

Thyroidectomy for Amiodarone-Induced Thyrotoxicosis: Mayo Clinic Experience

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Context: Amiodarone-induced thyrotoxicosis (AIT) is a difficult diagnostic and management challenge, especially during severe thyrotoxicosis accompanied by cardiovascular compromise.

Objective: To evaluate thyroidectomy for the management of AIT.

Design: Retrospective cohort study of adults with noncongenital heart disease with AIT after >3 months of amiodarone who underwent thyroidectomy from 1 November 2002 to 31 December 2016.

Setting: Referral center.

Patients: The group was comprised of 17 patients.

Main Outcome Measures: Thyroid function, left ventricular ejection fraction (LVEF), and surgical complications were the main outcome measures.

Results: Patients had median age of 60 years, 82.4% were male, and 47% had systolic heart failure. At diagnosis, median TSH was 0.005 mIU/L, median free T4 was 3.25 ng/dL, and total T3 was 198.5 ng/dL. We classified five patients as type 1 and type 2 and two patients as mixed; five patients remained undefined. The most common surgical indications were medically refractory disease, worsening cardiac status, and severe thyrotoxicosis requiring prompt resolution. Within 1 week post-thyroidectomy, median TSH was 0.565 mIU/L, and free T4 was 1.8 ng/dL. Median LVEF improved by 8% in patients with systolic heart failure. Seven patients had a complication within 30 days postsurgery (rehospitalization, n = 4; cervical hematoma, n = 2; recurrent arrhythmia, n = 2; symptomatic hypocalcemia, n = 1; death, n = 1). A larger thyroid gland was a risk factor for complications.

Conclusions: Thyroidectomy resulted in rapid resolution of thyrotoxicosis. Its complication rate was higher than for non-AIT indications but lower than previously reported in a similar population of high-risk surgical patients.

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Freeform/Key Words: amiodarone induced thyrotoxicosis, thyroidectomy, thyroid surgery

Abbreviations: AIT, amiodarone-induced thyrotoxicosis; ATD, antithyroid drug; CDF, color Doppler flow; LVEF, left ventricular ejection fraction; MNG, multinodular goiter; RAIU, radioactive iodine uptake.

Amiodarone administration has been reported to cause thyroid dysfunction in 15% to 20% of cases [1–3], with the incidence of thyrotoxicosis being ~3% to 9% [3–5]. Although amiodarone-induced hypothyroidism is more common in iodine-replete regions such as North America, the less commonly encountered entity of amiodarone-induced thyrotoxicosis (AIT) is universally recognized as a difficult diagnostic and management challenge, at times leading to life-threatening complications. This is due to the prolonged half-life of amiodarone and the fact that its discontinuation is not always feasible in the setting of life-threatening arrhythmias refractory to conventional antiarrhythmic medications.

Type 1 AIT is characterized by iodine-induced hyperthyroidism due to excess hormone synthesis, usually occurring in patients with underlying thyroid disease. On the other hand, type 2 AIT is characterized by destructive thyroiditis causing excessive thyroid hormone release and is reported to occur in patients with normal thyroid or small goiter [1]. Assessing thyroid gland vascularity on ultrasound, the history of underlying thyroid disease, radioactive iodine uptake (RAIU) values, and the presence of antithyroid autoantibodies can help differentiate between these two processes and guide management. Type 1 AIT has been more commonly reported in iodine-deficient areas, whereas type 2 AIT is more prevalent in iodine-replete areas [1, 6] and is the most frequent form of AIT overall [7]. However, mixed and refractory forms commonly occur [8–10] and are associated with increased mortality in older individuals with impaired ventricular function likely due to a combination of preexisting cardiac dysfunction and a superimposed high-output thyrotoxic state, precipitating heart failure in these patients [1, 11, 12]. This increased mortality underscores the importance of rapid restoration and maintenance of euthyroidism in such cases.

Near-total thyroidectomy is an effective way to rapidly control thyrotoxicosis. However, it is usually instituted as a last resort for medically refractory AIT because it has been associated with higher perioperative morbidity and mortality when compared with thyroidectomy instituted for management of Graves hyperthyroidism or toxic multinodular goiter [13]. Our group has previously reported on our surgical experience for severe AIT from April 1985 through November 2002 [14], which showed an operative mortality rate of 9%. We aimed to update our surgical experience at Mayo Clinic, Rochester, regarding the demographic characteristics, severity, course, and outcomes in adults with AIT who underwent total or near-total thyroidectomy over the subsequent 14 years.

1. Materials and Methods

A. Database Used

After obtaining approval from Mayo Clinic Institutional Review Board, we retrospectively identified a cohort of adults with noncongenital heart disease without prior history of hyperthyroidism or thyroidectomy who developed thyrotoxicosis after ≥ 3 months of amiodarone therapy. All these patients had provided consent for their medical records to be used for research. From this cohort, we identified those who underwent total or near-total thyroidectomy for management of AIT from 1 November 2002 through 31 December 2016 at Mayo Clinic, Rochester. These cases were identified by reviewing the pathology reports for thyroidectomy specimens and then corroborated with the medical record. Demographics data, AIT clinical presentation, diagnostic testing, treatment selection, surgical information, response to treatment, and complications of AIT as well as surgical complications were abstracted by two of the authors (A.K. and J.C.). Any discrepancies were addressed by confirming with the surgeons (G.T., T.M., M.L.) and the principal investigator (M.S.).

B. Outcome Measures and Definitions

In this study, AIT was defined as a suppressed TSH with elevated or normal T4 and/or T3 levels in the outpatient setting or the same laboratory parameters in the inpatient setting after exclusion of sick euthyroid syndrome and drug effects (*i.e.*, heparin, dopamine,

glucocorticoids). We incorporated previously reported criteria [1, 15, 16] as well as our clinical expertise in addition to information obtained from thyroidectomy surgical pathology to classify AIT subtypes. We used the lower limit of normal radioactive iodine uptake (RAIU) in our population at the time the cohort started as we have reported in previous publications [17, 18]. Type 1 AIT was defined by (1) the presence of a nodular thyroid or diffuse goiter >15 g or positive TSH receptor antibody titer with normal/increased thyroid vascularity on ultrasound color Doppler flow (CDF) or (2) 24-hour RAIU >8%. Type 2 AIT was defined by the presence of a normal thyroid or small diffuse goiter <15 g with negative TSH receptor antibody titer and low thyroid vascularity on ultrasound CDF. AIT was classified as “mixed” when there was a nodular thyroid or diffuse goiter >15 g or positive TSH receptor antibodies with low thyroid vascularity on ultrasound CDF. AIT was classified as “unidentified” in cases where ultrasound CDF was not performed as long as 24-hour RAIU was <8% or also not performed. In terms of preoperative management, AIT was considered to be “observed” if no intervention targeting pathophysiology was performed; β -blockers were considered symptomatic therapy and did not change the observed status of the case. If an intervention targeting pathophysiology was performed after >1 week from the date of AIT diagnosis, that case was considered to have been “initially observed.” We considered the resolution of AIT to be the day of thyroidectomy.

Thyroidectomy was performed either urgently or emergently in these patients. Cardiac status was evaluated through echocardiography-measured left ventricular ejection fraction (LVEF). Perioperative events were recorded, including type of operation, operative mortality, length of hospital stay, and complications. Postoperative complications were determined to be those that occurred within 30 days after thyroidectomy. The last comprehensive visit with the cardiologist, endocrinologist, or surgeon at our institution marked the duration of follow-up. The last visit or communication with someone at our institution determined survival. Data were evaluated to determine the factors influencing the clinical response as well as possible complications from thyroidectomy.

C. Statistical Analysis

Summary statistics for continuous variables were expressed as median and interquartile range due to the small sample size and non-normal data distribution. Categorical variables were summarized as number (n) and percentages (%). Statistical analyses comparing the groups of patients with and without surgical complications were carried out using non-parametric tests, including Wilcoxon rank sum test for continuous variables and Fisher exact test for binary variables. A *P* value <0.05 was used for establishing statistical significance.

2. Results

A. Incidence and Baseline Characteristics at Amiodarone Initiation

Of ~370 total AIT cases, 17 cases (4.6%) underwent total or near-total thyroidectomy at Mayo Clinic for management of AIT over the 14 years of the study cohort. These 17 cases represent the subjects of our study. Patient baseline characteristics and clinical data are presented in **Table 1**. Eighty-two percent of the subjects were male, and patients had a median age of 60 years. Atrial fibrillation was the indication for amiodarone initiation in about two-thirds of the sample because these patients had not responded to other antiarrhythmic medications. Forty-one percent of patients had underlying coronary artery disease. The median LVEF was 52%, with 47% classified as having systolic heart failure due to LVEF <45% prior to amiodarone initiation.

B. Patient Characteristics During AIT

Patient characteristics are shown in **Table 2**. Median time on amiodarone before development of AIT was 24 months, and median time between the diagnosis of AIT and

Table 1. Patient Characteristics at the Time of Initiation of Amiodarone

Baseline Characteristics at Amiodarone Initiation	All Samples (n = 17) ^a
Age, y	60 (50.5–72)
Men	14 (82.4)
Weight, kg	82 (72.5–111)
BMI, kg/m ²	25 (24–33)
Cigarette smoking	
Current	0 (0)
Former	4 (23.5)
Never	13 (76.5)
Family history of thyroid disease	2 (11.8)
History of goiter	4 (23.5)
History of autoimmune thyroid disease	0 (0)
Indication for amiodarone	
Atrial fibrillation	13 (76.5)
Ventricular tachycardia	4 (23.5)
Cardiac disease	
Coronary heart disease	7 (41.2)
Arrhythmogenic heart disease	5 (29.4)
Idiopathic dilated cardiomyopathy	2 (11.8)
Valvular heart disease	3 (17.7)
ICD present	9 (52.9)
LVEF, %	52 (20–60)
Systolic heart failure (defined by LVEF <45%)	8 (47.06)

Abbreviations: BMI, body mass index; ICD, implantable cardioverter defibrillator; IQR, interquartile range.

^aValues are median (IQR) or n (%).

thyroidectomy was 2 months. All subjects were symptomatic, with palpitations and weight loss being the most common symptoms. At the time of AIT diagnosis, median TSH was 0.005 mIU/L, median free T4 was 3.25 ng/dL, and median total T3 was 198.5 ng/dL. Based on these criteria, we classified five subjects each as type 1 and type 2 and two subjects as mixed. In five cases, AIT type was unidentified due to the inability to assess thyroid gland vascularity by ultrasound CDF. Preoperative therapy included β -blockers alone in 18% of patients; β -blockers and antithyroid drug (ATD) in 12%; and β -blockers, ATD, and prednisone in 70% (two of these were initially observed).

C. Thyroidectomy Data

Surgical indications included one or more of the following: medically refractory disease for >2 weeks (70%), worsening cardiac status (47%), severe thyrotoxicosis requiring prompt resolution (35%), intolerance or contraindication to ATD (24%), and patient/physician preference for definitive management to prevent AIT recurrence (12%). In 41% of all cases, amiodarone was continued. The rest of the data are presented in [Table 3](#).

D. Surgical Outcomes (Benefits)

Five out of the eight patients (63%) with prethyroidectomy systolic heart failure (LVEF <45%) underwent follow-up echocardiography after thyroidectomy, and LVEF improved in all patients (median, 8%; interquartile range, 5% to 21%) ([Table 3](#)). In the rest of the cohort that did not undergo follow-up echocardiography, there was no clinical evidence of worsening cardiac function. Within 1 week postsurgery, median TSH increased to 0.565 mIU/L, free T4 decreased to 1.8 ng/dL ([Table 4](#)), and the clinical features of thyrotoxicosis were resolved or improved. Individual patient free T4 response (available for 13 patients) is shown in [Fig. 1](#).

Table 2. Patient Characteristics, Clinical Presentation, and Management During AIT

Patient Characteristics During AIT	All Samples (n = 17) ^a
Average amiodarone dose before AIT, mg/kg/d	2.6 (1.9–2.9)
Time on amiodarone before AIT, mo	24 (6–40)
Time between AIT diagnosis and thyroidectomy, mo	2 (1–3.5)
TSH at diagnosis, mIU/L ^b	0.005 (0.005–0.01)
Free T4 at diagnosis, ^c ng/dL	3.25 (2.4–6.9)
Free T3 at diagnosis, ^d pg/mL	5.4 (4.7–12.9)
Total T3 at diagnosis, ^e ng/dL	198.5 (117–389.3)
Amiodarone-induced hepatotoxicity	3 (17.4)
Amiodarone-induced pulmonary toxicity	1 (5.9)
AIT type	
1	5 (29.4)
2	5 (29.4)
Mixed	2 (11.8)
Unidentified	5 (29.4)
First episode of AIT	16 (94.1)
Hospitalization during initial AIT	8 (47.1)
AIT symptoms at presentation	
Edema	2 (11.8)
Weight loss despite good appetite	7 (41.2)
Tremor	1 (5.9)
Fatigue	5 (29.4)
Heat intolerance and diaphoresis	4 (23.5)
Palpitations	11 (64.7)
Hyperdefecation	2 (11.8)
Muscle weakness	3 (17.6)
Insomnia	1 (5.9)
Preoperative management in addition to β -blockers	
Observation	3 (17.6)
Initial observation followed by ATD + prednisone	2 (11.8)
ATD alone	2 (11.8)
ATD + prednisone	10 (58.8) (n = 1 received perchlorate, cholestyramine, iodine)

^aValues are median (interquartile range) or n (%).

^bTSH <0.01 mIU/L substituted by 0.005 mIU/L; TSH reference range 0.3–4.2 mIU/L.

^cFree T4 >7.5 ng/dL substituted by 10.5 ng/dL in newer assay and >12 ng/dL substituted by 15 ng/dL in older assay; Free T4 reference range 0.9–1.7 ng/dL.

^dFree T3 >20 ng/dL substituted by 30 ng/dL; Free T3 reference range 2–3.5 pg/mL.

^eTotal T3 reference range 80–200 ng/dL.

E. Surgical Outcomes (Complications)

None of the subjects who underwent thyroidectomy for AIT management sustained a recurrent laryngeal nerve injury. Seven (41%) experienced a complication <30 days post-surgery, including rehospitalization (n = 4), cervical hematoma requiring evacuation (n = 2, both on anticoagulation), recurrent arrhythmia (n = 2), and symptomatic hypocalcemia (n = 1). One patient who was on anticoagulation and had undergone emergent thyroidectomy to manage uncontrolled hyperthyroidism with worsening arrhythmias died during the 30-day postoperative period after developing stroke and cardio-respiratory failure. Median duration of follow-up on the patient cohort was 32.9 months. Survival rate at 1 and 6 months was 94%.

Differences between those with any complication (n = 7) and those without (n = 10) were analyzed with respect to the variables of age, sex, time between AIT diagnosis and thyroidectomy, AIT type, immediately preoperative thyroid function tests, hospital stay during thyroidectomy, and surgical thyroid size. Of these, only thyroid size (a larger thyroid gland) was found to be associated with surgical complications (median weight, 24.1 g vs 13.9 g; $P = 0.03$).

Table 3. Thyroidectomy Data Including Surgical Indications, Hospital Stay, and Outcomes

Thyroidectomy Data	All Samples (n = 17) ^a
Indications for thyroidectomy	
Medically refractory AIT (>2 wk)	12 (70.1)
Worsening cardiac status	8 (47.1)
Severe thyrotoxicosis requiring prompt resolution	6 (35.3)
Intolerance to ATD	4 (23.5)
Patient or physician preference for definitive therapy	2 (11.8)
Type of thyroidectomy	
Total	11 (64.7)
Near-total	6 (35.3)
Hospital days during thyroidectomy	3 (2.0–6.5)
Surgical weight, g	23 (12.9–29.9)
Patients with surgical weight >15 g	11 (64.7)
Complication rate within 30 d postsurgery	
Total patients with any complication	7 (41.2)
Rehospitalization	4 (23.5)
Cervical hematoma	2 (11.8)
Recurrent arrhythmia	2 (11.8)
Symptomatic hypocalcemia	1 (5.9)
Stroke	1 (5.9)
Respiratory failure	1 (5.9)
Death	1 (5.9)
LVEF within 6 mo post-thyroidectomy, %	50.5 (27–65.2)
LVEF change among systolic heart failure cases (n = 8), %	8 (5–21)
Post-thyroidectomy follow-up duration, mo	32.9 (2.8–106.1)
Survival at 1 and 6 mo post-thyroidectomy	16 (94.1)

Also, all the patients with a complication had a thyroid surgical weight >15 g as compared with only 40% of those without a complication ($P = 0.03$).

3. Discussion

AIT is an uncommon complication of amiodarone use in iodine-replete regions that can often be difficult to manage. This is especially true for the mixed form, which may not respond to medical management despite combination therapy with ATDs and glucocorticoids. The European Thyroid Association guidelines recommend total thyroidectomy without delay in patients with AIT with deterioration of cardiac function or severe underlying cardiac disease, in patients whose thyrotoxicosis is unresponsive to medical therapies or who have adverse effects of medical therapy, and for patients who are at risk for AIT recurrence while they need

Table 4. Biochemical Response to Thyroidectomy

Laboratory Thyroid Function Tests	Immediately Presurgery	~1 wk Postsurgery	~4 wk Postsurgery	Reference Range
TSH, ^a mIU/L	0.005 (0.005–0.225) ^b	0.565 (0.03–1.1)	10 (1.425–29)	0.3–4.2
Free T4, ^c ng/dL	3.5 (2.1–8.1)	1.8 (1.15–2.55)	1.25 (0.85–1.65)	0.9–1.7
Free T3, ^d pg/mL	5.2 (4.4–55)	—	—	2–3.5
Total T3, ng/dL	73 (70–149)	—	—	80–200

^aTSH <0.01 mIU/L substituted by 0.005 mIU/L.

^bValues are mean (interquartile range).

^cFree T4 >7.5 ng/dL substituted by 10.5 ng/dL in newer assay and >12 ng/dL substituted by 15 ng/dL in older assay.

^dFree T3 >20 ng/dL substituted by 30 ng/dL.

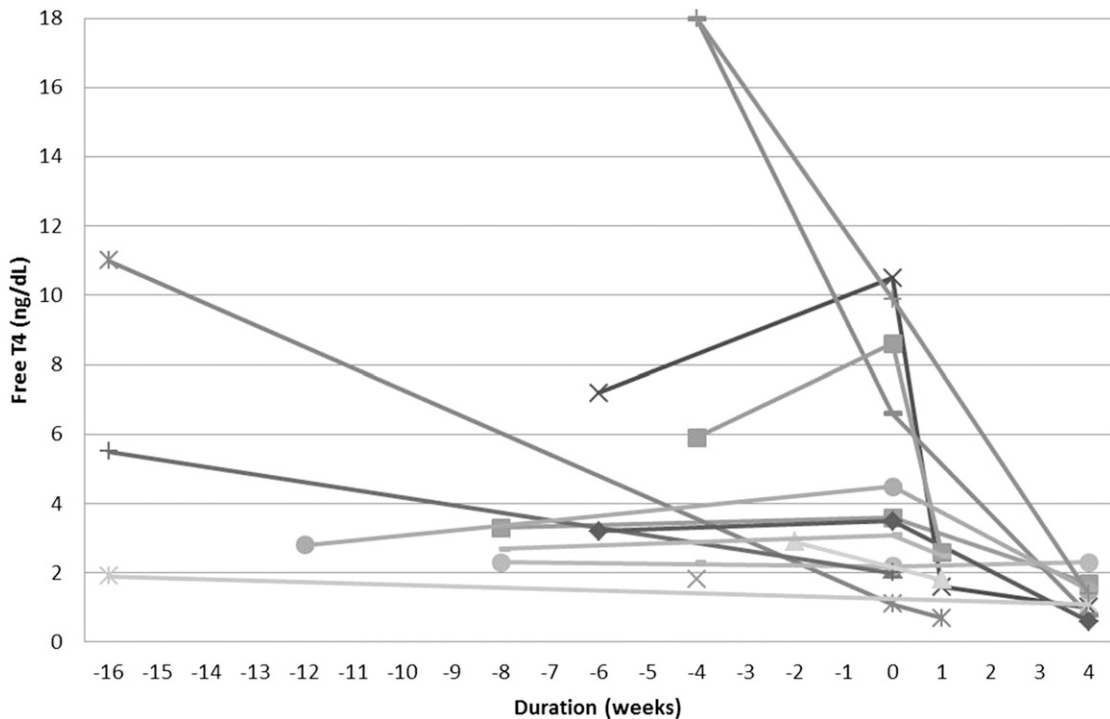


Figure 1. Changes in free T4 of patients before and after thyroidectomy. Week 0 indicates date of thyroidectomy.

to continue amiodarone [15]. Given the prior well-documented perioperative risk at Mayo Clinic [14], we aimed to review our recent surgical experience and reassess the balance of risk vs benefit in these patients. The AIT cohort described in our study was composed of predominantly older individuals, most with substantial cardiac dysfunction. Thyroidectomy was performed most commonly in patients with medically refractory disease of >2 weeks duration or in the setting of severe thyrotoxicosis requiring prompt resolution. In these cases, severe thyrotoxicosis superimposed on existing marginal cardiac function could not be tolerated by the patient, and immediate treatment was needed. Additionally, in a large percentage of patients, AIT was refractory to initial medical management and patients experienced ongoing or worsening thyrotoxicosis, CHF, or arrhythmia despite alternative therapies. These scenarios align with the European Thyroid Association guideline recommendations [15], which we endorse. In our cohort, thyroidectomy was followed by rapid resolution of thyrotoxicosis in all cases and LVEF improvement in all those with systolic heart failure who underwent follow-up echocardiography. This is similar to the improvement in LVEF reported by Tomisti *et al.* [19] in patients with initial LVEF <40%. Thyroidectomy also allowed the continuation of amiodarone without concern for AIT recurrence, which could result in worsening cardiac status.

The complication rate seen in our AIT cohort was higher than that for other thyrotoxic etiologies, like Graves disease and toxic multinodular goiter (MNG) [13]. However, this cohort of patients was older and had worse cardiac status, most with systolic heart failure and recurrent cardiac arrhythmias at the time of surgery. The overall complication rate in our series was 41%, with seven patients experiencing at least one complication. In terms of specific complications, permanent symptomatic hypoparathyroidism developed in one case (5.9%), which is less frequent than with Graves disease (12.4%) or with toxic MNG (7.3%) [13] and less than 2 of 24 (8%) reported by Tomisti *et al.* [19] for surgically managed AIT. The rate of postoperative cervical hematoma, seen in 11.8% of our cohort, was higher than for Graves disease (2.8%) and toxic MNG (2.1% in national data [13] and 1% in a previous Mayo Clinic

study [20]); however, the increased necessity of anticoagulation in our cohort in the setting of atrial fibrillation was probably the major contributing factor for this complication. There were no cases of vocal cord paralysis in our series as compared with Graves disease (0.9%) and toxic MNG (1.1%–2%) [13, 20] and compared with 8% in the AIT cohort reported by Tomisti *et al.* [19]. Stroke occurred in 5.9%, which was more than for Graves disease (0%) or toxic MNG (0.3%) [13]. Respiratory failure complications developed in 5.9%, which was more than in Graves disease (2.4%) or toxic MNG (3.1%) [13]. Overall mortality of 5.9% in our series was also more than in Graves disease (0.2%) or toxic MNG (0.4%) [13]. In a surgically managed AIT cohort reported by Tomisti *et al.* [19], there were no deaths in 24 cases during 2 months of postoperative follow-up. However, compared with our previously reported Mayo Clinic series on thyroidectomy for AIT, mortality at 5.9% was lower than the previously reported rate of 9% [14]. These two patient populations seem to be similar: both populations had high percentages of patients with cardiac dysrhythmias, more advanced age, and preprocedural underlying cardiac disease. From a surgical perspective, the approach to thyroid resection between the two cohorts has not changed significantly. However, the more recent preoperative management demonstrated more frequent use of β -blockers and antithyroid drugs in this cohort. Additionally, the use of cardiac anesthesia for high-risk cardiovascular cases may play a role in decreasing the complication rate. A higher thyroid surgical weight associated with surgical complications likely reflects the impact of a larger thyroid contributing to a more technically difficult or prolonged operation. Previous studies have suggested that high-volume thyroid surgeons have lower hospital length-of-stay and lower complication rates when compared with lower-volume surgeons [21]. In our series, all thyroidectomies were performed by high-volume thyroid surgeons.

Although our attempt to distinguish the AIT subtypes has been laborious, some cases defied classification. Thus, some cases were thought to be of a mixed subtype, whereas others remained unidentified due to the retrospective nature of the study. With this caveat, no AIT subtype showed a strong association for thyroidectomy. Decisions to proceed with thyroidectomy were predicated more by the presence of clinical features that were not safely tolerable in the presence of underlying cardiac disease or dysrhythmia or worsening thyrotoxicosis that was unresponsive to combination pharmacologic therapy. In a few cases, patients were intolerant of pharmacologic therapy and needed definitive therapy by surgical means.

The main limitations of our study include the retrospective design and the small sample size. The retrospective design limited our ability to determine outcomes with complete accuracy and introduced record-keeping bias in the determination of perioperative complications or risk prediction for such. Our classification of patients into various AIT subtypes was also limited by the information available through the medical record. However, AIT managed surgically is rare, and waiting longer to acquire a larger sample will lead to development of other changes in practice. That will make the population too heterogeneous to preserve its external validity, and likely the information would lose some of its practical value. Thus, we feel that, even with the small sample size, the results of this study need to be reported.

In summary, thyroidectomy was required for AIT management in a small proportion of cases, mostly due to medically refractory disease or the need for prompt control of severe thyrotoxicosis affecting cardiac status. Thyroidectomy resulted in rapid resolution of thyrotoxicosis in all patients and improvement in cardiac function in the subset of patients with systolic heart failure monitored by echocardiography. The complication rate was higher than for other thyrotoxic etiologies but was similar to or lower than reported for AIT previously. Hence, thyroidectomy remains a valuable option for AIT management, particularly for patients with suboptimal response to medical therapy and high risk for cardiac complications. Although it is difficult to decipher the specific factors contributing to the successful management in these sick patients, the outcomes most likely derive from the coordinated efforts of endocrinologists, thyroid surgeons, cardiac anesthesiologists, and all of the support teams.

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