CASE REPORT

Amiodarone-induced thyrotoxicosis: type 1 or type 2?

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SUMMARY

A 69-year-old man presented with a 6-week history of shortness of breath on exertion, unintentional weight loss, altered bowel habits and lethargy. He was diagnosed with atrial fibrillation 2 years previously and started on amiodarone and warfarin. He subsequently reverted to sinus rhythm and his medication was stopped 1 year prior to presentation. He denied history of thyroid dysfunction. On examination, he had a small firm goitre of grade I. His skin was warm and sweaty. Thyroid function tests showed him to be thyrotoxic. He was started on carbimazole 20 mg; however, he further became significantly thyrotoxic. Given the severity of his presentation and lack of any clinical or biochemical improvement, oral prednisolone 30 mg once daily was coadministered. His symptoms subsequently resolved and he became euthyroid. The prednisolone was tapered down and stopped while the carbimazole was incrementally reduced to 10 mg daily.

BACKGROUND

Amiodarone, a benzofuranic iodine-rich agent, is a widely used antiarrhythmic drug for atrial and ventricular arrhythmias, especially if not controlled with standard therapies. It has a number of well-known side effects including thyroid dysfunction: either hypothyroidism or hyperthyroidism. It causes thyroid dysfunction in 15–20% of cases.¹ Amiodarone chemically resembles thyroxine and its binding to the nuclear thyroid receptor might contribute to some of its pharmacological and toxic actions.² Although amiodarone-induced hypothyroidism does not pose many problems, amiodarone-induced thyrotoxicosis (AIT) type 1 or 2 is a diagnostic and therapeutic challenge. Since the physical and psychological consequences of long-term therapy with either condition are too large to ignore, it is crucial to differentiate between the two types of AIT. A clinical conundrum arises in trying to diagnose patients with no previous thyroid function testing and in deciding appropriate treatment. This article is to make clinicians aware of the entity of AIT and how to manage a case where there is ambiguity between AIT type 1 and 2.

CASE PRESENTATION

A 69-year-old man presented to the endocrinology clinic with a 6-week history of shortness of breath on mild exertion and unintentional weight loss, losing a stone in weight. He also reported altered bowel habits with loose stools and feeling generally lethargic. The patient denied any thyroid problems in the past; however, he had not had his thyroid

function checked previously. He also denied any family history of thyroid disorders. His medical history included atrial fibrillation, diagnosed 2 years previously. He was started on amiodarone and warfarin but he reverted to sinus rhythm spontaneously at which point the amiodarone and warfarin were stopped (1 year prior to his presentation to the endocrinology clinic). On examination, the patient had a small firm goitre of grade I according to WHO classification. His heart rate was found to be irregular at 90 bpm. His skin was felt to be warm and sweaty. At that time, when his thyroid function was assessed, he was found to be thyrotoxic; he did not have a T3 level or thyroid peroxidase antibody level checked. A clinical impression of AIT was made; however, the clinicians were unable to clarify whether this was type 1 or 2. The patient had already been started on carbimazole 20 mg once daily by his general practitioner recently so an iodine uptake scan was not beneficial. Given his presentation with worsening thyrotoxicosis and no improvement biochemically or clinically a decision was made to treat both types of AIT.

INVESTIGATIONS

- ▶ 15 August 2012—thyroid-stimulating hormone (TSH) 2.6, free T4 not checked
- ▶ 27 June 2013—TSH: suppressed, free T4: 66.9
- ▶ 18 July 2013—TSH: suppressed, free T4: 34.4; antithyroid peroxidase <50 (normal <50)
- ▶ 21 August 2013—TSH: undetectable, free T4: 27.3
- ▶ Ultrasound of the thyroid—small nodule in left lobe of thyroid measuring 0.8 cm in diameter
- ▶ 08 October 2013—TSH: undetectable, free T4: 20.4

Normal values: TSH, 0.4–4.5 mU/L; T4, 10–24 pmol/L.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is related to those conditions that could cause hyperthyroidism. This could be either a coincidental underlying autoimmune condition such as Grave's disease, a viral thyroiditis or toxic multinodular goitre or adenoma. However, given the development of symptoms following recent amiodarone use, AIT is the most likely diagnosis. The differentiation between the two types of AIT is difficult and discussed below.

TREATMENT

The patient's carbimazole was increased to 40 mg and he was concurrently started on prednisolone 30 mg once a day. He was reviewed a few weeks

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later in the clinic and showed significant improvement with less symptoms and features of thyrotoxicosis. Owing to his improvement his prednisolone was slowly tapered down and stopped. His carbimazole was incrementally reduced until he was stable on a maintenance dose of 10 mg once a day.

OUTCOME AND FOLLOW-UP

On his last appointment, the patient was clinically and biochemically euthyroid. He stated that his symptoms had settled since the start of carbimazole and prednisolone. His weight has remained stable during the course of his treatment. On examination, there was no tremor, sweating or heat intolerance. His prednisolone was tapered down and completely stopped after his last appointment. His carbimazole was further reduced to 10 mg once a day. He remains stable and due for further follow-up in the clinic with a view to stopping his carbimazole completely.

DISCUSSION

AIT is the term given to thyrotoxicosis arising either during or following amiodarone treatment in patients. Amiodarone is structurally similar to thyroxine, which contributes to its effects on the thyroid gland. It can cause hypothyroidism and hyperthyroidism.³ The thyrotoxicosis is mediated by amiodarone's iodine content.⁴ In each 200 mg tablet, there is 75 mg of iodine (37% of amiodarone's mass) and approximately 10% of the iodine is released as free iodide daily.^{5 6} The estimated half-life of amiodarone is between 50 and 100 days.⁷ The effects of amiodarone on the thyroid gland can be seen within a few weeks of starting treatment and/or up to several months after its discontinuation.^{8 9} It may occur up to 3 years after treatment initiation.¹⁰ However, the usual time period is between 2 and 47 months.¹¹ The signs and symptoms of AIT are several and shown in box 1.⁴ Cardiac manifestations may be absent due to amiodarone's effect on the heart.⁴

AIT can be divided into two types: AIT type 1 is a form of iodine-induced hyperthyroidism whereas AIT type 2 is a drug-induced destructive thyroiditis.¹ Table 1 presents different features of the two types.¹² There are reports that mixed forms do exist and may be caused by both pathogenic mechanisms.¹ AIT type 1 is more common in iodine deficient parts of the world such as Europe and usually occurs in abnormal thyroid

Table 1 Different features of type 1 2 amiodarone-induced thyrotoxicosis¹¹

	Type 1	Type 2
Underlying thyroid abnormality	Yes	No
Goitre	Multinodular or diffuse goitre	Small, firm and sometimes tender
Pathogenesis	Excess hormone synthesis	Excess release of preformed hormone
Thyroidal RAI uptake	Normal/raised	Very low
Thyroid ultrasound	Nodular, hypoechoic	Normal/increased volume

glands.¹³ It affects patients with latent or known thyroid disorders, such as Grave's disease, diffuse goitre and nodular goitre.⁸ It results in excessive, uncontrolled synthesis of thyroid hormone by autonomously functioning thyroid tissue in response to iodine.⁸ A colour flow Doppler sonography will show a hyper-functioning gland, hypervascularity and excess thyroid hormone synthesis.¹⁴ It usually responds to thionamides. However, sometimes potassium perchlorate is added to increase the response to thionamides by inhibiting thyroid iodine uptake.¹

However, AIT type 2 is prevalent in iodine sufficient parts of the world, such as the USA and the UK.¹³ It develops in apparently normal thyroid glands. In this type, amiodarone exerts direct cytotoxic effects on thyroid follicles and triggers inflammation.^{5 14–17} As a result of follicular disruption, preformed thyroid hormones are released.^{5 14–17} It is difficult to predict, has an acute onset and may develop at any time during treatment, often increasing in severity over a short period.¹³ A colour flow Doppler sonography will show decreased blood flow through the gland.⁸ It is best treated by oral glucocorticoids to settle the inflammation. The response very much depends on the thyroid volume and the severity of thyrotoxicosis. Mixed/indeterminate forms may require a combination of thionamides, potassium perchlorate and steroids.

Distinction between the two types is important as specific treatment exists for both. Choosing the wrong therapy will lead to ineffective or delayed response and may expose patients to unjustifiable drug side effects. Diagnosis of the two types is made on the basis of several factors such as physical examination (presence of goitre in type 1), review of whether previous thyroid function tests have shown abnormality prior to the start of amiodarone, ultrasonography (hypervascularity noted in type 1, absent vascularity in type 2), antibody tests (thyroid peroxidase antibodies, thyroglobulin antibodies and thyroid stimulating immunoglobulin—when positive will lead to diagnosis of type 1) and thyroid radioactive iodine (RAI) uptake values.⁸ Thyroid RAI uptake values are unreliable but are generally normal or increased

Box 1 Signs and symptoms⁴

Non-cardiac signs

- Unexplained weight loss
- Tremor
- Muscle weakness
- Low-grade fever
- Restlessness
- Enlarging goitre

Cardiac signs

- Sinus tachycardia
- Atrial fibrillation
- Ventricular tachycardia
- Angina
- Heart failure

Laboratory signs

- Total and free T4 levels increased
- Total and free T3 levels increased
- Thyroid-stimulating hormone dramatically decreased

Table 2 Management of amiodarone-induced thyrotoxicosis: type 1 and 2⁸

Type 1	Type 2
Thionamide (eg, carbimazole ~30 mg/day or propylthiouracil ~300 mg/day) for as long as needed	Prednisolone 30–40 mg/day, taper over 2–3 months
Potassium perchlorate (perchloracaps 200 mg tablets), no more than 5/day. Stop or taper after 30 days	

in type 1 despite the iodine load and typically very low/suppressed in type 2.⁸ Interleukin 6 has shown to be a better marker of thyroid gland destruction. It is markedly elevated in patients with type 2 AIT, and normal or minimally increased in type 1.¹⁸ However, exceptions to this rule are common, thus limiting the clinical significance of this test. So far, colour flow Doppler sonography has shown to have better efficacy for the rapid and early diagnosis of AIT type 1 and 2.

Management of AIT is challenging due to the difficulty in diagnosing the correct type. Sometimes, if differentiation is not possible, it is safe to treat for both with a combination of steroids and thionamide with a view to weaning down one over the other and assessing response. The decision to stop amiodarone also presents a dilemma because the patient may need it to control his/her arrhythmia. It is also important to bear in mind the long half-life and incidence of late onset AIT after discontinuation of amiodarone. Unless amiodarone is ineffective in controlling the arrhythmia, it is usually continued while treating AIT. A summary of medical management is presented in table 2.

Learning points

- ▶ Amiodarone-induced thyrotoxicosis (AIT) is common and should be suspected in anyone who presents with symptoms of thyrotoxicosis and has a history of taking amiodarone.
- ▶ All patients started on amiodarone should have free thyroxine and thyroid-stimulating hormone levels measured at start and thereafter at 3 or 4 months interval during treatment and for at least 1 year after amiodarone has been discontinued.
- ▶ It is important to differentiate between the two types of AIT. If this is not possible, treat with a trial of thionamides and steroids to control symptoms and gradually reduce one to see if it keeps the patient's symptoms under control.
- ▶ It is important to take into account the long-term effects of thionamides and steroids, and a decision regarding tapering down or stopping one should become a priority once the patient's symptoms are stable to avoid possible sequelae.
- ▶ Patients with AIT should be ideally managed in tandem by a cardiologist and an endocrinologist.

RAI is usually unfeasible in AIT because iodine uptake by the gland is inhibited by the iodine of amiodarone. However, thyroidectomy represents a valid option in resistant cases or in very sick patients who must continue amiodarone.¹

Competing interests None.

Patient consent Obtained.

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