Chapter 4
Amiodarone-Induced Hyperthyroidism

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Objectives

Amiodarone is a potent antiarrhythmic drug that is associated with a wide array of adverse effects, including both hypothyroidism and hyperthyroidism. Here, we report the case of a 65-year-old man who was started on amiodarone for recurrent atrial fibrillation and 2 years later developed hyperthyroidism. We briefly review the normal changes in thyroid function tests that are seen with amiodarone. We then discuss the proposed etiologies, evaluation, and treatments of patients with amiodarone-induced thyrotoxicosis (AIT) type 1 and type 2.

Case Presentation

A.B. is a 65-year-old man with a past medical history of hypertension, atrial fibrillation, and hyperlipidemia, but no history of thyroid disease. He was referred to the endocrine clinic for evaluation of probable amiodarone-induced hyperthyroidism. Five years ago, the patient developed recurrent atrial fibrillation. After several failures of cardioversion, he was placed on amiodarone. Two years later, he noted weakness in his legs while walking or climbing stairs, and difficulty sleeping, hyperdefecation, and mild nervousness. He had no significant weight loss, palpitations, tremor, dysphagia, or neck pain.

Prior to the initiation of amiodarone therapy and for almost the first 2 years of it, the patient was euthyroid. Thyroid function tests drawn at the onset of the above symptoms revealed a thyroid-stimulating hormone (TSH) $< 0.02\ \mu U/mL$ (normal, 0.5–5.0), free thyroxine (T_4) 5.23 ng/dL (normal, 0.8–1.8), and triiodothyronine (T_3) 330 ng/dL (normal, 72–170).

On physical examination, the blood pressure was 110/68, and the pulse was 82 and irregularly irregular. Mild proptosis was present with full extraocular

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movements. The thyroid was enlarged approximately twofold, and it was firm and nontender. There were no discrete nodules appreciated and no bruits auscultated. Lungs, heart, and abdomen were unremarkable. The skin was warm and moist, there was no tremor, and deep tendon reflexes were normal.

Antithyroperoxidase (anti-TPO) and antithyroglobulin antibody titers were low, and thyroid-stimulating immunoglobulins (TSIs) activity was normal at 92% (normal, <125%). A thyroid sonogram revealed an enlarged right lobe and multiple small nodules, the largest being 1 cm in diameter. There was normal thyroidal blood flow on Doppler. A 24-hour radioiodine uptake was <0.1% (normal, 20–25%).

Background

Amiodarone is a class III antiarrhythmic agent that has been associated with a wide array of serious cardiac, pulmonary, hepatic, ocular, and thyroid side effects. Because about 37.5% of the mass of amiodarone is made up of iodine, a patient taking a daily dose of 200 mg of amiodarone consumes about 75 mg of organic iodine daily [1]. Metabolism of this amount of iodine releases an amount of free iodine into the circulation that is about 20 to 40 times higher than the daily iodine intake in the United States [1].

Although amiodarone therapy is associated with an increased risk of thyroid dysfunction, the majority of patients receiving amiodarone remain euthyroid, due to adjustments made in the body to handle the excess iodine load while maintaining normal thyroid function [1]. Also, amiodarone has direct inhibitory effects on peripheral T_4 to T_3 conversion, leading to a decrease in T_4 metabolism and concomitant elevation in serum total T_4 and free T_4. Even though total and free serum T_4 levels are high-normal or high, TSH levels are generally normal after the first few months of drug exposure. Amiodarone-treated patients remain euthyroid because the serum concentration of T_3, the thyroid hormone that interacts with target cells and mediates end-organ effects, is in the low-normal range [2]. The alterations in thyroid function tests are usually divided into acute (≤3 months) and chronic (>3 months) phases following the initiation of amiodarone therapy [1]. These adjustments are summarized in Table 4.1.

Table 4.1 Effects of amiodarone on thyroid function tests in euthyroid subjects [1]

Thyroid hormone	Acute effects (≤3 months)	Chronic effects (>3 months)
Total and free T_4	↑ 50%	Remains ↑ 20–40% of baseline
T_3	↓ 15–20%, remains in low-normal range	Remains ↓ 20%, remains in low-normal range
Reverse T_3	↑ >200%	Remains ↑ >150%
TSH	↑ 20–50%, transient, generally remains <20 mU/L	Normal

Thyroid dysfunction occurs in about 14% to 18% of patients receiving long-term amiodarone therapy, and either hypothyroidism or thyrotoxicosis can occur [3]. In iodine-sufficient parts of the world, such as the United States, hypothyroidism is more common compared to iodine-deficient areas where thyrotoxicosis prevails [4].

Amiodarone-Induced Thyrotoxicosis

Amiodarone-induced thyrotoxicosis (AIT) is usually divided into type 1 (iodine-induced) and type 2 (drug-induced thyroiditis). Table 4.2 summarizes the major differences between the two types.

Type 1

Type 1 typically appears after 1 to 2 years of therapy. It occurs in patients with underlying thyroid disease and is believed to be iodine-induced [1]. The high

Table 4.2 Comparison of amiodarone-induced hyperthyroidism types 1 and 2 [1]

Factor	AIT type 1	AIT type 2
Preexisting thyroid disease	Yes (either multinodular goiter or latent Graves' disease)	No
Physical examination	Goiter, 1 or more nodules	Normal to slightly firm; occasionally tender
Duration of amiodarone therapy	Shorter (1–2 years)	Longer (>2 years)
Thyroid function tests	High free T_4, T_3 normal or high	High free T_4, T_3 normal or high
Thyroid autoantibodies	Absent (unless Graves' disease is present)	Absent
Radioiodine uptake	Low	Very low
Thyroid ultrasound	Underlying thyroid disease (multinodular goiter, Graves' disease)	Normal or minimally enlarged; heterogeneous pattern
Color flow Doppler of thyroid	Increased parenchymal blood flow	Normal or decreased parenchymal blood flow
Serum interleukin-6	Normal or low	Elevated, (?only in iodine-deficient parts of the world)
Therapy	• Stop amiodarone if possible • High-dose antithyroid drugs; perchlorate; lithium	• Discontinuation of amiodarone may not be essential • Prednisone taper over >2 months • Lithium
Subsequent hypothyroidism	No	Often

iodine load from the drug triggers excess thyroid hormone synthesis and release (Jod-Basedow phenomenon) or, less commonly, the development of Graves' disease [1]. The mechanisms that mediate these effects are poorly understood.

Type 2

Type 2 typically appears after 2 years of therapy or longer in those without apparent preexisting thyroid disease [5]. It results from the direct cytotoxic effect of amiodarone and its metabolites on thyroid follicular epithelial cells, leading to a destructive inflammatory thyroiditis and the release of preformed thyroid hormone into the circulation [1].

Diagnosis

Distinguishing between type 1 and type 2 AIT may be difficult. Table 4.2 lists certain elements in the history as well as laboratory and diagnostic tests that may be helpful in the differentiation between the two types. For example, the presence of a preexisting multinodular goiter favors type 1 AIT. Although measurement of serum levels of interleukin-6 (IL-6) has been reported to be helpful as a marker of inflammation (and thus it would be elevated in type 2 AIT) [6], this has not been the experience of others [7, 8]. Color flow Doppler ultrasound assessment has emerged as an important diagnostic tool, as thyroidal blood flow is high in type 1 AIT and normal or low in type 2 AIT [9].

Treatment

If the diagnosis of AIT type 1 is confirmed by history and increased color Doppler flow, cessation of amiodarone therapy is usually recommended, unless life-threatening ventricular arrhythmias are present [1]. Large doses of antithyroid drugs including methimazole (40 to 80 mg/day) or propylthiouracil (PTU) (400 to 800 mg/day) have been used. Unfortunately, these drugs are less effective when the thyroidal iodine content is high, as is the case in AIT. Furthermore, because of an increased risk of side effects with high drug doses, including agranulocytosis [10], caution is advised. In patients who do not respond adequately to antithyroid drugs, potassium perchlorate, which blocks thyroidal iodine uptake, has been recommended as potential therapy [11]. Potassium or sodium perchlorate, however, is no longer available in the United States.

While some patients with mild type 2 AIT often have spontaneous resolution of their thyroid dysfunction and may not require treatment, prednisone is considered the treatment of choice for type 2 AIT, although there are no prospective randomized placebo-controlled trials [1]. Unlike the case with type 1 AIT, amiodarone discontinuation may not be necessary in type 2 AIT, and patients have been shown to improve with glucocorticoids while amiodarone therapy is continued [8]. Improvement in

thyroid function is often seen within 1 week of starting high doses of prednisone (40 to 60 mg/day). However, because exacerbations of hyperthyroidism can occur if steroids are tapered too quickly, glucocorticoid therapy should be slowly tapered over 2 to 3 months (e.g., by 10 mg every 2 weeks) [12].

If thyroid function tests do not improve after several months of treatment with either antithyroid drugs or glucocorticoids, it is very likely that the patient has a "mixed" form of AIT that may respond to both agents together [1]. When mixed AIT is suspected at the outset, or if the underlying diagnosis is uncertain, some have suggested starting patients on both antithyroid drugs and prednisone (0.50 to 1.25 mg/kg/day) [13]. If improvement in thyroid function is seen within 1 to 2 weeks, then the patient is likely to have type 2 AIT. Antithyroid drugs may then be withdrawn, and prednisone should be continued and tapered gradually; if the patient does not respond to both drugs within 2 weeks, then both antithyroid medications and prednisone could be continued until an improvement in thyroid function is noted over the next 1 to 2 months [1]. There are resistant cases that do not respond to either mono- or dual therapy with antithyroid drugs and/or glucocorticoids. Other therapeutic recommendations in such cases include lithium [14], plasmapheresis [15], and ultimately thyroidectomy [16].

How the Diagnosis Was Made

In the case described above, the suppressed serum TSH and elevated serum free T_4 and T_3 confirmed the diagnosis of hyperthyroidism, likely due to amiodarone therapy. Although the patient had what appeared to be proptosis, as well as a small goiter, the lack of clinical and laboratory data to support the diagnosis of Graves' disease (TSI <125%), and the long time lag between the initiation of amiodarone therapy and the onset of symptoms of hyperthyroidism (2 years later) suggested the diagnosis of amiodarone-induced hyperthyroidism type 2. The lack of previous history of thyroid disease, and the normal (rather than elevated) parenchymal blood flow on Doppler also favored a diagnosis of Type 2 AIT thyroiditis.

Amiodarone was continued, and the patient was started on prednisone 40 mg daily and responded promptly within 2 weeks with a decrease in fee T_4 from 5.13 to 2.3 ng/dL and total T_3 from 336 to 100 ng/dL. However, as prednisone was being tapered during the first month of therapy, the patient had a recurrence of hyperthyroidism necessitating a more protracted tapering period over 5 months, while amiodarone therapy was continued. He subsequently developed mild hypothyroidism, which persisted for several months, and he was ultimately started on thyroxine therapy with normalization of thyroid function.

Lessons Learned

1. A 200-mg dose of amiodarone contains 75 mg of organic iodine. Metabolism of this amount of iodine releases a concentration of free iodine into the circulation

that is about 20 to 40 times higher than the daily iodine intake in the United States [1].
2. The majority of patients receiving amiodarone remain euthyroid [1].
3. Thyroid dysfunction occurs in about 14% to 18% of patients receiving long-term amiodarone therapy, and results in either hypothyroidism or thyrotoxicosis [3].
4. In iodine-sufficient parts of the world, such as the United States, hypothyroidism is more common compared to iodine-deficient areas where thyrotoxicosis seems to prevail [4].
5. A miodarone-induced thyrotoxicosis (AIT) is divided into type 1 and type 2. The major differences between the two types are summarized in Table 4.1.
6. Type 1 AIT typically appears after 1 to 2 years of therapy and is believed to be iodine-induced; type 2 AIT typically appears after 2 years of therapy or longer and it results from the direct cytotoxic effect of amiodarone and its metabolites on the thyroid gland [1].
7. Distinguishing between type 1 and 2 AIT may be difficult (see Table 4.2).
8. Treatment for type 1 AIT usually involves discontinuation of amiodarone, unless a life-threatening ventricular arrhythmia is present. Also, large doses of antithyroid drugs are used to treat this type of AIT.
9. For patients with type 2 AIT, prednisone therapy with a slow taper over a period of $\geq$2 months is considered to be the treatment of choice.
10. When "mixed" AIT is suspected, some have suggested starting patients on both antithyroid drugs and prednisone [13].
11. There are severe cases that do not respond to either mono- or dual therapy with antithyroid drugs and/or glucocorticoids. Recommendations in such cases include lithium [14], plasmapheresis [15], and ultimately thyroidectomy [16].

References

1. Basaria S, Cooper DS. Amiodarone and the thyroid. Am J Med 2005;118(7):706–714.
2. Lambert MJ, Burger AG, Galeazzi RL, Engler D. Are selective increases in serum thyroxine (T4) due to iodinated inhibitors of T4 monodeiodination indicative of hyperthyroidism? J Clin Endocrinol Metab 1982;55:1058–1065.
3. Bogazzi F, Bartalena L, Gasperi M, Braverman LE, Martino E. The various effects of amiodarone on thyroid function. Thyroid 2001;11(5):511–519.
4. Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. Ann Intern Med 1997;126(1):63–73.
5. Savoie JC, Massin JP, Thomopoulos P, Leger F. Iodine-induced thyrotoxicosis in apparently normal thyroid glands. J Clin Endocrinol Metab 1975;41(4):685–691.
6. Bartalena L, Grasso L, Brogioni S, Aghini-Lombardi F, Braverman LE, Martino E. Serum interleukin-6 in amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 1994;78(2):423–427.
7. Eaton SE, Euinton HA, Newman CM, Weetman AP, Bennet WM. Clinical experience of amiodarone-induced thyrotoxicosis over a 3-year period: role of colour-flow Doppler sonography. Clin Endocrinol (Oxf) 2002;56(1):33–38.
8. Daniels GH. Amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 2001;86(1):3–8.

9. Bogazzi F, Bartalena L, Brogioni S, et al. Color flow Doppler sonography rapidly differentiates type I and type II amiodarone-induced thyrotoxicosis. Thyroid 1997;7:541–545.
10. Rosove MH. Agranulocytosis and antithyroid drugs. West J Med 1977;126(5):339–343.
11. Newnham HH, Topliss DJ, Le Grand BA, Chosich N, Harper RW, Stockigt JR. Amiodarone-induced hyperthyroidism assessment of the predictive value of biochemical testing and response to combined therapy using propylthiouracil and potassium perchlorate. Aust N Z J Med 1988;18:37–44.
12. Bartalena L, Brogioni S, Grasso L, Bogazzi F, Burelli A, Martino E. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge results of a prospective study. J Clin Endocrinol Metab 1996;81:2930–2933.
13. Broussolle C, Ducottet X, Martin C, et al. Rapid effectiveness of prednisone and thionamides combined therapy in severe amiodarone iodine-induced thyrotoxicosis. Comparison of two groups of patients with apparently normal thyroid glands. J Endocrinol Invest 1989;12:37–42.
14. Dickstein G, Shechner C, Adawi F, Kaplan J, Baron E, Ish-Shalom S. Lithium treatment in amiodarone-induced thyrotoxicosis. Am J Med 1997;102:454–458.
15. Aghini-Lombardi F, Mariotti S, Fosella PV, et al. Treatment of amiodarone iodine-induced thyrotoxicosis with plasmapheresis and methimazole. J Endocrinol Invest 1993;16:823–826.
16. Brennan MD, Van Heerden JA, Carney JA. Amiodarone-associated thyrotoxicosis (AAT) experience with surgical management. Surgery 1987;102:1062–1067.

Multiple-Choice Questions

1. Which of the following is considered to be the most helpful test in differentiating type 1 from type 2 amiodarone-induced hyperthyroidism?

   A. Antithyroid antibody titers
   B. Serum interleukin-6 (IL-6) levels
   C. 24–hour radioiodine uptake
   D. Color-flow Doppler of the thyroid
   E. All of the above

   Answer: D. Refer to the text (diagnosis section) for an explanation.

2. A 67-year-old man is seen in consultation for amiodarone-induced hyperthyroidism (AIT). His history and laboratory data are suggestive of type 2 AIT. You decide to begin therapy. Which of the following is the preferred treatment strategy?

   A. Discontinue amiodarone, start prednisone 40 mg daily, and taper over 1 month.
   B. Discontinue amiodarone, start prednisone 40 mg daily, and taper over 2 to 3 months.
   C. Discontinue amiodarone, start methimazole 40 mg daily, start prednisone 40 mg daily, and taper over 2 to 3 months.
   D. Continue amiodarone, start prednisone 40 mg daily, and taper over 1 month.
   E. Continue amiodarone, start prednisone 40 mg daily, and taper over 2 to 3 months.

   Answer: E. Refer to the text (treatment section) for an explanation.

3. Mr. A. is a 61-year-old computer engineer who is currently on amiodarone for atrial fibrillation. TSH, free T_4, T_3, and anti-TPO antibodies checked prior to starting amiodarone were within normal limits. Thyroid function tests drawn 3 months later showed a TSH of 8.7 μU/mL (normal, 0.5–5.0), free T_4 of 2.1 ng/dL (normal, 0.9–2.0), and T_3 of 65 ng/dL (normal, 72–170). The patient denies any symptoms of hypo- or hyperthyroidism. He is concerned about these results because he has read articles on the Internet lately regarding the potential side effects of amiodarone on the thyroid gland. His father died of a "brain cancer" and his family history is significant for thyroid disease and arthritis. Your best initial approach in managing this patient is:

   A. Reassure him, observe and repeat thyroid function tests in 3 months.
   B. Discontinue amiodarone, start methimazole or PTU since an elevated free T_4 level is suggestive of hyperthyroidism.
   C. Discontinue amiodarone and start levothyroxine since an elevated TSH level is consistent with hypothyroidism.
   D. Continue amiodarone, start prednisone 40 mg daily, and taper over 2 to 3 months.
   E. Refer patient for a magnetic resonance imaging scan of the brain since the elevation of both TSH and feee T_4 is suggestive of a diagnosis central (pituitary) hyperthyroidism that is independent of amiodarone therapy.

   Answer: A. Refer to the text for an explanation.