

Refractory Amiodarone-induced Thyrotoxicosis: The Surgical Option

Avraham Ishay, Julia Carmeli, Ehud Rozner, Rafael Luboshitzky

ABSTRACT

Amiodarone-induced thyrotoxicosis is often poorly tolerated owing to underlying cardiac disease, and frequently resistant to medical therapy. We describe a 48-year-old patient with severe cardiac disease who developed amiodarone-associated thyrotoxicosis, refractory to standard medical therapy. Due to the unremitting thyrotoxicosis, a total thyroidectomy was performed without complications resulting in rapid correction of the thyrotoxicosis and enabling resumption of amiodarone therapy. Despite the concerns inherent to severe cardiac disease, total thyroidectomy can be performed safely in patients with resistant amiodarone-induced thyrotoxicosis. We believe that surgery should be considered early in the treatment planning.

Keywords: Amiodarone, Thyroidectomy, Amiodarone-induced thyrotoxicosis.

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INTRODUCTION

Amiodarone is a potent, iodine rich (37% by molecular weight), class III antiarrhythmic drug widely used for the management of both supraventricular and ventricular arrhythmias. Because of its high iodine content and direct cytotoxic effects this drug may induce thyroid dysfunction. The adverse effects of amiodarone may be seen months after discontinuation because its long half-life (107 days).^{1,2} In contrast to amiodarone-induced hypothyroidism, which can be easily treated by L-thyroxin replacement therapy, amiodarone-induced thyrotoxicosis (AIT) may sometimes develop as a life-threatening complication. There are two types of AIT, but the distinction between them may be tricky and in fact mixed forms do exist. Type I AIT is typically seen in patients with pre-existing nodular goiter or latent Graves disease. In these patients the exposure to large amounts of iodine, provided by amiodarone, will result in excessive thyroid hormone production. Type II AIT occurs usually in patients without underlying thyroid disease and is due to a direct toxic effect of amiodarone on thyroid follicular cells which cause release of preformed hormone. This destructive inflammatory thyroiditis is the most frequent form of AIT.^{3,4} The prevalence of AIT, as well as its distribution by type, varies by geographical region.

In iodine-deficient regions, type I AIT is more common and occurs in about 10 to 12% of patients treated with amiodarone. In iodine-repleted areas, like USA, type II AIT is more prevalent and occurs in 3 to 5% of patients.^{5,6} Although AIT may present as a mild disorder alleviated by discontinuing amiodarone, its management is generally challenging. AIT is notoriously resistant to medical therapy.⁷⁻⁹ AIT is usually treated with a combination of thionamides, such as mercaptizol or propylthiouracil, and glucocorticoids. However, the high intrathyroidal iodine content reduces the effectiveness of thionamides or cholecystographic agents and precludes the administration of radioactive iodine. Other medications are frequently not available (potassium perchlorate), lack efficacy or may have serious adverse effects (lithium). Thyroidectomy may therefore represent a valid alternative for patients with AIT refractory or not suitable to medical therapy.

CASE REPORT

A 48-year-old man, active smoker, with known non-obstructive hypertrophic cardiomyopathy was admitted for worsening of heart failure (New York Heart Association Class III). Review of medical records revealed that he suffered from long standing poorly controlled hypertension, coronary artery disease with inferior wall myocardial infarction in 2006, type II diabetes mellitus, chronic renal failure (stage 3A), chronic lung disease and had several episodes of transient ischemic attacks. Due to persistent episodes of paroxysmal atrial fibrillation, treatment with amiodarone was initiated since 2008. At admission, the patient was in mild respiratory distress with irregularly irregular pulse at a rate of 120 beats per minute. The blood pressure was 190/65. Staring gaze with lid lag and fine tremor of hands were noted. At palpation, the thyroid was of normal size and not tender. A 12-lead electrocardiogram demonstrated atrial fibrillation. Echocardiography revealed enlargement of the left atrium with preserved systolic function (left ventricular ejection fraction of 50%) and grade II diastolic dysfunction. Laboratory analysis showed increased levels of free T4 (75.2 pmol/l, normal: 9.9-22.7), free T3 (12.9 pmol/l, normal: 3.5-6.5) and suppressed thyrotropin level (<0.03, normal: 0.4-4.2 mIU/ml). Antibody testing, including thyroid peroxidase, thyroglobulin and thyroid stimulating hormone (TSH) receptor antibodies, was

negative. Radioactive iodine uptake (RAIU) study and color-Doppler sonography could have helped in discriminating type I from type II AIT but because of the instability and severity of the cardiac disease these studies were not performed. In addition, owing to the severe protracted and refractory thyrotoxicosis, we planned to relieve the thyrotoxicosis as rapidly as possible that is surgically. Moreover, as a rule, the high iodine load blocks the uptake of the radioactive tracer precluding radioiodine therapy in the short term. The diagnosis of AIT (most probably type II) was made and amiodarone was stopped. Treatment with methimazole 40 mg/d and prednisone 40 mg/d was initiated. In the subsequent weeks, the patient suffered from recurrent pulmonary edema with respiratory failure, hypertensive crisis, recurrent episodes of supra-ventricular and ventricular tachycardia and deterioration of renal function. Drug management included high doses of beta blockers, calcium channel blockers, clonidine, hydralazine, nitrates, nitroprusside and angiotensin receptor blockers. Supporting measures encompassed mechanical ventilation and hemodialysis. Despite this treatment, there was no change in thyroid function tests. Methimazole was substituted by propylthiouracil 800 mg/d and prednisone by dexamethasone without significant improvement. Due to concerns regarding the protracted thyrotoxicosis and its deleterious effects on the cardiac function, we decided to carry out total thyroidectomy. Preoperative evaluation was completed by the expert panel that included cardiologist, endocrinologist, ENT surgeon, anesthesiologist, in which issues such as the risks and benefits of conservative and operative treatment were discussed. Surgery was performed under balanced general anesthesia (fentanyl, midazolam, vecuronium, nitrous oxide/oxygen/sevoflurane) with invasive blood pressure monitoring and connection to external defibrillator. Blood pressure was controlled by continuous infusion of beta blockers. There were no intraoperative complications. Thyroidectomy was performed after a collar curvilinear incision was created 2 cm above the sternal notch and the clavicles. The recurrent laryngeal nerves were identified and preserved. Macroscopic examination of the specimen showed a small and fibrotic diffuse goiter. Microscopically, thyroid follicular cells were degenerated with picnotic nuclei. Infiltration with foamy histiocytes was noted. Postoperative period was characterized by prolonged mechanical ventilation and weaning succeeded after performing percutaneous tracheostomy. Blood pressure was partially controlled with appearance of episodes of flash pulmonary edema. During late postoperative treatment course, there was muscle weakness in the back and extremities which was most probably related to steroid treatment and prolonged

mechanical ventilation. Within 2 weeks after surgery the patient develop hypothyroidism and levothyroxine therapy was started. Amiodarone was afterward resumed.

DISCUSSION

The use of amiodarone is associated with a widearray of side effects which may affect skin, lung, eyes, liver, cardiovascular and nervous systems as well as thyroid.¹⁰ AIT occurs invariably in patients with pre-existing cardiac dysfunction and history of arrhythmias that are often resistant to other antiarrhythmic agents. This patient population tolerates poorly a state of thyrotoxicosis. AIT patients have a significant higher rate of major adverse cardiovascular events when compared with amiodarone-treated patients who remain euthyroid (7 vs 1.3% respectively).¹¹ When compared with other forms of thyrotoxicosis, AIT is associated with a significant increase in mortality rate (10 vs 0%). Moreover, in these patients, age and low left ventricular ejection fraction correlate with fatal events.¹² In order to avoid cardiac decompensation in patients with unstable cardiac disease, it is therefore crucial to obtain a prompt restoration of euthyroidism. Medical therapy may be an acceptable option for AIT management if cardiac function is stable and the heart may sustain protracted thyrotoxicosis without deleterious consequences. Differentiation of the two types of AIT, although challenging, is essential, because therapeutic options and outcomes differ greatly between the two forms of AIT. RAIU values are classically normal or increased in most type I AIT patients and low or undetectable in those in type II AIT, but the high intrathyroid iodine load and environmental iodine supply often cause misclassification of type I AIT patients as type II because of low uptake.^{13,14} Color flow Doppler sonography (CFDS) is a promising and useful tool showing invariably absence of hyper-vascularization (pattern 0), despite high thyroid hormone levels in type II AIT patients and hypervascularization in type I patients.¹⁵ Unfortunately, it is not always possible to label accurately AIT. In fact, mixed cases of AIT are believed to occur in 15 to 27% of cases.^{5,16} Treatment of type I and mixed forms of AIT is based on the use of thionamides (generally with higher doses than those required to treat hyperthyroidism unrelated to amiodarone), usually in association with a short course of potassium perchlorate.¹⁷ If treatment is not rapidly effective oral glucocorticoids are added. Definitive therapy (radioiodine ablation if feasible, or thyroidectomy) may be relevant as hyperthyroidism has abated. Glucocorticoids are the treatment of choice for type II AIT. They need to be continued for 2 to 3 months at a relatively high dose (40-60 mg prednisone per day) and slowly tapered to avoid relapse of thyrotoxicosis. Amiodarone

should be discontinued whenever it is possible from cardiac standpoint. Continuation of amiodarone has been associated with delayed restoration of euthyroidism in patients with type II AIT.¹⁸ Some patients may worsen under standard therapy. Also, in type II AIT patients, time to restore euthyroidism may be particularly long. This time may be predicted by using an algorithm which takes into account the basal thyroid hormone levels and the estimated thyroid volume.¹⁹ Patients with a predicted rapid resolution of thyrotoxicosis (<30 days), may benefit of a short course of glucocorticoids. Patients with predictable delayed response to glucocorticoids, severe thyrotoxicosis and medical treatment failure, or high risk of cardiac decompensation, need rapid reversal of thyrotoxicosis. This is best achieved by total thyroidectomy. Operative treatment may be also indicated if amiodarone cannot be withdrawn of the patient because of the underlying cardiac arrhythmia. Thyroidectomy is ideally performed when the patient is euthyroid, but most often surgery is needed before an euthyroid state is reached. Pre-existing cardiac disease and thyrotoxicosis place AIT patients to higher risk of perioperative morbidity and mortality. Thyroid storm following thyroid surgery is a particularly dreaded, although extremely rare event. In a retrospective review of 34 patients treated surgically at Mayo Clinic, Rochester USA, the authors report an overall complication rate of 29% which is more higher than that reported for thyroidectomy performed for any other reason, but no thyroid storm event was noted.²⁰ However, most studies have shown that total thyroidectomy was performed in AIT patients under general anesthesia with surprising low morbidity and mortality.²¹⁻²⁴ Anesthetic considerations include meticulous control of blood pressure, heart rate, temperature with awareness of early recognition and treatment of thyroid storm and arrhythmias.^{25,26} A large majority of the published cases were performed under general anesthesia, and only few case reports under regional and local anesthesia were described.^{27,28} Close collaboration between endocrinologists, cardiologists, endocrine surgeons and anesthesiologists is essential to complete thyroidectomy successfully.

CONCLUSION

Evidence suggests that total thyroidectomy can be performed safely under general anesthesia in patients with severe AIT. We believe that surgery should be considered early in the course of treatment for patients with resistant AIT and underlying severe cardiac disease.

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ABOUT THE AUTHORS

Avraham Ishay

Senior Physician and Lecturer, Department of Endocrinology, Haemek Medical Center, Afula; The B Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Correspondence Address: Endocrine Institute, Haemek Medical Center, Rabin Road, 18101 Afula, Israel, Phone/Fax: 972-4-6495556 e-mail: ishay_av@clalit.org.il

Julia Carmeli

Senior Physician, Department of Anesthesiology, Haemek Medical Center, Afula, The B Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Ehud Rozner

Senior Physician, Heart Institute, Haemek Medical Center, Afula, Israel

Rafael Luboshitzky

Associate Professor, Department of Endocrinology, Haemek Medical Center, Afula, The B Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel