Case Report

Thyroid arterial embolization in a patient with congenital heart disease and refractory amiodarone-induced thyrotoxicosis

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Number of Figures: 4
Word count: 2704
Keywords: Amiodarone; Thyrotoxicosis; Embolization; Congenital Heart Disease
Established Facts and Novel Insights

Established Facts

- Amiodarone induced thyrotoxicosis (AIT) can be refractory to a combination therapy of thionamides and glucocorticoids.
- Restoration of euthyroidism is of paramount importance in heart failure patients.
- Emergency thyroidectomy for AIT unresponsive to medical therapy is recommended in patients with severe underlying cardiac disease or deteriorating cardiac function.

Novel Insights

- Thyroid arterial embolization (TAE) appeared as a salvage therapy in this patient.
- To the best of our knowledge, few case reports in the literature have described the embolization of the four thyroid arteries in AIT context.
- Endovascular embolization techniques are a valuable therapeutic option and can be considered in cases where standard forms of treatment are ineffective or involve unacceptable risks.
Abstract

Introduction: Amiodarone induced thyrotoxicosis (AIT) can sometimes lead to life-threatening complications, especially in patients with congenital heart disease (CHD). We report the case of a patient with refractory AIT that was successfully treated with thyroid arterial embolization (TAE).

Case Report: 34-year-old man with complex cyanotic CHD complicated with heart failure (HF), pulmonary hypertension, and supraventricular tachyarrhythmias, was treated with amiodarone since 2013. In March 2019 he presented worsening of his cardiac condition and symptoms of thyrotoxicosis confirmed by laboratory assessment. Thiamazole 30mg/day and prednisolone 40mg/day were prescribed, but the patient experienced worsening of his cardiac condition with several hospital admissions in the next five months, albeit increasing dosages of thionamide and glucocorticoid and introduction of cholestyramine and lithium. Thyroidectomy was excluded due to the severity of thyrotoxicosis and plasmapheresis was contraindicated due to the cardiac condition. Thyroid arterial embolization of the four thyroid arteries was then performed with no immediate complications. Progressive clinical and analytical improvement ensued with gradual reduction and suspension of medication with the patient returning to euthyroid state and his usual cardiac condition previous to the AIT.

Conclusion: For patients with medication refractoriness and whose condition precludes thyroidectomy, embolization of thyroid arteries may be an effective and safe option.
Introduction
The number of patients with congenital heart disease (CHD) reaching adulthood has largely increased due to advances in percutaneous and surgical techniques. Repaired and unrepaired CHD is commonly associated with atrial and ventricular tachyarrhythmias. The more complicated the congenital heart defect and the palliation required, the higher and earlier the incidence of atrial arrhythmias. [Stan M. N. et al. 2012] These are associated with thromboembolic phenomena and hemodynamic compromise and are, thus, a major cause of morbidity and mortality. Amiodarone is widely considered to be the most effective antiarrhythmic drug, even for the CHD population. Treatment with this class III antiarrhythmic drug is commonly used in these patients as it is very effective for both supra and ventricular tachyarrhythmia, is hemodynamically well tolerated by patients with impaired inotropic function and/or pre-existent hypotension and, also prevents sudden cardiac death. [Isaacs M. et al. 2018]

Due to its high iodine content (37.5% of its molecular weight) and structural similarity to thyroxine, abnormalities in thyroid function are common, especially with long-term use. The reported incidence of thyrotoxicosis is 3% to 9% in the general population, increasing to 21% in adults with CHD. [Thornes S.A. et al. 1999; Cohen-Lehman J. et al. 2010] Two main forms of amiodarone induced thyrotoxicosis (AIT) can occur: type 1 AIT is an iodine-induced hyperthyroidism in nodular goiter or in latent Graves’ disease; type 2 AIT is an amiodarone-induced destructive thyroiditis occurring in a normal thyroid gland. A mixed type is also recognized. AIT can be a dangerous condition because it may exacerbate underlying cardiac abnormalities leading to increased morbidity and mortality, especially in patients with left ventricular dysfunction. [Yiu KH W. et al. 2009] Restoration of euthyroidism is of paramount importance in heart failure patients; it may be difficult to achieve with medication and it can also be refractory to a combination therapy of thionamides and glucocorticoids, making this a challenging scenario. [Isaacs M. et al. 2018]

The European Thyroid Association recommends emergency thyroidectomy for AIT unresponsive to medical therapy in patients with severe underlying cardiac disease or deteriorating cardiac function. [Bartalena L. et al. 2018] Nevertheless, this decision must be made by a multidisciplinary team assessing the balanced risk-benefit in the individual patient. Thyroid arterial embolization (TAE) has been successfully used in toxic goiter, recurrent goiter, Graves’ disease and thyroid carcinoma. However, there are few reported cases of TAE in the context of AIT.[Kaminski G. et al. 2014]
We describe the case of a male patient with complex cyanotic CHD, who developed AIT refractory to medical therapy that was controlled with thyroid arterial embolization.

Case Report

A 34-year-old Caucasian male, born with a complex cyanotic CHD (D- transposition of the great arteries and interventricular communication), was submitted to palliative cardiac surgery (Senning procedure) when he was 2 years old. Heart failure and pulmonary hypertension were early recognized in the course of the disease. In 2010, the patient had an episode of severe hemoptysis with arterial embolization of collateral bronchial arteries. In 2013, due to supraventricular tachyarrhythmias (atrial fibrillation and flutter), treatment with amiodarone was initiated. In March 2019, he presented to his cardiologist with accentuation of fatigue and cyanosis, weight loss, irritability and tremor of the extremities that had started in the previous 3 months. Laboratory studies showed Hb 22.1 g/dL, Hct 63.6%, TSH 0.02 uIU/mL [0.35-4.94], FT4 2.12ng/dL [0.70-1.48], FT3 5.86 pg/mL [1.88-3.18]. The patient was referred to our Endocrinology Department in April 2019. On physical examination, patient’s blood pressure was 100/60 mmHg with an arrhythmic pulse of 78 beats per minute and a respiratory rate of 18 cycles per minute. BMI was 20.8 Kg/m$^2$ (weight 63.7 Kg; height 1.75 m). Skin and mucous membranes were severely cyanosized and flushed, with no signs of ophthalmopathy. A normal sized and fibroelastic thyroid gland was palpable, with no nodules.

Analytic reassessment showed TSH <0.01 mIU/L FT4 4.60 ng/dL FT3 14.57 pg/mL, and TSH-receptor antibody (TRAb), anti-thyroperoxidase and anti-thyroglobulin were negative. Thyroid ultrasound showed a mobile and well-defined gland, with slightly increased dimensions: right lobe - 55x20x27mm; left lobe – 52x18x24mm (longitudinal/transverse/anteroposterior diameters); isthmus - 9mm - diffusely hypoechoic, heterogeneous and hypovascular, with no nodules or adenomegaly. Thyroid scintigraphy was not performed. He started treatment with thiamazole 30mg/day and prednisolone 20mg/day.

On the 11th day of treatment, the patient had worsening of his cardiac condition with ventricular tachyarrhythmia and syncope, requiring hospitalization in the intensive care unit (ICU) for 17 days and an implantable cardioverter-defibrillator placement. During this period, amiodarone was replaced by dofetilide, bisoprolol was initiated (2.5 mg twice daily) and thiamazole and prednisolone dosages were increased (45 mg and 40 mg daily, respectively). On discharge, there was a substantial clinical and biochemical improvement: TSH <0.01 mIU/L, FT4 2.25 ng/dL, FT3 6.23 pg/mL.
On the 50th day of treatment, despite some clinical improvement, the laboratory check showed an increase in FT4 and FT3 (2.37 ng/dL and FT3 7.28 pg/mL, respectively) leading to a further increase in thiamazole dosage (60mg/day).

On the 72nd day, he presented worsening cyanosis and tiredness, palpitations, peripheral tremor as well as cushingoid facies and the analytical results showed: TSH <0.01 mIU/L, FT4 3.95 ng/dL, FT3 12.19 pg/mL. There was some concern regarding patient treatment compliance as he admitted skipping some of the cardiology pills. Therefore, it was decided to hospitalize the patient to stabilize his clinical condition and ensure proper medication intake, increasing daily medical therapy dosages (thiamazole 75mg and dexamethasone 10mg) and introducing cholestyramine 16g/day and lithium 400 mg/day, as adjunctive therapies. Given the clinical and biochemical improvement (TSH <0.01 mIU/L, FT4 3.54 ng/dL, FT3 6.97 pg/mL), the patient was discharged three weeks later, on thiamazole 60mg, prednisolone 60mg, cholestyramine 16g and lithium 400mg daily.

For the following 15 days, he maintained his usual condition in NYHA class II-III. However, on the 119th day, the patient experienced abrupt worsening of cardiac condition, being unable to carry out any physical activity without discomfort and presenting with polynnea, severe bilateral peripheral edema, jugular vein distension, and weight gain (63.4Kg to 69.1 Kg). At this point, patient corroborated that all drugs were taken except for cholestyramine. He was admitted to the ICU and laboratory evaluation showed TSH < 0.01 mIU/L, FT4 5.00 ng/dL, FT3 9.9 pg/mL, urinary iodine 1080 mcg/24h.

Despite intense diuretic therapy and optimized thyrotoxicosis treatment (thiamazole 75mg, dexamethasone 10mg, cholestyramine 24g and lithium 800mg daily) no significant improvement was observed, and since drug dosages and treatment duration were already reaching reasonable risk vs. benefit, a multidisciplinary meeting – endocrinology, endocrine surgery, cardiology and nephrology teams - was held to assess definitive therapeutic possibilities. Radioiodine therapy was ruled out due to his high urinary iodide and salvage thyroidectomy was declined in face of patient’s cardiac condition and severe thyrotoxicosis. Plasmapheresis, as a bridge to surgery, turned to be an impractical option, as the necessary volume overload would put the patient at an unacceptable risk.

Thyroid arterial embolization of the four thyroid arteries was decided as a salvage therapy, which the patient accepted, after informed consent. The procedure was performed, on September 2019, by the interventional radiology team with polyvinyl alcohol 250–300-micron particles using an hybrid angiography and CT scanner (Nexaris, Siemens, Marburg, Germany).
shown in Figures 1 and 2. Both inferior arteries and then the superior arteries were successfully embolized, using a microcatheter 2.7F (Progreat, Terumo, Tokyo, Japan). Procedure took approximately 2 hours and was done under local anaesthesia, with no immediate complications. Slight sore throat and burning sensation over the anterior neck were reported by the patient in the next few days, but without relief medication needed.

On the 3rd day after TAE, blood tests showed TSH 0.01 mIU/L, FT4 5.0 ng/dL, FT3 20.0 pg/mL, and thiamazole was replaced by propylthiouracil. Analytical and clinical improvement were notably progressive and hence cholestyramine and lithium were stopped, dexamethasone was gradually reduced and switched to hydrocortisone on physiologic doses, and propylthiouracil was reduced accordingly.

Four months after TAE, no tachycardia episodes were reported and the patient referred physical condition improvement with growing tolerance for exercise. At this point, he had cortisol 9.1 mg/dL, ACTH 22.7 pg/mL, TSH 25.2 mIU/L, FT4 0.63 ng/dL, and FT3 3.06 pg/mL; hydrocortisone and propylthiouracil were stopped and levothyroxine 25 mcg was introduced.

Nine months after TAE, levothyroxine was suspended and thyroid function reevaluation showed TSH 2.82 mIU/L, FT4 1.04 ng/dL, and FT3 3.69 pg/mL. At the last clinical observation, more than a year and a half after TAE, the patient was on bisoprolol 5 mg od, dofetilide 500 mcg bid, bosentan 125mg bid, furosemide 20 mg od, apixaban 2.5 mg bid, being able to carry out considerable physical effort as he was before the AIT episode. Laboratory evaluation showed TSH 3.5 mIU/L, FT4 1.0 ng/dL, FT3 2.9 pg/mL, Urinary iodine 160 mcg/dL (100-199). Thyroid ultrasound performed 18 months after embolization showed a homogeneous gland measuring right lobe - 54x18x17mm (volume of 9cc, volume reduction of 44%); left lobe – 50x14x14mm (volume of 4cc, volume reduction of 58%) (longitudinal/transverse/anteposterior diameters); isthmus - 5mm (reduction of 44%) – the diffusely hypoechoic, heterogeneous and hypovascular echogenicity of the thyroid gland was replaced with a standard hyperechoic echogenicity, with no signs of scaring or nodules (Figure 4).

**Discussion**

AIT is recognized as a diagnostic and management challenge, sometimes leading to life-threatening complications. [Yiu KH W. et al. 2009] The lipophilicity of the drug results in tissue storage for long periods, the reason why thyrotoxicosis may take several months to subside after amiodarone is suspended. [Bogazzi Z. et al. 2001] The decision to maintain or discontinue amiodarone is a matter of debate in AIT. In our patient, the drug was stopped early in the course

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of disease, according to the Cardiologist’s advice. AIT is traditionally classified in two main types: type 1 AIT, characterized by an iodine-induced hyperthyroidism, less common; and type 2 AIT, as a result of destructive thyroiditis. Sometimes, mixed forms are recognized, where both pathogenic mechanisms are present. Thyroid scintigraphy was not performed but the doppler ultrasound showed a hypovascular thyroid, characteristic of type 2 AIT. [Bartalena L. et al. 2018] In addition, the time elapsed from the onset of amiodarone to development of thyrotoxicosis, the absence of goiter and TRAb are also characteristic of this type of AIT. [Bartalena L. et al. 2018] However, increased thyroid dimensions on ultrasound, the persistently high levels of FT3, the resistance to treatment with high doses of glucocorticoids for such long period and the maintenance of euthyroidism even after cure, do not favor this hypothesis. [Bartalena L. et al. 2018] Due to the patient’s cardiac condition, thyrotoxicosis’ exuberance and urgency to ameliorate symptoms, a mixed type AIT was assumed and thionamide and glucocorticoids were started, as they are the mainstay therapy, aiming to address both forms of AIT. [Bartalena L. et al. 2018] As already mentioned, treatment’s refractoriness with worsening of patient’s clinical and analytical condition, despite the institution of high-dose glucocorticoids, forced an increase in thionamide’s dose in an attempt to stabilize thyroid hormones’ levels, even considering its potential toxic effects which remained monitored with complete hemogram and measurements of liver enzymes. In cases of poor response or refractoriness to this therapy, adjunctive medical treatment is required, namely when a euthyroid state is urgent to achieve. Cholestyramine, by interfering with enterohepatic circulation and recycling of thyroid hormones, can reduce its levels [9] and lithium decreases thyroid hormone secretion [Bogazzi F. et al. 2010]. Hence, these two drugs were added to our patient, but no clear efficacy was observed despite increasing dosages. Potassium perchlorate by inhibiting thyroidal iodine uptake, may increase response to thionamides [Wolff J. 1998], but this was not an option owing to its unavailability. Sodium perchlorate, as an alternative, was also unavailable. The refractoriness of thyrotoxicosis after several months of multimodal medical therapy and the patient poor cardiac condition demanded other approach to achieve euthyroidism. Thyroidectomy was then considered as the European Thyroid Association recommends [Bartalena L. et al. 2018]. Studies concerning thyroidectomy as treatment for AIT patients are lacking, data on survival for these patients are heterogeneous, and no recognized factors could identify patients who
might benefit from it. Recently, D. Cappellani et al. (2020) compared outcomes on survival of total thyroidectomy vs. medical therapy in AIT patients, demonstrating that overall mortality and cardiac-specific mortality were lower in the surgery group, even before euthyroidism was restored. [Cappellani D. et al. 2020]

Given our patient’s cardiac condition and hyperthyroid state, performing thyroidectomy would require intraoperative monitoring of his hemodynamic status to preclude the dreadful possibility of a thyroid storm through invasive blood pressure monitoring and echocardiographic imaging of the heart. Furthermore, the risk of associated dysrhythmias caused by release of catecholamines and even thyroid hormones due to gland manipulation was a major concern. In order to prevent these complications, these physiologic responses would have to be blunted with further medication. The mandatory need to avoid any further increase in pulmonary arterial pressure, excessive adrenergic stimulation and maintain systemic vascular resistance would turn to be a major challenge while performing thyroidectomy in our patient.

After considering these cumbersome facts, the medical team decided to postpone thyroidectomy as definitive treatment, but only after stabilization of thyroid hormone levels to near normal limits, which would be possible after apheresis, in order to minimize some of the described risks above. Plasmapheresis can be used in patients with severe thyrotoxicosis when first-line therapies fail or cannot be used, leading to a decrease in the hormone concentrations. This effect is transient and hormone levels typically rise again in the next few days. [Padmanabhan A. et al. 2019] When considering apheresis, some complex issues have arisen in this case. On one hand, the procedure would imply volume overload, a further increase in pulmonary arterial pressure (already at 120 mmHg) and excessive adrenergic stimulation, which the patient would not be able to tolerate. [El-Asmar J.M. et al. 2020] On the other hand, the necessary fluids would dilute blood hemoglobin (in this patient around 21.0 g/dL) which would compromise oxygenation. [Padmanabhan A. et al. 2019] At this point, plasmapheresis turned to be an impractical option, and so was thyroidectomy.

Thyroid arterial embolization (TAE) appeared as a salvage therapy in this patient. It has been used for critically ill patients whose condition is refractory to medical therapy and too unstable to undergo thyroidectomy. [Xiao H. et al. 2002; Zhao W. et al. 2009] However, TAE is a procedure without established protocols and has been used in a few cases of thyroid disease, namely large goiters, Graves’ disease, and thyroid carcinoma, although rarely reported in AIT, with no published controlled trials. [Dedecjus M. et al. 2009; Brzozowski K. et al. 2012] Most
authors describe its effects as similar to subtotal thyroidectomy, suggesting that the number of embolized arteries should depend on arterial supply evaluated by previous angiography. [Galkin E.V. et al. 1994; Xiao H. et al. 2002] Main facts about previously reported TAE for the treatment of thyrotoxicosis are summarized in table 1.

In this patient, due to the emergent need to control thyroid function we decided to perform TAE of the four thyroid arteries. To the best of our knowledge, few case reports in the literature have described the embolization of the four thyroid arteries in AIT context [Zhao W. et al. 2009; Rohr A. et al. 2016].

The rise in thyroid hormone levels on the first week after the procedure was expected, owing to the release of thyroid hormones due to ischemia and necrosis of embolized thyroid tissue. Although TAE reduces thyroid blood supply, the veins remain unconstrained and colloid from dying thyrocytes (comprising thyroglobulin, T3, T4 and, probably, other biochemical compounds) gets into circulation. [Dedecjus M. et al. 2009] Although the rise in thyroid hormone concentration was related to the destructive process due to the procedure, thiamazole was replaced by propylthiouracil as the latter has inhibitory effect on T4 conversion to T3. Despite this, no worsening of symptoms of hyperthyroidism occurred. Neck pain referred by the patient is reported in nearly 85% of the cases.[ Brzozowski K. et al. 2012] Parathyroid glands are believed to be supplied by blood vessels originating from inferior thyroid arteries. As a prevention of potential parathyroid function harm, it has been recommended not to embolize both of them. [Kaminski G. et al. 2014] Concerning this fact, calcium homeostasis was evaluated immediately after the procedure and in the subsequent blood analysis, but no significant changes in serum calcium levels were observed.

Given the four thyroid arteries embolization, permanent hypothyroidism could be expected. However, it turned out to be transitory as the patient stayed euthyroid after levothyroxine withdrawal. The authors believe that incomplete ischemic destruction and/or neovascularization processes or partial recanalization of embolized arteries might be the explanation. [Xiao H. et al. 2002]

In conclusion, thyroid arterial embolization proved to be the only effective treatment in this patient. Endovascular embolization techniques are a valuable therapeutic option and can be considered in cases where standard forms of treatment are ineffective or involve unacceptable risks.
Statement of Ethics

Patient has given his written informed consent to publish his case (including publication of images)

Conflict of Interest Statement

The authors have no conflicts of interest to declare.
References


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Fig. 1. Angiography - Left superior thyroid artery before (A) and after (B) embolization
Fig. 2. CT scan confirming left superior thyroid artery vascularization
Fig. 3. Analytical and therapeutics evolution. ATA – Antithyroid agent; CCT – Corticosteroid; TMZ – Thiamazol; PTU – Propylthiouracil; PDN – Prednisolone; DXM – Dexamethasone; HC - Hydrocortisone; CLT – Cholestyramine; L – Lithium; LVT – Levothyroxine

Analytical and therapeutics follow-up
Reference values: FT4 0.7-1.48 ng/dL; FT3 1.88-3.18 pg/mL
Fig 4. Thyroid ultrasound performed before (A) and 18 months after thyroid embolization (B) depicting a volume reduction of the right lobe of 44%, of the left lobe of 58% and of the isthmus of 44%.
Table 1. Previously reported thyroid artery embolization for treatment of thyrotoxicosis. GD – Graves’ disease; HT - hyperthyroidism; NI – No information; TG – Toxic Goiter

<table>
<thead>
<tr>
<th>Authors</th>
<th>Disease</th>
<th>Number of patients</th>
<th>Number of embolized arteries</th>
<th>Arteries embolized</th>
<th>Procedure Lenght (hours)</th>
<th>Surgery</th>
<th>Complications (n)</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Dedecjus et al.</td>
<td>TG</td>
<td>10</td>
<td>3</td>
<td>2 superior + 1 inferior</td>
<td>&lt;1</td>
<td>Thyroidectomy in the next 36h</td>
<td>Hematoma 2, Fever 2, Neck pain 2</td>
<td>Shorter operation time, Reduced drainage and blood loss</td>
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<tr>
<td>Xiao et al.</td>
<td>GD</td>
<td>22</td>
<td>2 in 17</td>
<td>All 2 superior + 1 inferior in 5</td>
<td>&lt;1.5</td>
<td>Thyroidectomy in 6 2 weeks after</td>
<td>Neck pain 22, Fever 19</td>
<td>Thionamide maintenance 2</td>
</tr>
<tr>
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<td>GD</td>
<td>28</td>
<td>3 in 22</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>Neck pain 28, Transient hypocalcemia 1</td>
<td>Euthyroidism 22, Reembolization 2, Thyroid elimination 5, Recurrence 1</td>
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<td></td>
<td></td>
<td></td>
<td>2 in 6</td>
<td>NI</td>
<td>NI</td>
<td>None</td>
<td>None</td>
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<td>GD</td>
<td>5</td>
<td>2 in 67%</td>
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<td>8</td>
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<td></td>
<td>NI</td>
<td>Neck pain 2, Fever 12</td>
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<td>Volume reduction by half</td>
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