Treatment of toxic adenoma and toxic multinodular goiter

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INTRODUCTION — Toxic adenoma and toxic multinodular goiter are common causes of hyperthyroidism, second in prevalence only to Graves' disease. Twenty to 80 percent of toxic adenomas and some nodules of multinodular goiters have somatic mutations of the thyrotropin (TSH) receptor gene that confers autonomous hyperactivity [1,2].

Because treatment of hyperthyroidism differs according to the etiology, the correct diagnosis must be made before therapy is instituted. (See "Disorders that cause hyperthyroidism").

- A classic clinical presentation for toxic adenoma is a hyperthyroid patient with a palpable thyroid nodule that corresponds to an area of increased radioiodine concentration on thyroid scintigraphy; there should also be suppression of radioiodine uptake in surrounding and contralateral tissue.

- Toxic multinodular goiter, in comparison, typically presents with one or more focal areas of increased radioiodine uptake, which may or may not correspond to palpable nodules. Nonfunctioning ("cold") nodules are also present in some patients. Some patients have obstructive symptoms, providing an additional indication for treatment [3]. (See "Radioiodine therapy for nontoxic multinodular goiter").

There are two clinical situations in which establishing the diagnosis of a toxic adenoma or toxic multinodular goiter is more difficult. First, the autonomously functioning tissue may be sufficiently diffuse that it is difficult to differentiate a toxic multinodular goiter from Graves' disease by thyroid scintigraphy alone. When it is important to distinguish these disorders, a high serum concentration of TSH receptor antibodies indicates Graves' disease, but a low titer does not exclude the diagnosis. Second, in iodine-induced hyperthyroidism, the exogenous iodine load can dilute the radioiodine tracer and result in

both a low radioiodine uptake and a poor image on scintigraphy. Repeat scanning weeks or months later may be necessary.

THERAPEUTIC REGIMEN — Treatment of hyperthyroidism consists of both symptomatic relief and decreasing the production of thyroid hormone [4]. Beta blockers ameliorate many of the symptoms of hyperthyroidism [5]. In the absence of a contraindication, they are often started as soon as the diagnosis of hyperthyroidism is made, even before obtaining a 24-hour radioiodine uptake or scan. We usually give atenolol (25 to 50 mg/day), which has the advantages of single daily dosing and beta-1 selectivity, but all drugs of this class effectively reduce symptoms in patients with hyperthyroidism. (See "Beta blockers in the treatment of hyperthyroidism").

There are three major approaches for treating patients with a toxic adenoma or toxic multinodular goiter:

- Therapy with a thionamide
- Therapy with radioiodine or surgery

Thionamide administration — The thionamides, methimazole (MMI) and propylthiouracil (PTU), are first-line therapy for patients who have moderate or severe symptoms of hyperthyroidism, who are elderly, or who have underlying cardiovascular disease [6]. MMI is preferred, except during pregnancy, because of its longer duration of action (allowing for single daily dosing) and a lesser degree of toxicity. (See "Thionamides in the treatment of Graves' disease").

Unlike Graves' hyperthyroidism, toxic nodules and toxic multinodular goiter rarely resolve spontaneously with prolonged thionamide therapy. Toxic adenomas may undergo hemorrhage or infarction, leaving a patient euthyroid, but this is rare. As a result, the goal of thionamide therapy in these patients is to attain a euthyroid state before therapy with radioiodine or surgery. (See "Radioiodine in the treatment of hyperthyroidism" and see "Surgery in the treatment of hyperthyroidism").

Iodine-induced hyperthyroidism may be an exception, because it can resolve in several months if the source of the iodine is discontinued [7]. These patients can be treated with a thionamide alone. However, many clinicians still prefer radioiodine therapy or surgery, because the patients are at risk for recurrent hyperthyroidism if given iodine again.

Not all patients require antithyroid drug therapy prior to radioiodine treatment. Young, otherwise healthy individuals do not need pretreatment. In older patients or in those with heart disease, diabetes, or other co-morbidities, MMI, 10 mg once daily can be used. In comparison, those with larger goiters and more severe hyperthyroidism are usually started on 20 to 30 mg daily. When patients experience nausea on higher doses of MMI, taking the pills with food or in divided doses may be helpful.

Patients who refuse radioiodine or surgery should be treated with long-term thionamide administration. In them, the dose of MMI is tapered to a maintenance dose with the goal of maintaining a euthyroid state. Thyroid function should be assessed at four to six week intervals by measurement of serum free thyroxine (T4) and TSH until the patient is stabilized on maintenance thionamide therapy.

Administration of iodinated radiocontrast agents or iodine — Patients with very severe hyperthyroidism or hyperthyroidism in the setting of myocardial infarction, stroke, or other severe co-morbidity may benefit from treatment with radiocontrast agents ipodate and iopanoic acid (currently, neither is available in the United States). They not only provide inorganic iodine, but also are potent inhibitors of the peripheral conversion of T4 to triiodothyronine (T3) [8]. (See "Iodinated radiocontrast agents in the treatment of hyperthyroidism"). These agents or inorganic iodine should not be used as primary therapy in patients with a toxic adenoma or toxic multinodular goiter, because the iodine load can exacerbate the hyperthyroidism. However, they can be given safely and effectively after thionamide therapy has been started; thionamides prevent the thyroid from using iodine as substrate for new hormone synthesis within two hours after the initial dose. Thionamide therapy should therefore be started first and continued without interruption because administration of iodine alone can exacerbate hyperthyroidism in these patients.

Ipodate or iopanoic acid (500 to 1000 mg/day), when coadministered with MMI, rapidly ameliorate severe hyperthyroidism and can be used to prepare a hyperthyroid patient for early surgery. Iodine solutions are also effective and can be used with the same precautions as the radiocontrast agents. A typical dose is 10 drops of saturated solution of potassium iodide (SSKI) daily. (See "Iodine in the treatment of hyperthyroidism").

Radioiodine therapy — Radioiodine is widely used for therapy of patients with toxic adenomas or toxic multinodular goiters [9]. It is administered as an oral solution or capsule of sodium 131-I, which is rapidly concentrated in thyroid tissue. It induces extensive tissue damage, resulting in destruction of the adenoma or autonomous foci within six to 18 weeks. Unlike Graves' disease, in which the goal of radioiodine therapy is destruction of the gland with eventual hypothyroidism, most patients with toxic adenomas and toxic multinodular goiters are euthyroid after radioiodine therapy because the radioiodine preferentially accumulates in the hyperfunctioning nodules.

As noted above, radioiodine can be given as primary therapy to patients with mild, well-tolerated hyperthyroidism. In comparison, patients who are more symptomatic, elderly, or have underlying heart disease are usually pretreated with a thionamide as described above before radioiodine administration. Pretreatment with PTU, but not MMI, may decrease the success rate of the subsequent radioiodine therapy. Therefore, MMI is preferred in this setting [10]. If the patient is pretreated with a thionamide, radioiodine ideally should be given before the serum TSH concentration normalizes to prevent the accumulation of radioiodine into paranodular tissues, thereby minimizing the risk of

hypothyroidism [11]. (See "Radioiodine in the treatment of hyperthyroidism" for a discussion of dosing and complications).

Among patients with toxic adenomas, radioiodine therapy not only ameliorates hyperthyroidism but also reduces the size of the adenomas [12,13]. For example, in a study of 62 patients treated with radioiodine, hyperthyroidism was controlled in all, usually in three months, and total thyroid volume decreased by 35 percent in three months and 45 percent in 24 months; five patients became hypothyroid during a three-year follow-up period [12].

Patients with large nodular goiters that include both autonomous and non-functioning nodules (as determined by scintigraphy) are often not ideal candidates for radioiodine therapy. These patients have a substantial decrease in the size of the autonomous nodules after radioiodine treatment, but because uptake may be suppressed in non-autonomous tissue, they may not have a reduction in non-autonomous nodules to the extent seen during radioiodine treatment of patients with nontoxic multinodular goiter. (See "Radioiodine therapy for nontoxic multinodular goiter").

Approximately 10 to 20 percent of patients fail to reach a euthyroid state following the first dose of radioiodine and require a second or subsequent dose. These patients typically have severe hyperthyroidism or large goiters.

Surgery — Surgery is used more commonly for the treatment of patients with a toxic adenoma or toxic multinodular goiter than it is for Graves' hyperthyroidism. It is indicated for patients with obstructive goiters or very large goiters or those who need rapid and definitive correction of hyperthyroidism. Surgery would also be a consideration in children and adolescents and, as noted above, may be preferable in patients with coexistent non-functioning nodules, especially if the goiters are large. (See "Surgery in the treatment of hyperthyroidism"). A cost-benefit analysis that measured outcomes in quality-adjusted life years after therapy concluded that surgery was slightly more cost-effective than radioiodine for treatment of toxic adenoma in patients under age 60 years [14].

Ethanol injection — Ethanol injection of toxic adenomas under ultrasound guidance is a nonsurgical method of destroying the adenomas [15]. Ethanol is injected percutaneously at weekly intervals for five to eight weeks. In one series of 117 patients with autonomous thyroid adenomas followed for an average of 2.5 years, all 40 patients with adenomas who had subclinical hyperthyroidism were cured, while 60 of 77 patients (80 percent) with hyperthyroidism (60 with a single adenoma and 17 with a multinodular goiter) also were cured [16]. No patient had recurrent hyperthyroidism. In a study in which radioiodine and ethanol injection were compared, reduction in adenoma volume was similar (67 percent for radioiodine vs. 78 percent for ethanol), and radioiodine was more likely to result in hypothyroidism, but also more likely to cure the hyperthyroidism [17]. This form of therapy is not widely used in the United States.

RECOMMENDATIONS — The choice of radioiodine or surgery involves active discussion between the physician and patient. Patients with symptomatic hyperthyroidism are usually treated with a thionamide and euthyroidism is attained before a decision regarding further therapy is made. In the absence of one of the indications for surgery, we prefer radioiodine therapy for most patients. Radiation safety regulations in some states and countries advise mothers receiving radioiodine to severely limit the time spent with their infants for up to 5 days. As a result, if suitable child care is unavailable, patients may opt to take thionamides for several years, or rarely may choose surgery over radioiodine.

The individual patient's fears regarding radiation exposure, general anesthesia, or surgical complications often influence the decision, and some patients refuse both radioiodine and surgery. For them, prolonged thionamide therapy is acceptable as long as it is tolerated and the hyperthyroidism is controlled. Treatment may need to be continued indefinitely because, unlike Graves' hyperthyroidism, spontaneous remissions do not occur.

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