyroidism is rare and occurs in less than 2% of newborns that are the offspring of a mother with a history of Graves' disease (101), a condition with an estimated incidence of about 2 of every 1000 pregnancies (97). In these infants, the congenital hyperthyroidism is caused by transplacental passage of stimulating TSH receptor autoantibodies (102). Antibody-induced neonatal hyperthyroidism usually resolves within the first few months of life as the maternal antibodies are cleared from the circulation. Occasionally, thyroid hormone may be fluctuating between elevated and decreased levels because of the concomitant presence of stimulating and blocking antibodies (103). Constitutively activating germline neomutations in the TSH receptor have been found in a total of 15 patients with sporadic congenital non-autoimmune hyperthyroidism (Chapter 16 A) (104)(For recent review see:(98)). Congenital hyperthyroidism due to a toxic adenoma harboring a somatic TSH receptor mutation was reported as an unusual variant (8). The patients with non-autoimmune congenital hyperthyroidism must be differentiated from the much more common and transient autoimmune form of neonatal hyperthyroidism, because these patients have pronounced hyperthyroidism requiring a more aggressive therapeutic approach that may necessitate surgery and ablative radiotherapy early in life. Several of the children with severe neonatal hyperthyroidism were reported to have mild mental retardation (104-106), suggesting that high levels of thyroid hormone may have a negative impact on brain development (107). Alternatively, mental development may have been impaired because of premature closure of the cranial sutures. A subset of these children had proptosis (88, 89). Computer

tomography of the retroorbital tissue in one of these children did, however, not demonstrate infiltration of the eye muscles (88).

TSH-SECRETING PITUITARY ADENOMA

Definition and Epidemiology

TSH-secreting adenomas (TSHomas) account for less than 2% of all pituitary adenomas and are a rare cause of thyrotoxicosis (Chapter 13) (108, 109). TSHomas and RTH form the two syndromes of ï¿½inappropriate TSH secretionï¿½ defined by normal or elevated TSH levels in combination with increased (free) T4 and T3 levels.

Clinical presentation

Patients with TSHomas present with signs and symptoms of hyperthyroidism and an enlarged thyroid. In patients with RTH, the phenotype is more complex as some tissues are resistant to the action of the elevated peripheral hormones and thus hypothyroid, whereas other tissues can be excessively stimulated. The physiological negative feedback normally exerted by thyroid hormones is not operating in both conditions. TSHomas secrete TSH in an autonomous fashion, in RTH the thyrotropes are resistant to the high levels of thyroid hormone. Most patients are older, but TSHomas have also been documented in children (110).

Diagnosis

Magnetic resonance imaging (MRI) of the pituitary will reveal a pituitary adenoma in patients with TSHomas. TSH is formed of a specific ⬥ subunit and the glycoprotein ⬥ subunit common to TSH, FSH and LH/CG. Some clinicians measure the glycoprotein ⬥ subunit as a marker to distinguish between TSHomas and RTH. The ⬥ subunit and the ⬥ subunit /TSH ratio are often elevated in patients with TSHomas (111). However, in one series of TSHomas, normal ⬥ subunit levels were observed in more than 60% of the patients, particularly in microadenomas (112). The TSH secreted by TSHomas is normal in terms of amino acid sequence, but has variable biological activity and is secreted in fluctuating amounts (113). Compared to controls, TSH burst frequency and basal secretion are increased, TSH secretion patterns are more irregular, but the diurnal rhythm is preserved at a higher mean in all patients (114). A more sensitive and specific test than measuring the ⬥ subunit consists in the T3 suppression test (80ï¿½100 ï¿½g of T3 per day per 8ï¿½10 days), which does not result in complete inhibition of T3 secretion in patients with TSHomas (108, 112, 115). An alternative consists in the TRH-stimulation test, but TRH is currently not available in the United States. After injection of TRH (200 ï¿½g i.v.) TSH and the ⬥ subunit do not increase in patients with TSHomas (108).

Treatment

Transsphenoidal surgery is the cornerstone for therapy of TSHomas. Complete resection may not be possible because these tumors can invade the sinus cavernosus and other adjacent structures. Prior to surgery, the hyperthyroidism should be controlled with thionamides and beta-blockers. In patients with residual tumor tissue and persistent secretion of TSH, both ⋎-knife radiotherapy (10 ï¿½ 25 Gy)

and medical therapies can be considered. The latter include the use of somatostatin analogues, such as octreotide and lanreotide. TSHomas express somatostatin receptors and somatostatin analogues are highly effective in reducing TSH secretion by neoplastic thyrotropes (116). If tolerated, somatostatin analogues are effective in reducing TSH secretion in more than 90% of patients with consequent normalization of thyroid hormone levels and restoration of the euthyroid state. Tumor shrinkage does occur in about 45% of patients (117). Dopamine receptors are also present in TSHomas and dopamine agonists such as bromocriptine or cabergoline have been used in order to control TSH secretion (108). The response is, however, highly heterogeneous and best in tumors secreting both TSH and prolactin. In the case of a surgical cure, the postoperative TSH is undetectable and may remain low for weeks or months, causing central hypothyroidism. Permanent central hypothyroidism may also occur due to the mass effect exerted by the tumor or after radiotherapy. Thus, transient or permanent substitution therapy with levothyroxine may be necessary. Long-term evaluation of all pituitary axes is important, particularly in patients who underwent radiotherapy, in order to recognize and treat anterior pituitary deficiencies in a timely manner.

Pathogenesis

The molecular mechanisms leading to the formation of TSHomas remain unknown. TSHomas have been shown to be monoclonal by X-inactivation analyses suggesting that they arise from a single cell harboring one or several mutations in genes controlling proliferation and perhaps function (108).

RESISTANCE TO THYROID HORMONE

The syndrome of Resistance to Thyroid Hormone (RTH) is described in detail in Chapter 16 D. RTH is defined by elevated circulating levels of free thyroid hormones due to reduced target tissue responsiveness and normal, or elevated, levels of TSH (118, 119). Patients with RTH typically present with goiter. Their metabolic state may appear euthyroid or include signs of hypo- and hyperthyroidism. With the exception of the first studied kindred, a single sibship harboring a deletion of the entire coding sequence of the entire TRβ gene and a recessive pattern of inheritance, RTH is most commonly caused by monoallelic mutations of the *TRβ* gene. The mutation can be inherited in an autosomal dominant manner or occur as *de novo* mutation. The mutant receptors act in a dominant negative fashion to block the activity of the normal allele, thereby explaining the dominant inheritance. The gene defect remains unknown in about 15% of subjects with a RTH phenotype. It is likely that mutations in cofactors that are required for normal TR function are involved in the pathogenesis of RTH in these patients. The generation of mice with targeted deletion of TRβ, as well as TR knockin models, have been essential for elucidating the physiology of thyroid hormone action and the pathophysiology of RTH (120).

HCG-INDUCED GESTATIONAL HYPERTHYROIDISM

Thyrotoxicosis and other forms of thyroid dysfunction in the pregnant patient are discussed in detail in Chapter 14.

Definition and Epidemiology

Gestational transient thyrotoxicosis of non-autoimmune origin is caused by stimulation of the TSH receptor through hCG (121, 122). hCG-induced hyperthyroidism occurs in about 1.4 % of pregnant women, mostly when hCG levels are above 70-80,000 IU/l (123, 124) .

Clinical presentation

Many signs and symptoms of hyperthyroidism are not specific and overlap with those of normal pregnancy (125). Hence, the accuracy of clinical diagnosis is limited. Because of the decrease in the levels and bioactivity of hCG later in pregnancy, hCG-induced gestational hyperthyroidism is usually transient and limited to the first 3 ï¿½ 4 months of gestation. In a subset of women, the manifestations of hCG-induced hyperthyroidism are more severe and they are often associated with hyperemesis. Goodwin et al. studied the relationship of serum hCG, thyroid function, and severity of vomiting among 57 hyperemesis patients and 57 controls matched for gestational age (126). Hyperemesis patients had significantly greater mean serum levels of hCG, free T4, total T3, and estradiol, and lesser serum TSH concentrations compared to controls. The degree of biochemical hyperthyroidism and hCG concentration correlated directly with the severity of vomiting. The hyperemesis may be caused by a marked hCG-induced increase in estradiol levels (122). However, the relation between hyperemesis and gestational hyperthyroidism varies among patients, and additional, unidentified mechanisms may be involved.

Diagnosis

The diagnosis is established by measuring TSH, free or total T4, and T3. The physiological decrease in TSH levels and the increase in total thyroid hormone concentrations associated with the increase in thyroxine-binding globulin (TBG) have to be considered when interpreting the results. TBG levels increase in response to elevated estradiol levels and plateau by about 20 weeks of gestation (127). Therefore, total T4 and total T3 levels increase by approximately 1.5 fold. If free T4 levels are determined by analogue assays, serum concentrations are usually significantly lower than values in non-pregnant women (128).

Treatment

Treatment with antithyroid medications is often not necessary. Women with hyperemesis need therapy with antiemetics. In patients in whom total T4 levels are higher than 1.5 times the upper reference range, therapy with antithyroid drugs may be indicated. Propylthiouracil (PTU) is the preferred medication during the first trimester and methimazole during the remainder of pregnancy in the United States (129, 130). A review by Mandel and Cooper has specifically addressed the use of thionamides during pregnancy and lactation (131). Overtreatment with antithyroid drugs can result in hypothyroidism in the fetus. Therefore, free T4 should be kept close or slightly above the normal range with the lowest possible dose of antithyroid drugs.

Pathogenesis

The pathophysiology of hCG-induced gestational thyrotoxicosis has been reviewed by Hershman (132). hCG and TSH share the common glycoprotein ⋄ subunit and the ⋙ subunit is highly homologous. At high doses, hCG cross-reacts with the TSH receptor, and this stimulation can lead to an

increase in secretion of T4 and T3, with subsequent suppression of TSH secretion (124, 133). The levels of hCG and TSH are inversely correlated during the first trimester (121). Free T4 levels determined between weeks 6-20 of gestation increase and show a linear relationship with the rising hCG levels (134). The thyroid gland of normal pregnant women may be stimulated by hCG to secrete slightly excessive quantities of T4 and induce a slight suppression of TSH, but it only induces overt hyperthyroidism in a subset of pregnant women. The increased secretion of hCG result only in the physiological decrease in TSH levels that are characteristic for the first trimester of pregnancy, or in overt hyperthyroidism. Of note, elevations of hCG are particularly pronounced in twin pregnancies (135). In a study characterizing the activity of hCG on the human thyroid gland, 1.0 U hCG was found to be roughly equivalent to 0.27 mU of TSH (136). LH also has intrinsic thyroid stimulating activity, but it is lower compared to hCG. TSH-binding and TSH-induced adenylyl cyclase stimulation are more effectively inhibited by desialylated variants of hCG than unmodified hCG (137). Nicked hCG preparations, obtained from patients with trophoblastic disease or by enzymatic digestion of intact hCG, showed approximately 1.5- to 2-fold stimulation of recombinant hTSH receptor compared with intact hCG (122). Deglycosylation and/or desialylation of hCG enhance its thyrotropic potency. Basic hCG isoforms with lower sialic acid content extracted from hydatiform moles were more potent in activating the TSH receptor. From these and other studies it seems that the biological effect of hCG is predominantly confined to hCG containing little or no sialic acid. hCG has also been found to increase iodide uptake in cultured FRTL-5 cells and it also causes a dose related increase of adenylyl cyclase activity and thymidine uptake (138, 139).

FAMILIAL HYPERSENSITIVITY TO HCG

An unusual form of familial gestational hyperthyroidism caused by a mutant TSH receptor displaying hypersensitivity to normal levels of hCG has been identified by Rodien et al. (140). The index patient had a history of two miscarriages that were accompanied by hyperemesis. Subsequently, she had two pregnancies that were complicated by hyperthyroidism, severe nausea and vomiting. She did not have any antibodies against the TSH receptor or TPO. Her hCG levels, determined during the second pregnancy, were in the normal range for the first trimester. The patientï¿½ s mother had a history of one miscarriage and two pregnancies that were complicated by hyperemesis gravidarum. Sequence analysis of the *TSH receptor* gene in the proband and her mother revealed the presence of a monoallelic point mutation resulting in the substitution of K183R. Functional studies in COS-7 cells transfected with the mutated receptor documented no differences in membrane expression, and similar levels of basal and TSH stimulated cAMP accumulation. In contrast to the wild-type TSH receptor, which reacts only minimally to high doses of hCG, the K183R mutant is hypersensitive to hCG, although it still is 1000 times less responsive to hCG than the LH/CG receptor. The K183R TSH receptor mutation is unique because sensitivity is increased for hCG but remains unaltered for the cognate ligand TSH (140). This observation also supports the possibility of an hCG-independent connection between hyperthyroidism and hyperemesis gravidarum.

TROPHOBLAST TUMORS: HYDATIFORM MOLES AND CHORIOCARCINOMA

Definition and Epidemiology

Gestational trophoblastic diseases comprise hydatiform moles, invasive moles, choriocarcinomas and placental site trophoblastic tumors (141). Hydatiform moles and choriocarcinomas that secrete high amounts of hCG can cause hyperthyroidism (142). In 1955 Tisnï¿½ et al. described a patient with molar pregnancy that had increased thyroidal uptake of radioactive iodine and clinical signs of hyperthyroidism (143). Earlier reports also described molar pregnancies in combination with hyperthyroidism and in all cases a rapid return to normal thyroid function occurred after removal of the mole (143). In men, choriocarcinomas can arise in the testis and cause hyperthyroidism by secreting hCG (144). In a study of 20 patients with gestational trophoblastic neoplasias, 2 patients were overtly thyrotoxic and this was confirmed by elevated serum T4 levels (145). These 2 patients had extremely high serum (3,220,000 IU/l and 6,720,000 IU/l) and urine hCG levels, which correlated closely with TSH-like activity exerted by the serum of these patients in a mouse thyroid bioassay. Patients with moderately increased serum hCG levels (110,000-310,000 IU/l) associated with trophoblastic neoplasia were euthyroid. A similar correlation between serum hCG levels and thyroid stimulating activity in both serum and urine was found in women who had widely metastatic choriocarcinoma and marked hyperthyroidism (145). In another patient with gestational choriocarcinoma serum thyroid stimulating activity correlated precisely with serum T4, with the ⧳ subunit of hCG, and with the quantification of the tumor burden (146). Hyperthyroidism associated with choriocarcinoma in the male is extremely rare, but has been reported repeatedly (122). Orgiazzi et al. compiled four cases from the literature and reported a patient who had choriocarcinoma of the colon associated with gynecomastia and hyperthyroidism (147). Thyroid stimulating activity, measured by a mouse bioassay, was detected in the serum. Serum thyroid stimulating activity was partly inactivated by antibovine-TSH antiserum, but was completely neutralized by anti-hCG antiserum.

Clinical presentation

Most women with hydatiform moles present with uterine bleeding in the first half of pregnancy. The size of the uterus is large for the duration of gestation (141). Many women with molar pregnancies have nausea and vomiting, some have pregnancy-induced hypertension or (pre)-eclampsia. The signs and symptoms of thyrotoxicosis are present in some women, but they may be obscured by toxemic signs. The characteristic features belonging to Graves' disease are missing. The thyrotoxicosis is usually not severe because of a relatively short duration. Women with choriocarcinomas present within one year after conception. The tumor may be confined to the uterus, more frequently it is metastatic to multiple organs such as the liver and lungs, among others. In men, choriocarcinomas of the testes is often widely metastatic at initial presentation. Gynecomastia is a common finding.

Diagnosis

Measurement of serum hCG concentrations is needed for the diagnosis of moles and choriocarcinomas, and hCG serves as a sensitive and specific tumor marker during therapy and surveillance (145). In women, hCG concentrations are significantly higher than those found during normal pregnancies. Ultrasonography of the uterus shows a characteristic ï¿½snowstormï¿½ pattern. The

diagnosis of thyrotoxicosis relies on the measurement of TSH, (free) T4 and T3. elevated thyroid hormone levels. Thyroidal radioiodine uptake is elevated.
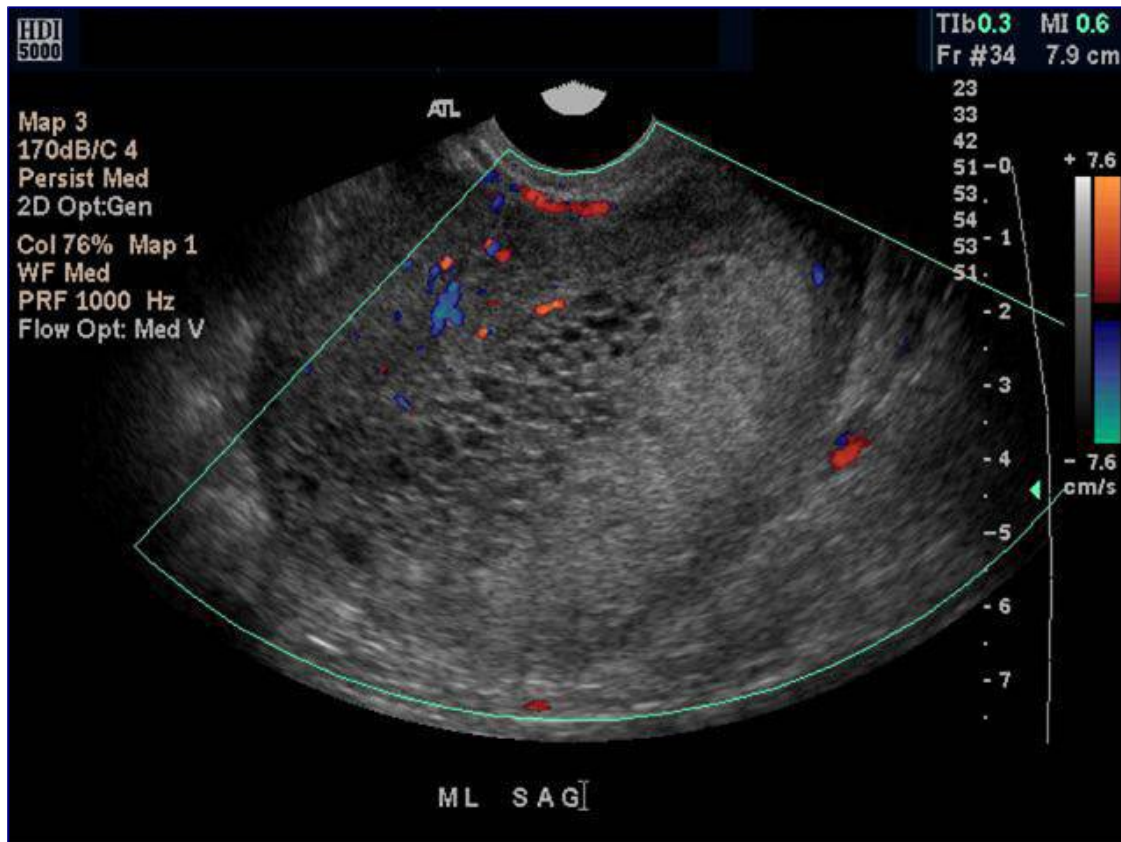

Figure 13-2. Ultrasound of the uterus of a patient with hydatiform mole demonstrating the characteristic ï¿½snowstormï¿½ pattern. Picture courtesy of Leeber S. Cohen, MD, Department of Gynecology, Feinberg School of Medicine, Northwestern University.

Treatment

Hydatiform moles are treated by suction rather than curettage (148). Serum T4, T3, TSH, and hCG levels normalize rapidly after removal of the mole. Choriocarcinomas can be divided into two groups: 1) a low risk group treated by monotherapy, most often with methotrexate or actinomycine D and a success rate close to 100%, and 2) a high risk group treated with polychemotherapy (etoposide, methotrexate, actinomycine D, cyclophosphamide, vincristine) with a response of about 86%. In patients that are not responding to chemotherapy, the 5-year survival rate is about 43%. Longitudinal measurement of hCG as specific and sensitive tumor marker is key for long-term surveillance (148). Placental-site trophoblastic tumors, a rare form of gestational trophoblastic disease that does not secrete hCG, requires stage-adapted management with surgery, or surgery in combination with chemotherapy (149).

STRUMA OVARII

Definition and Epidemiology

Struma ovarii is a rare tumor consisting primarily of thyroid components occurring in a teratoma or dermoid in the ovary (150). It forms less than 1% of all ovarian tumors and 2 to 4 % of all ovarian teratomas; 5 to 10% are bilateral, and 5 to 10% are malignant (151, 152). Thyrotoxicosis occurs in about 8% of affected patients (153).

Clinical presentation

The clinical presentation may include the finding of an abdominal mass, ascites, pelvic pain, and, rarely, a pseudo-Meigs syndrome with pleural effusions (154). A subset of women present with subclinical or overt thyrotoxicosis. Goiter is only presented in patients with associated thyroid disease. For example, coexistence of Graves' disease and struma ovarii has been reported (155).

Diagnosis

In patients with thyrotoxicosis, TSH is suppressed and T3 and T4 levels are elevated. Thyroglobulin is secreted by benign and malignant ovarian strumae. Radioiodine uptake will reveal uptake in the pelvis, while the uptake in the thyroid is diminished or absent (156). Cross-sectional imaging with computed tomography or magnetic resonance imaging will demonstrate of uni- or bilateral ovarian masses (156). CA125 may be elevated (154). Malignant thyroid tissue shows the characteristic patterns of papillary or follicular thyroid cancer and can be positive for mutations in BRAF (157). Metastasis is uncommon but has been reported repeatedly (158).

Treatment

Unilateral or bilateral open or laparoscopic oophorectomy is the primary therapy (159). Thyrotoxic women should be treated with antithyroid drugs and, if needed, with beta-blockers prior to surgery. In the case of malignant lesions, the patient should undergo thyroidectomy followed by treatment with 131iodine (157). The subsequent surveillance for residual or recurrent thyroid cancer does not differ from primary thyroid carcinomas.

IODINE-INDUCED HYPERTHYROIDISM

I. IODINE-INDUCED THYTOXOICOSIS

Definition and Epidemiology

An excess of iodine through dietary intake, drugs or other iodine-containing compounds can lead to thyrotoxicosis through increased thyroid hormone synthesis in the presence of underlying thyroid disease, particularly multinodular goiters that contain zones of autonomy (160, 161). Iodine-induced thyrotoxicosis (IIT) has been recognized as early as 1821 by Coindet, who reported that goitrous

individuals treated with iodine developed hyperthyroidism (162). The condition is now commonly called Jod-Basedow (Jod = iodine in German; Karl von Basedow = German physician describing the signs of thyrotoxicosis associated with exophthalmos and goiter, i.e. Graves' disease) (163). IIT may occur in patients from endemic goiter areas, patients with multinodular goiters in non-endemic areas, individuals with Graves' disease, and in individuals without previously apparent thyroid disease (164). The sources of iodide leading to IIT are manifold (Table 13-2). IIT has been reported after initiating iodine supplementation, but also with the use of iodinated drugs, contrast agents, and food components (165, 166). Use of non-ionic contrast agents does not prevent the development of IIT (167).

Table 13-2 Iodine-containing compounds potentially associated with IIT

Radiological contrast agents

Diatrizoate

Ipanoic acid

Ipodate

Iothalamate

Metrizamide

Diatrozide

Topical iodine preparations

Diiodohydroxyquinolone

Iodine tincture

Povidone iodine

Iodochlorohydroxyquinolone

Iodoform gauze

Solutions

Saturated potassium iodide (SSKI)

Lugol solution

Iodinated glycerol

Echothiopate iodide

Hydriodic acid syrup

Calcium iodide

Drugs

Amiodarone

Expectorants

Vitamins containing iodine

Iodochlorohydroxyquinolone

Diiodohydroxyquinolone

Potassium iodide

Benziodarone

Isopropamide iodide

Food components

Kelp, Kombu and other algae

Food colors: Erythrosine

Iodine containing food: Hamburger thyroiditis

For adults, the Dietary Reference Intake for iodine is 150 ï¿½g (168). The Tolerable Upper Intake Level for adults has been set to 1,100 ï¿½g/day and was assessed by analyzing the effect of supplementation on TSH (169). The thyroid gland needs no more than 70 ï¿½g/day to synthesize the required daily amounts of T4 and T3 (170). The higher recommended daily allowance (RDA) levels of iodine are recommended for optimal function of a number of organs such as the lactating breast, gastric mucosa, salivary glands, oral mucosa, thymus, epidermis, and the choroid plexus. The normal thyroid protects itself from acute excessive amounts of iodide by the Wolf-Chaikoff effect, which consists of an immediate reduction in iodide uptake, iodide organification, thyroid hormone biosynthesis and secretion (171). Remarkably, most individuals with a normal thyroid gland also tolerate a chronic excess of 30 mg up to 2 g iodide per day without clinical symptoms (161). Thyroid function tests remain within the reference range although T4 and T3 drop, and TSH rises (161). However, in some individuals, even exposure to modest amounts of excessive iodine can induce IIT or hypothyroidism. Fears that iodine supplementation would lead to IIT led to opposition against iodination programs in Switzerland, but initiation of salt supplementation with very low doses of iodine (3.75 parts per million) were shown to be safe (172). This contrasts with the observations from other iodination programs using higher amounts of iodide. For example, a steep rise of IIT has also been documented in 1966 in Tasmania (Australia), an area of iodine deficiency with a high prevalence of goiter (173). This was associated with the addition of potassium iodide to bread in early 1966. The increased incidence occurred predominantly in subjects older than 40 years, in whom a rise in incidence from 50 to a maximum of 130 cases per 100,000 was seen between 1967 and 1968. By 1974, the incidence decreased to the pre-epidemic level. Most thyrotoxic patients had nodular goiters and few patients had underlying Graves' disease. Later it was recognized that there was already a pre-epidemic increase in the incidence of thyrotoxicosis caused by the use of iodofor disinfectants on dairy farms (174, 175). Recent supplementation programs using inadequately high amounts of iodide in endemic goiter regions in Zimbabwe and eastern Zaire also resulted in a significant number of cases of severe and long-lasting IIT (176, 177). Three years after starting supplementation with iodized salt in China, the prevalence of overt hyperthyroidism in three cohorts was 1.6%, 2.0% and 1.2%, irrespective of the nutritional iodide intake, which varied between mildly deficient, adequate or excessive ((178, 179). The incidence of IIT during the first three years of supplementation was not determined. In these three communities, the cumulative 5-year incidences of overt hyperthyroidism for the 4th to 8th year of supplementation were 0.4%, 1.2% and 1.0%. At first glance, this seems to indicate a very low risk of IIT. However, the calculated 1-year incidence rates are 80, 240 and 200 per 100,000 individuals per year, figures that are much higher than the incidence rates published in other countries (180).

In some patients, iodine excess causes overt clinical hypothyroidism. Patients with a history of Graves' disease treated with radioiodine or partial thyroidectomy, partial thyroidectomy for thyroid nodules, or autoimmune thyroiditis appear to be particularly predisposed to iodine-induced hypothyroidism (181-184). Even relatively small excessive doses of 750 ï¿½g may be sufficient to induce hypothyroidism (185).

Clinical presentation

The clinical presentation includes the typical signs of thyrotoxicosis and in most patients the finding of a multinodular goiter. Other patients may have underlying autoimmune thyroid disease. A pre-existing thyroid disorder is been present in at least 20% of patients.

Diagnosis

The diagnostic considerations are the same as for toxic nodular goiters.

Treatment

Spontaneous reversal to an euthyroid state may occur after a mean period of 6 months in about 50% of patients. Return to euthyroidism may be preceded by subclinical hypothyroidism (186). In patients with multinodular goiters, the therapeutic considerations are the same as discussed for toxic nodular goiters.

Pathogenesis

In a classical study, four euthyroid patients with a single autonomous nodule from the slightly iodine-deficient Brussels region received a supplement of 500 μg iodide per day (187). This caused a slow but constant increase of thyroid hormone. After four weeks, the patients became hyperthyroid . Later studies confirmed the original interpretation that the nodules were not producing excessive amounts of thyroid hormones because of the low iodine intake, but that they became toxic once presented with high amounts of iodine (188). The autonomy of function was secondary to gain-of-function mutations in the TSH receptor (54). Individuals with multinodular goiters living in iodine-replete regions can also develop hyperthyroidism, albeit at much higher doses of iodine (up to 180 mg) (189). Taken together, these observations confirm that individuals with (multi)nodular goiters are particularly prone to developing IIT (161). In regions with iodine deficiency, nodular goiters disappear slowly after the introduction of iodine supplementation and the incidence of hyperthyroidism then gradually decreases over the years (190, 191). More recent data suggest that autonomous nodules are not the only explanation for the pathogenesis of IIT. Several human and animal studies suggest that chronic excessive iodine intake may modulate thyroid autoimmunity and lead to thyrotoxicosis in genetically susceptible individuals. Mice prone to developing autoimmune disease that are first fed an iodine-deficient diet and then switched to iodine excess develop dose-dependent ultra-structural changes in thyrocytes that are consistent with autoimmune disease (192). A necrotic effect of excessive amounts of iodide has been demonstrated *in vivo* in various animal species and also in human thyroid follicles *in vitro* (193). Epidemiologic studies performed in China, Turkey and Denmark suggest that supplementation with iodized salt increases the prevalence of autoimmune thyroid disease, resulting in clinical or subclinical hypothyroidism (178), autoimmune hyperthyroidism (194), or both (195). In a population-based, cross-sectional study with 1085 participants exposed to excessive amounts of iodide (40-100 mg/kg salt) from Brazil, the prevalence of chronic autoimmune thyroiditis was 16.9%, women were more commonly affected (21.5 versus 9.1%), 8% were hypothyroid, and 3.3% were hyperthyroid (196). The authors concluded that the excessive iodine may have increased the prevalence of autoimmune thyroid disease and hypothyroidism in this population (196). In Denmark, a moderately iodine-deficient country, introduction of iodized salt at a dose that was calculated to increase iodine intake by only 50 ï¿½g per day, an increased incidence of hyperthyroidism was found mainly in younger patients between the age of 20 and 39 years and was presumably induced by autoimmune thyroid disease (194). In contrast, a study on children in Morocco did not find an effect of iodine supplementation on thyroid autoimmunity (197). It is noteworthy that IIT was also observed in individuals who probably had normal thyroid glands (164, 186, 198). It is well recognized that contrast agents may cause IIT. They contain between 30-50% of iodine and several grams are used freqeuently for radiological studies. Individuals with multinodular goiters or subjects who live in countries where iodine intake is low are at particular risk for developing IIT secondary to exposure to contrast agents (160). Clinicians should be aware that IIT often develops several weeks after their administration.

Follow-up of such patients after radiological procedures is therefore advisable and in some cases prophylactic therapy with methimazole prior to the administration of contrast agents may be indicated. Considering the wide use of contrast agents, the probability of inducing IIT by these substances appears to be relatively low. However, the incidence of IIT appears to be inversely related to the nutritional iodine intake.

II. AMIODARONE INDUCED THYROID DISEASE

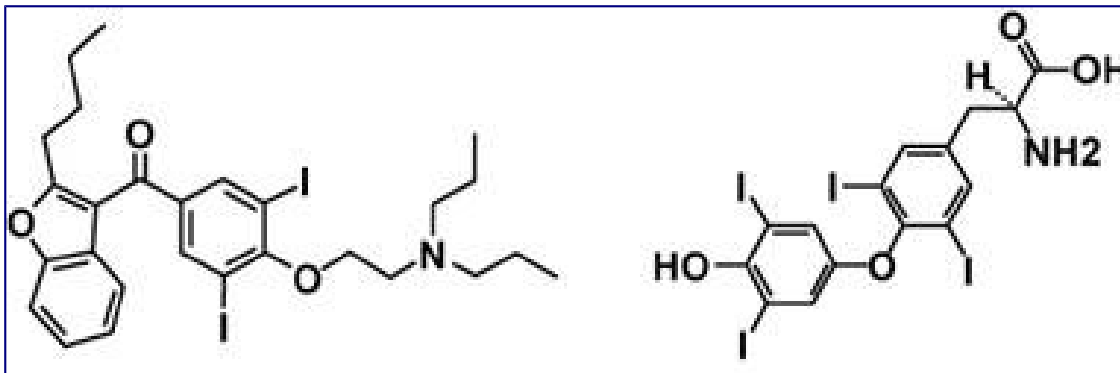## Definition and Epidemiology

Figure 13-2. Structure of amiodarone (left) and thyroxine (right).

Amiodarone is a widely used anti-arrhythmic agent used for the therapy of ventricular and supraventricular arrhythmias, among them atrial fibrillation. It has a very high iodine content of 37.3% by weight. About 3 mg of iodine are released into the circulation per 100 mg of amiodarone ingested. For comparison, the RDA for iodide is 150 ï¿½g per day. Its molecular structure has some similarities with iodothyronines and it may interfere with thyroid hormone transport into cells and with intracellular thyroid hormone metabolism and action (Figure 13-2) (199, 200). Amiodarone interferes with 5′-monodeiodination of thyroid hormones leading to a decrease of both intra- and extracellular T3 concentrations.

Amiodarone-induced hyper- and hypothyroidism play an important role in clinical practice (200, 201). Amiodarone-induced thyrotoxicosis (AIT) is more common in iodine-deficient regions, but also occurs in patients with a normal nutritional iodine intake. Amiodarone-induced hypothyroidism is usually seen in iodine-sufficient areas.

Reported incidences of AIT vary between 0.003% and 11.5%. In a study involving 1448 patients treated with amiodarone, 30 developed AIT (164). AIT is differentiated into two forms. AIT Type I is caused by increased hormone synthesis because of exposure to high amounts of iodine, AIT Type II results from cytotoxic destruction of thyrocytes (200). Hypothyroidism occurs predominantly in patients with preexisting thyroid autoimmune disease and in areas of normal iodine intake (199, 202). AIT is more common in men than in women (203).

Clinical presentation

The signs of thyrotoxicosis are not apparent in all patients with AIT. They may be obscured by the underlying cardiac condition. Some patients have a nodular goiter.

Diagnosis

The total or free T4 levels are elevated in euthyroid, hypothyroid and hyperthyroid patients treated with amiodarone because of its inhibition of 5′-monodeiodination. In hyperthyroid patients, TSH is suppressed and T3 is elevated. The distinction between AIT Type I and II can be difficult on clinical grounds. The radioiodine uptake is typically low to normal in AIT Type I, and low to suppressed in AIT Type II. Serum interleukin 6 levels are normal to high in AIT Type I and markedly elevated in AIT Type II, but there is significant overlap and the test is of insufficient sensitivity. On Doppler ultrasound, AIT Type I is associated with normal to increased vascularity with patchy distribution, while Type II shows absent vascularity (204, 205).

Treatment

The therapy of AIT is a challenge. An algorithm for the management of patients with AIT is shown in Figure 13-3 (200). If possible, amiodarone should be discontinued. Patients with type 1 AIT are preferably treated with methimazole (initially 40ï¿½60 mg/day, followed by gradual adjustment of the dose), but the response to thionamides is modest. In selected patients, treatment with potassium perchlorate (1 g/day for 4 to 6 weeks) can be considered. Potassium perchlorate is a drug that can cause aplastic anemia and its use should be limited to patients who cannot be controlled by methimazole, or who are allergic to thionamides. For patients with AIT Type II, prednisone (0.5 ï¿½ 0.7 mg /kg body weight per day) can be used for several months. Because the distinction between AIT Type I and II is difficult and not always clear, and because some patients have mixed forms of AIT, these therapies are occasionally combined. Patients with a history of AIT type II are at risk for developing hypothyroidism if exposed to high amounts of iodide.
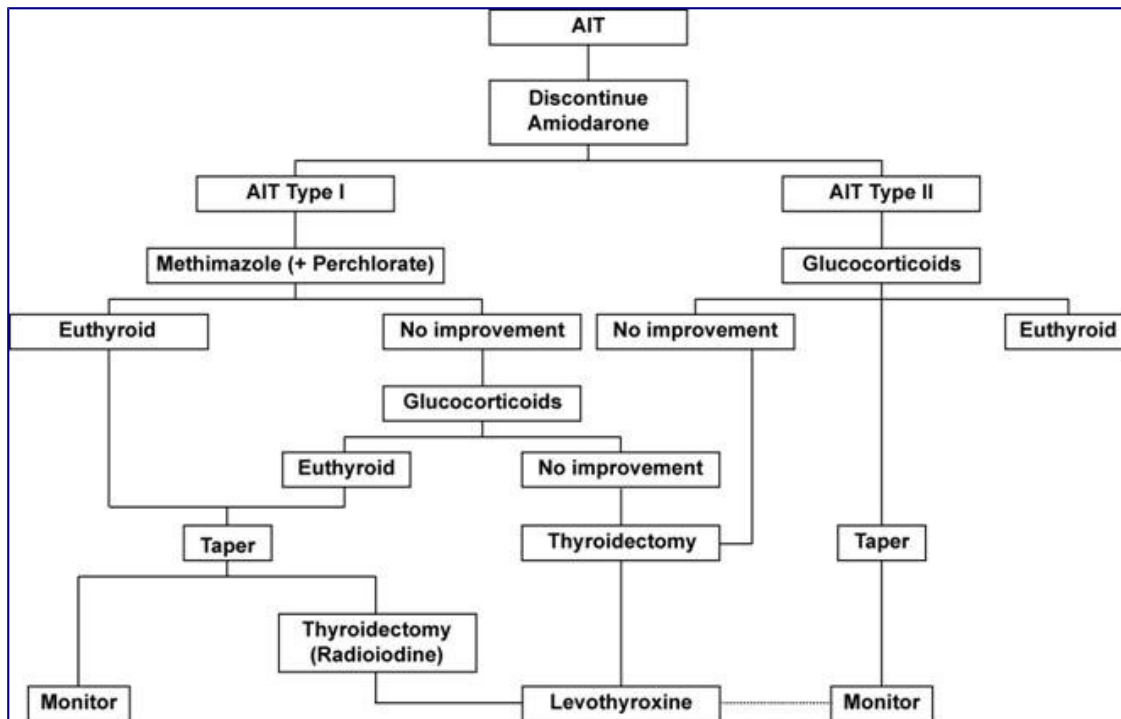
Figure 13-3. Algorithm for the management of patients with AIT. Modified after Bogazzi F et al. J Clin Endocrinol Metab 95:2529-2535, 2010 ((200).

Pathogenesis

Two distinct mechanisms result in AIT. AIT Type I results from the iodine-induced increase in thyroid hormone synthesis. Patients developing AIT Type I usually have a preexisting nodular goiter. AIT Type II is caused by cytotoxic effects of the medication that results in the release of preformed thyroid hormones.

Pathology

On electron microscopy imaging, AIT Type II shows characteristic multilamellar lysosomal inclusions and intramitochondrial glycogen inclusions, and a morphological picture of thyrocyte hyperfunction (206). No inflammatory changes are present.

THYROIDITIS

Any form of thyroiditis can be associated with a thyrotoxic phase because the disruption of thyroid follicles can result in an increased release of stored iodothyronines. The thyrotoxic phase may be followed by transient or permanent hypothyroidism.

I. ACUTE OR SUBACUTE (DE QUERVAIN'S) THYROIDITIS

Definition

This disorder, which is discussed in Chapter 19, leads to temporary thyrotoxicosis in approximately half of the patients due to discharge of stored hormone from the thyroid gland.

Clinical presentation

Patients with subacute thyroiditis often present with a history of a preceding respiratory tract infection (207). They may have fever, malaise, and soreness, and the gland is exquisitely tender on palpation and often displays a substantially increased consistency.

Diagnosis

The laboratory findings will fluctuate with the course of the disease and typically present with initial thyrotoxicosis, followed by a hypothyroid phase. The thyroid function may normalize or result in permanent underfunction. The erythrocyte sedimentation rate is markedly elevated. Thyroid antibodies are usually not detectable. The radioiodine uptake is extremely low or absent. Thyroglobulin levels are elevated because of the destruction of thyroid follicles.

Treatment

Symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAID) or aspirin is often sufficient. A subset of patients needs therapy with prednisone for variable amounts of time. Addition of a beta-blocker should be considered based on the severity of the thyrotoxic signs. Therapy with levothyroxine may be necessary during the hypothyroid phase of the illness. While the majority of patients recover completely, about 10% of cases develop permanent hypothyroidism.

Pathogenesis

The pathogenesis is thought to involve a viral infection.

Pathology

Cytology and histology show characteristic giant cells.

II. SILENT OR PAINLESS THYROIDITIS

Definition and Epidemiology

Silent thyroiditis is characterized by lymphocytic infiltration and can lead to thyrotoxicosis and hypothyroidism (208). Although the terms silent thyroiditis and painless thyroiditis are used most

commonly, many other names have been used for this disorder including sporadic thyroiditis (208), destructive thyroiditis (209), hyperthyroiditis (210), spontaneously resolving lymphocytic thyroiditis (211), transient painless thyroiditis (212), painless thyroiditis with transient hyperthyroidism (213), painless subacute thyroiditis (214), occult subacute thyroiditis (215), atypical thyroiditis (216) and transient thyrotoxicosis with lymphocytic thyroiditis (217). Silent thyroiditis has been diagnosed frequently in the 1970s, but its incidence seems to be lower now. A retrospective survey conducted in Wisconsin from 1963 through 1977 showed that silent thyroiditis was not found until 1969 and was uncommon up to 1973 (212). The frequency then increased and silent thyroiditis was thought to be responsible for about 20% of all cases of thyrotoxicosis in this geographical area (211). This high incidence has not been reported in other regions of the United States, Asia and Europe. In a study from Japan, an incidence of 10% was found in the 1980s, but in New York it was only 2.4% (218). Schneeberg reported data obtained from a random poll; the obtained data suggest that silent thyroiditis was uncommon in Argentina, Europe and the East- and the West coast of the United States, but occurred more frequently around the Great Lakes and in Canada (219). The variable incidence rates may be due to an ascertainment bias or to the development of thyrotoxicosis secondary to the ingestion of meat contaminated with bovine thyroid tissue. Two epidemics of thyrotoxicosis thought to reflect silent thyroiditis were found to be explained by meat contamination (220, 221). Affected patients are mostly between 30 and 60 years of age and the female to male ratio is about 1.5: 1 (211). The condition is currently rarely recognized.

Clinical presentation

Patients present with abrupt onset of thyrotoxicosis that can be associated with the development of a goiter or enlargement of a preexisting goiter. Repeated episodes may occur in the same individual (211). In a review on 112 patients, 68 were female and the age at onset was 32.4 ï¿½ 18.5 in females and 24.9 ï¿½ 8.2 years in males (213). None of the patients presented with thyroid pain. The duration of the thyrotoxic phase was variable, but for the most part, it lasted less than one year. The mean duration was 3.6 months (range 1-12.5). Symptoms began 2.5 ï¿½ 2.2 months preceding the initial evaluation. This period is shorter than is usually seen with Graves' disease and much shorter than in patients with toxic multinodular goiter. Exophthalmos and pretibial myxedema were absent. The thyroid gland is typically firm in consistency. Forty three percent of patients had an enlarged thyroid, which was generally symmetrical and enlargement was in most instances mild. The clinical course of the disease consists usually of an initial hyperthyroid phase, followed by a hypothyroid phase, and subsequent restoration of a euthyroid metabolic state (Figure 13-4). 57 out of 112 patients became euthyroid and did not develop clinical hypothyroidism. After a brief period of euthyroidism, transient biochemical hypothyroidism developed in 17 patients. In 32 patients clinical hypothyroidism was present (213).
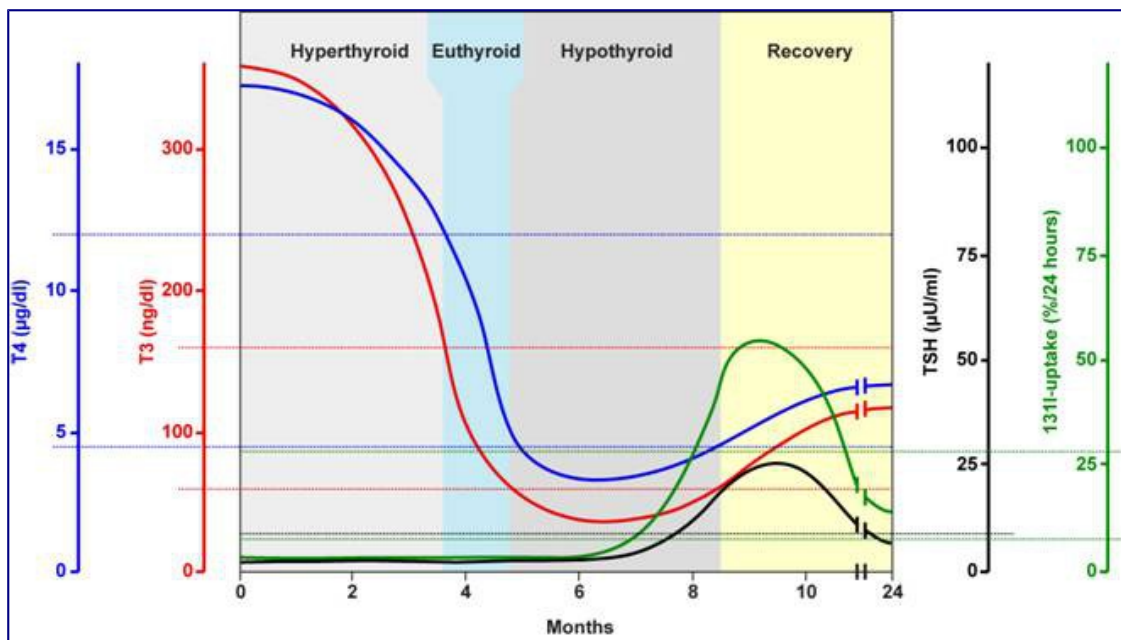
Figure 13-4. Schematic representation of the phases of silent thyroiditis. Modified after Woolf PD, Endocr Rev 1:411-420, 1980 (213).

Development of Graves' disease, after painless thyroiditis has been documented and TSH receptor antibodies have been found in these patients (222).

Diagnosis

During the first phase of the disease, discharge of hormone from the inflamed thyroid results in increases in serum T4, T3 and a decrease in serum TSH. During this phase, there is no uptake of radioactive iodine in the thyroid. If thyrotoxicosis factitia is considered in the differential diagnosis, measurement of serum thyroglobulin levels is useful. During ingestion of levothyroxine, little or no thyroglobulin is present whereas serum thyroglobulin levels are elevated in silent thyroiditis. In 17 out of 71 patients with silent thyroiditis, moderate elevations of antithyroglobulin antibodies were present (213). Antimicrosomal antibodies were examined in 53 patients using the complement fixation test or by microsomal fluorescence. Using the former technique, 22 patients had positive antibodies, and by the latter 4 out of 7 were positive (213). In a small series of 7 patients with silent thyroiditis evaluated with a more sensitive radioimmuno assay (RIA) for human antithyroglobulin antibodies, all were positive (209). The white blood cell count is generally normal. In 53 episodes, 34 had elevated erythrocyte sedimentation rate (ESR), but it was greater than 40 mm/hr in only 8 (213). This contrasts with the typical marked elevation of the ESR in patients with subacute thyroiditis and helps to differentiate the two conditions. T4 and T3 reach subnormal levels in the hypothyroid range in 40% of patients (213). After the hypothyroid phase, patients gradually enter the euthyroid phase, heralded by an increase in thyroid hormone levels and resumption of thyroidal radioactive iodine uptake. The hypothyroid phase may last several months. In 26 episodes, patients became euthyroid after a mean period of 62 months after the onset of the hyperthyroid symptoms. TSH levels may increase during the recovery phase, and can remain elevated for many months. The delayed increase of TSH is due to its suppression during the thyrotoxic phase. Permanent hypothyroidism occurs in about 7% of patients with silent thyroiditis, but a subset of patients may ultimately become permanently hypothyroid. The echogenicity is decreased and a correlation between the decrease in the echo signal at the onset and nadir of the T3 level has been suggested (223) (Figure 13-5).
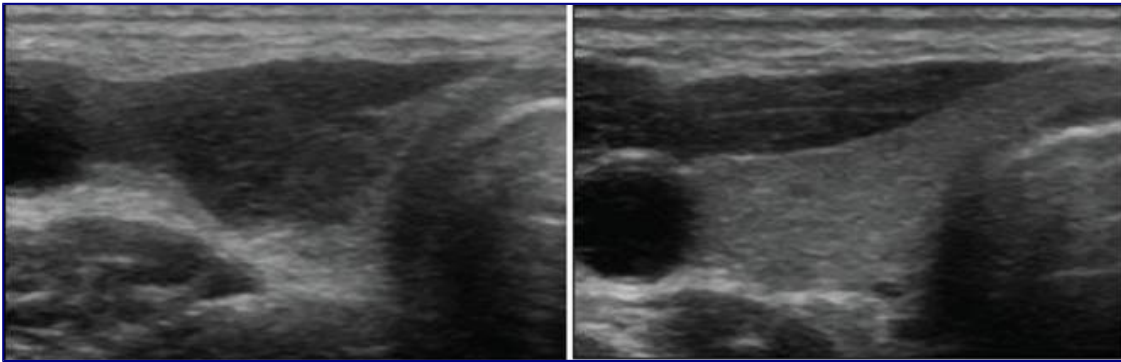
Figure 13-5. Ultrasound of a the right lobe of a patient with silent thyroiditis (left panel). The echogenicity is decreased. The right lobe of a patient with a normal thyroid is shown for comparison in the right panel.

Treatment

As thyrotoxicosis is usually mild in silent thyroiditis, there is often no need for any treatment. In some patients, therapy with a beta-blocker can be considered during the thyrotoxic phase. In patients with more severe thyrotoxicosis, administration of NSAIDs and prednisone may be of benefit (224). After the thyrotoxic phase, many patients become temporarily hypothyroid and therapy with levothyroxine should be initiated in symptomatic patients. After a few months, levothyroxine therapy should be gradually withdrawn in order to assess whether the hypothyroidism is transient or permanent. Only a small proportion of patients remain permanently hypothyroid. Some patients, who initially recovered, may ultimately develop permanent thyroid failure (225). In a series of 54 patients, Nikolai et al. reported that about half of the patients developed permanent hypothyroidism (225). This is in contrast with subacute thyroiditis where permanent hypothyroidism is less common.

Pathogenesis

Although the disease was earlier considered to be a mild form of subacute (De Quervain's) thyroiditis, there is now convincing evidence that it is a lymphocytic thyroiditis (208, 209, 212-217, 222, 226). Many patients with silent thyroiditis have a personal or a family history of other autoimmune diseases, thereby indirectly supporting the concept that it is an autoimmune thyroiditis (227). There is no significant association with viral infections (211). There is a significant association with HLA genotype DR3. Postpartum thyroiditis (see below) is considered to be a form of silent thyroiditis occurring after delivery (228).

Pathology

On histological examination, follicles are disrupted and infiltrated by lymphocytes and plasma cells (211, 229). The infiltration is diffuse and/or focal, sometimes with the formation of lymphoid follicles. The follicular cells are heterogeneous in appearance. They can be cuboidal or columnar when stimulated by TSH. Some of the hypertrophic follicular cells have an oxyphilic cytoplasm (Hï¿½rthle or Ashkenazy cells). Thyroid tissue obtained during the hypothyroid or early recovery phase may show regenerating follicles with little colloid. In some patients, persistent mild

lymphocytic thyroiditis is seen. Fibrosis is usually minimal, but can be extensive in some cases. Occasionally multinucleated giant cells, which are characteristic of subacute thyroiditis, are observed. The histological picture of postpartum thyroiditis is identical.

III. POSTPARTUM THYROIDITIS

Postpartum thyroiditis is considered to be a subform of silent (painless) thyroiditis (213). This condition is discussed in Chapter 14.

IV. HASHIMOTO'S THYROIDITIS

Occasionally, Hashimoto's thyroiditis is accompanied by mild symptoms of thyrotoxicosis, particularly in the early phases of the disease (230). This condition is discussed in Chapter 8.

THYROTOXICOSIS FACTITIA

Definition

Factitious thyrotoxicosis is due to the voluntary or involuntary intake of supraphysiological amounts of exogenous thyroid hormone (231). Most commonly, it is iatrogenic, either intentionally in order to suppress TSH in thyroid cancer patients or unintentionally in patients treated for primary hypothyroidism. In both instances, subclinical thyrotoxicosis is more common. The risk of atrial fibrilliation is increased in patients with long-standing suppression of TSH (232). Several cardiac parameters can be affected (233), but the severity of these effects is somewhat controversial (234). Suppressive doses of thyroid hormones can also affect bone mineral density (235), but this has not been confirmed in all studies (236). Non-iatrogenic thyrotoxicosis factitia can occur in patients of all ages with psychiatric illnesses (231, 237). In addition, some patients may take excessive amounts of thyroid hormones, sometimes prescribed by physicians, for weight loss, treatment of depression, or infertility (207). These patients often deny the intake of thyroid hormones or an excessive intake. In these instances, a heightened suspicion is needed in order to readily diagnose the disorder. Thyrotoxicosis induced by excessive thyroid hormone intake due to consumption of meat containing bovine thyroid tissue has been reported repeatedly. For example, two events of this so called ï¿½hamburger thyrotoxicosisï¿½ have been documented in the United States (220, 221). Inclusion of the thyroid in neck muscle trimmings is now prohibited by US Department of Agriculture regulations. Accidental dosing with veterinary levothyroxine preparations has also been reported as a cause of thyrotoxicosis factitia (238).

Clinical presentation

Patients are clinically thyrotoxic, however they do not show signs of endocrine ophthalmopathy. In patients with a history of thyroid cancer, the history and the finding of a necklace scar readily provide an explanation. The thyroid may be small because of long-standing suppression of TSH.

Diagnosis

Serum TSH is suppressed, (free) T4 and T3 levels are variably elevated. The T4 and T3 levels depend on the type of ingested thyroid hormone preparation. Both T4 and T3 are high with excessive intake of levothyroxine, while only T3 is elevated with the intake of T3 preparations. With combination therapies, the T4 and T3 increases are variable depending on the relative amounts. Poisoning with T3 may be particularly severe (239), but even very high doses are often well tolerated, especially by children (240). When the diagnosis of thyrotoxicosis factitia is suspected, measurement of serum thyroglobulin levels is useful. During ingestion of levothyroxine, little or no thyroglobulin is present. In contrast, serum thyroglobulin levels are elevated in silent thyroiditis. Mariotti et al. performed thyroglobulin measurements in 6 women with thyrotoxicosis factitia (241). They used a sensitive thyroglobulin assay and excluded the presence of thyroglobulin antibodies that can potentially interfere with the assay. In all 6 women thyroglobulin was undetectable in the serum (241). However, thyroglobulin levels may not be reliable in patients who have anti-thyroglobulin antibodies. In these patients, measurement of fecal T4 can be used to distinguish endogenous and exogenous thyroid hormone excess (242). The thyroidal uptake of radioiodine or technetium are decreased. Doppler sonography shows absent thyroidal vascularity and low-normal peak systolic velocity (243). In contrast, these signs are increased in Graves' disease (243). Thus, factitious thyrotoxicosis is not difficult to differentiate from thyrotoxic Graves' disease, toxic adenoma or toxic multinodular goiter, or subacute thyroiditis. However, it may be difficult to readily distinguish silent thyroiditis from thyrotoxicosis factitia. In both situations, radioiodine uptake is very low or absent. In silent thyroiditis the serum thyroglobulin is, however, elevated. Suppressed radioactive uptake of the thyroid gland in combination with thyrotoxicosis may also exist in patients with hyperfunctioning metastases of well-differentiated thyroid carcinomas (76, 77). However, in these extremely rare patients, the thyroglobulin levels are elevated and radioactive iodine uptake will be detected in metastases by using whole body scanning.

Treatment

In most patients, adjustment or discontinuation of the thyroid hormone preparation is sufficient to normalize thyroid function tests. Patients with surreptitious intake of thyroid hormones for eating disorders or psychiatric illnesses can be difficult to treat and may need psychiatric consultation and assistance. In patients with severe intoxication, beta-blockers can be useful. Gastric lavage, induced emesis, activated charcoal, and, very rarely, plasmapheresis and exchange transfusion, can be considered in patients seen after acute ingestion of large amounts of thyroid hormone (231).

SUMMARY

Thyrotoxicosis can has a broad spectrum of etiologies (Table I). While it is most commonly caused by Graves' disease, it is of importance to recognize other etiologies in order to choose the most appropriate therapeutic option and long-term surveillance. Toxic adenomas are characterized by a single hyperactive nodule in the thyroid leading to clinical and biochemical thyrotoxicosis. Autonomous or toxic adenomas are most commonly caused by somatic gain-of-function mutations in the TSH receptor or the stimulatory Gs◊ subunit. A toxic adenoma is readily recognized on a thyroid scan. Toxic adenomas appear to be more common in countries with a low iodine intake. The possibility of developing thyrotoxicosis in a patient with a hot nodule with a diameter of 3 cm or larger is 20% in 6 years. This risk is substantially less in smaller nodules. Older patients with a hot nodule are more likely to become toxic as compared to younger patients. Definitive treatment consists in the

administration of 131iodine, surgical removal of the nodule, or, less commonly used, percutaneous ethanol injection. The likelihood of malignancy in a toxic nodule is very low. In multinodular goiters, several nodules display an autonomous function. The pathogenesis is complex but may also include activating TSH receptor mutations. In addition to hyperthyroidism, some patients present with compressive signs. The diagnostic and therapeutic approach is in general similar to patients with a toxic adenoma, but may need cross-sectional imaging and pulmonary function tests in some patients. Therapeutically, surgery and radioiodine therapy are the most commonly used modalities. Well-differentiated thyroid carcinomas are only rarely associated with thyrotoxicosis. Treatment of patients with functioning thyroid carcinomas does not differ from the therapy of thyroid cancer patients without thyrotoxicosis, but appropriate control of the hyperthyroid state with antithyroid drugs and beta-blockers is important before submitting a patient to thyroid surgery or 131iodine therapy. Familial and sporadic forms of non-autoimmune hyperthyroidism are uncommon. They are caused by inherited or *de novo* germline gain-of-function mutations in the TSH receptor. Inappropriate TSH secretion by a TSH-secreting pituitary tumor is a rare cause of hyperthyroidism. Transsphenoidal surgery, in combination with radiotherapy and somatostatin analogues in some patients, are the therapies of choice. During pregnancy, transient gestational thyrotoxicosis may be due to stimulation of the TSH receptor by high levels of hCG. In a single instance, a mutation in the TSH receptor conferring hypersensitivity to hCG has been reported. Hydatiform moles or a choriocarcinomas can lead to high hCG levels and thyrotoxicosis. Hydatiform moles are treated by suction. Choriocarcinomas can now be treated successfully in most patients with chemotherapy. Struma ovarii, thyroid tissue in a ovarian teratoma, rarely causes hyperthyroidism. Most patients with struma ovarii are clinically and biochemically euthyroid. Treatment consists of surgical removal of the teratoma. Administration of moderate or high doses of iodine may induce thyrotoxicosis in patients with or without apparent pre-existing thyroid disease. There are numerous sources of iodine, for example drugs, contrast agents, disinfectants, and food components. A notorious iodine-containing agent is the anti-arrhythmic drug amiodarone, which may induce thyrotoxicosis because of its high iodine content and/or a drug-induced thyroiditis. Any form of thyroiditis can be associated with a thyrotoxic phase because the disruption of thyroid follicles can result in an increased release of stored iodothyronines. The thyrotoxic phase may be followed by transient or permanent hypothyroidism. All forms of thyroiditis can be associated with a thyrotoxic phase because the disruption of thyroid follicles can result in an increased release of stored iodothyronines. The thyrotoxic phase may be followed by transient or permanent hypothyroidism. The uptake of radioiodine is very low or absent in the thyrotoxic phase and serum thyroglobulin levels are high. Clinical thyrotoxicosis is often mild and treatment with beta-blocking agents is often sufficient. Although the majority of patients recover, a substantial subset of patients develops hypothyroidism in later years. Therefore, regular assessment of thyroid function is necessary. Thyrotoxicosis factitia, the excessive intake of exogenous thyroid hormones, can be iatrogenic, or due to voluntary or involuntary intake of thyroid hormones. The uptake of radioiodine is low and thyroglobulin levels are also very low or undetectable. The thyroid may be small. The therapy consists in appropriate dose adjustment or discontinuation of exogenous thyroid hormone.

ACKNOWLEDGMENT

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