Type 2 amiodarone-induced thyrotoxicosis in a patient with positive thyroid-stimulating hormone-receptor antibodies

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Introduction

The authors present a case of type 2 amiodarone-induced thyrotoxicosis in a 55-year-old man with positive thyroid-stimulating hormone-receptor antibodies, who had not been taking amiodarone for 8 months. This case highlights that the presence of thyroid-stimulating hormone-receptor antibodies does not necessarily imply the development of Graves' disease. It also demonstrates that amiodarone-induced thyrotoxicosis can present several months after withdrawal of amiodarone treatment. In this case, the rapid and dramatic drop in free triiodothyronine levels with glucocorticoid therapy suggested type 2 amiodarone-induced thyrotoxicosis.

Discussion

Amiodarone is one of the most potent antiarrhythmic drugs (Barra et al, 2022). Amiodarone therapy can be complicated by hypothyroidism and hyperthyroidism in 5–10% and 0.9–10% of cases respectively (Trohman et al, 2019).

There are two main forms of amiodarone-induced thyrotoxicosis. Type 1 more commonly occurs in cases of an abnormal thyroid gland and results from excess iodine-induced synthesis of thyroid hormones. The most common causes of underlying thyroid disease detected in type 1 amiodarone-induced thyrotoxicosis are Graves' disease and toxic nodular goitre (Trohman et al, 2019). Type 2 amiodarone-induced thyrotoxicosis is a destructive thyroiditis that results in the release of preformed thyroid hormones, usually occurring in patients

Case report

A 55-year-old man with a past medical history of atrial fibrillation presented to the emergency department with palpitations, fine tremor of the outstretched hands, loose stools and weight loss. He admitted to stopping amiodarone of his own accord 8 months before presentation. He was in fast atrial fibrillation (ventricular response rate of 153 beats per minute).

Laboratory investigations on admission revealed a thyroid-stimulating hormone level of <0.008 micIU/ml (normal values 0.3–3.0 micIU/ml), a free thyroxine level of 71.59 pmol/litre (normal values 11.9–20 pmol/litre) and a free triiodothyronine level of 30.2 pmol/litre (normal values 3.5–6.5 pmol/litre). The patient was euthyroid 8 months before this presentation. The impression was of amiodarone-induced thyrotoxicosis, as there were no features of Graves' disease on physical examination, so the patient was initiated on carbimazole 30 mg daily and prednisolone 30 mg daily. Rate control of the patient's atrial fibrillation was achieved using carvedilol. The patient had positive thyroid-stimulating hormone-receptor antibodies at 3.7 IU/litre (normal values 0.1–1.0 IU/litre) and minimally elevated IL-6 levels at 8.6 pg/ml (normal value <7 pg/ml). An ultrasound scan demonstrated slight enlargement of the thyroid gland with no evidence of hypervascularity.

After 17 days of combined carbimazole and glucocorticoid treatment, a repeat thyroid function test revealed a free triiodothyronine of 5.6 pmol/litre, ie >50% decrease in pre-treatment values. Despite his positive thyroid-stimulating hormone-receptor antibodies, the rapid decline in free triiodothyronine levels observed on prednisolone suggested a diagnosis of type 2 amiodarone-induced thyrotoxicosis. The patient was advised to stop carbimazole and continue treatment with glucocorticoids. He remained clinically well with further significant biochemical improvement in his thyroid function tests (Table 1). He was eventually rendered euthyroid and prednisolone was tailed down and stopped after 2 months.

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Table 1. Serial free thyroxine, free triiodothyronine and thyroid-stimulating hormone trend from the patient's initial presentation with thyrotoxicosis to eventual recovery to a euthyroid state

Date	Thyroid-stimulating hormone (micIU/ml)	Free thyroxine (pmol/litre)	Free triiodothyronine (pmol/litre)	Management
21 March 2022	<0.008	71.59	30.2	Initiation of carbimazole and prednisolone
7 April 2022	0.012	27.5	5.6	Cessation of carbimazole therapy
21 April 2022	0.089	12.54	4.0	
29 April 2022	0.426	13.8	N/A	
31 May 2022	0.549	15.65	N/A	Cessation of prednisolone
26 August 2022	1.109	13.75	N/A	

who do not have underlying thyroid disease. It may last for up to around 3 months until stores of thyroid hormones are depleted, a process which is hastened with glucocorticoid therapy (Trohman et al, 2019).

Differentiating between type 1 and 2 amiodarone-induced thyrotoxicosis requires a detailed history and clinical examination, and is also guided by laboratory and imaging investigations (Bartalena et al, 2018). Table 2 summarises the main diagnostic criteria for these types of amiodarone-induced thyrotoxicosis.

While these criteria aid diagnosis, differentiating type 1 and type 2 amiodarone-induced thyrotoxicosis may be challenging as some patients may have features of both subtypes and none of the proposed methods accurately discriminate between both subtypes (Tsang and Houlden, 2009; Wass et al, 2022). In practice, most patients initially present with an undefined form of amiodarone-induced thyrotoxicosis. In such cases, the European Thyroid Association guidelines for the management of amiodarone-induced thyrotoxicosis recommend either starting with thionamides +/- perchlorate, and adding glucocorticoids if there is no improvement in 4–6 weeks, or starting immediately with combined thionamide and glucocorticoid therapy (Bartalena et al, 2018). A review by Han et al (2009) recommends the latter approach. The response to glucocorticoid therapy in patients with type 2 amiodarone-induced thyrotoxicosis is usually rapid, with a dramatic improvement in free triiodothyronine levels seen within 1–2 weeks.

In the current case, initial laboratory investigations indicated features of type 1 amiodarone-induced thyrotoxicosis in view of positive thyroid-stimulating hormone-receptor antibodies and very minimally elevated levels of IL-6. However, the significant improvement in free triiodothyronine levels within 2 weeks of combined glucocorticoid

Table 2. Characteristics of type 1 and type 2 amiodarone-induced thyrotoxicosis

Criteria	Amiodarone-induced thyrotoxicosis 1	Amiodarone-induced thyrotoxicosis 2
Mechanism	Excessive hormone production	Destructive thyroiditis
Underlying thyroid abnormality	Often present	Usually absent
Colour flow Doppler ultrasound	Increased vascularity	No hypervascularity
Thyroid autoantibodies	Often present	Usually absent
Thyroid radioiodine uptake	Increased	Decreased
Interleukin-6 levels	Often normal	Usually twice the upper limit of normal
Response to glucocorticoids within 4 weeks	No	Yes
Subsequent hypothyroidism	No	Possible

Adapted with permission from Han et al (2009)

Learning points

- A detailed history, clinical examination and pertinent investigations can help differentiate between type 1 and type 2 amiodarone-induced thyrotoxicosis.
- A decline in serum free triiodothyronine levels by >50%, compared to pre-treatment values after 2 weeks of combined thionamide and glucocorticoid therapy initiation, suggests a diagnosis of type 2 amiodarone-induced thyrotoxicosis.
- A positive thyroid-stimulating hormone-receptor antibody status does not necessarily imply the development of Graves' disease or type 1 amiodarone-induced thyrotoxicosis in patients with a history of amiodarone use.
- Amiodarone-induced thyrotoxicosis may develop several months after amiodarone withdrawal, because of its long half-life.

and thionamide treatment initiation, the absence of hypervascularity on ultrasound and the long onset time of thyrotoxicosis following amiodarone's initiation and subsequent withdrawal favoured a diagnosis of type 2 amiodarone-induced thyrotoxicosis. In addition, this case highlights that the presence of thyroid-stimulating hormone-receptor antibodies does not necessarily imply the development of Graves' disease, a finding also demonstrated by Suzuki et al (2021).

Tomisti et al (2014) recommend monitoring thyroid function tests for at least 2 years after amiodarone withdrawal because it has a long terminal half-life (up to 60 days) (Connolly, 1999). The onset of type 2 amiodarone-induced thyrotoxicosis can occur for much longer after amiodarone withdrawal, while the onset of type 1 amiodarone-induced thyrotoxicosis after amiodarone withdrawal is rare (Tomisti et al, 2014).

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