BRIEF REPORT

Apathetic Hyperthyroidism as an Adverse Effect of Amiodarone for the Treatment of New-Onset Atrial Fibrillation for the Primary Care Physician

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KEYWORDS

Hyperthyroidism

Geriatrics

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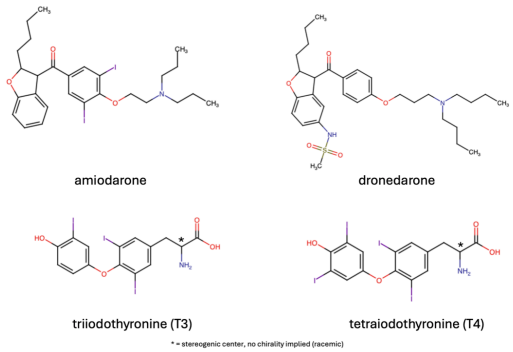
ABSTRACT

Amiodarone is the most used anti-arrhythmic drug worldwide.[1] Its effectiveness for the treatment of multiple arrhythmias including atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia is well documented.[2] Older adults, however, are especially prone to adverse drug effects; amiodarone being no exception to this concern. Thyroid disorders, including both hypothyroidism and hyperthyroidism, as well as liver disease and pulmonary fibrosis are among the idiopathic conditions associated with its use. Presented here is a case report of a patient who developed apathetic hyperthyroidism due to amiodarone use, and the subsequent clinical course and management.

INTRODUCTION

Amiodarone is the most used anti-arrhythmic drug worldwide and is indicated for the treatment of multiple arrhythmias including supraventricular tachycardia, ventricular tachycardia, junctional tachycardia, atrioventricular nodal re-entry tachycardia (AVNRT), and atrial fibrillation.[1] Structurally, amiodarone is highly lipophilic owing to its primary structure containing a di-iodo meta-substituted benzene and aliphatic substituents. These structural similarities are shared with both triiodothyronine (T3 hormone) and tetraiodothyronine (T4 hormone). It is primarily metabolized by the liver in the cytochrome P450 system.[2] In addition, due to its sequestration in adipose tissue, amiodarone may have a terminal half-life of up to 140 days.[2] (Figure 1) Dronedarone is structurally like amiodarone but does not have iodine substituents.[1,3]

FIGURE 1: Chemical structures[1,3]
(Chemical structures drawn at: https://www.rcsb.org/chemical-sketch)



The predisposition to thyroid disease because of amiodarone use is due to iodine serving as a principal substrate for thyroid hormone synthesis (Figure 2).[3] Autoregulation of iodine prevents hyperthyroidism (Wolff-Chaikoff effect), but individuals with underlying thyroid disease lack the ability to regulate iodine uptake. Amiodarone toxicity manifests due to parenchymal deposition of iodine.[4] A specific mechanism of pathophysiology implicated includes intrinsic amiodarone[5] inhibition of mono-deiodination responsible for converting T4 to T3.

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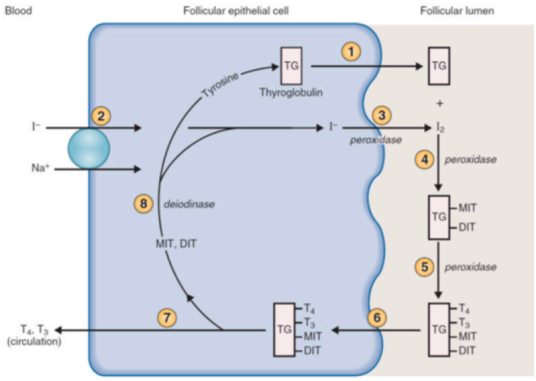
FIGURE 1: Thyroid hormone synthesis[3]



There are two types of apathetic hyperthyroidism, specifically termed amiodarone-induced thyrotoxicosis (AIT): (1) type 1 AIT and (2) type 2 AIT. In type 1 AIT, hyperthyroidism occurs due to an increased synthesis of T3 and T4 secondary to excess iodine from an amiodarone source providing a substrate for thyroid hormone production. Type 1 AIT is typically seen in patients with pre-existing multinodular goiter or other autoimmune thyroid diseases. Regarding type 2 AIT, hyperthyroidism occurs due to a destructive thyroiditis resulting in excess release of preformed T3 and T4 without increasing hormone synthesis. This occurs due to a direct toxic effect of amiodarone on the thyroid and is typically seen in patients without prior or underlying thyroid disease. The hyperthyroid phase is often followed by a hypothyroid phase with an eventual recovery and return to euthyroidism.

Hyperthyroidism is a type of thyrotoxicosis that occurs when the thyroid produces and releases too much thyroid hormone. Apathetic hyperthyroidism occurs primarily in older adults. It is characterized by depression, lethargy, weight loss, and insidious onset with the absence of adrenergic symptoms (palpitations, anxiety, tremors, and heat intolerance) of classical hyperthyroidism.[6] Other symptoms may include proximal muscle weakness, goiter, atrial fibrillation, and congestive heart failure. The pathogenesis of apathetic hyperthyroidism is unknown or unclear, but potential causes include an age-related decrease in adrenergic tone and change in the autonomic nervous system, along with tissue resistance to the effects of thyroid hormone or lack of magnesium due to reduced dietary intake and gastrointestinal absorption.[7] Sporadic cases have been reported in the literature,[8] and although this condition is relatively uncommon, it is not rare, particularly in the elderly.[9] The case presented here illustrates type 1 AIT.

CASE REPORT

A 72-year-old female (at the time of initial clinical presentation) presented to her primary care physician with a complaint of excessive fatigue, shortness of breath, and progressive dyspnea on exertion with minimal effort. Her symptoms were insidious in onset over the previous year. An electrocardiogram (EKG) done at this visit showed atrial fibrillation with a heart rate of 111 beats/minute. She was seen the next day by cardiology, who ordered a 2D echo and initiated anticoagulation due to an elevated CHA2DS2-VASc score, along with a beta blocker. The results of the 2D echo showed an ejection fraction of 35%-40% with global hypokinesis. Functionally, she met criteria for class III New York Heart Association heart failure (Figure 3).[8]

FIGURE 1: New York Heart Association heart failure classification[8]

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain.
IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort.

Subsequent follow-up with her primary care physician 1 month later showed profound bradycardia with a heart rate of 32 beats/minute. Her physical examination at that time showed increased lower-extremity edema for which she was treated effectively with furosemide. Her beta blocker was gradually reduced to avoid rebound tachycardia. She was maintained on appropriate guideline-directed medical therapy, and her ejection fraction ultimately improved to 55%-60%. She underwent two attempts at cardioversion, which were unsuccessful. In addition, a cardiac catheterization was unremarkable for coronary artery disease. Due to the patient's preference to avoid invasive procedures, medical therapy with amiodarone was attempted. She was on the medication for approximately 6 months with modest improvement, and she therefore consented to cardiac ablation.

Despite medical management and cardiac improvement on laboratory and imaging studies, her clinical status continued to decompensate. With the cardiac symptoms effectively managed, she began to complain of new symptoms such as fatigue without shortness of breath and generalized weakness. She was referred to a physiatrist who performed a thorough neurological examination including muscle strength, deep tendon reflexes, and sensation. She was noted to have profound proximal muscle weakness. An electromyogram (EMG) of the bilateral upper and lower extremities was ultimately

unremarkable. A thyroid-stimulating hormone (TSH) level done at the time of amiodarone initiation was unremarkable; a repeat approximately 9 months later showed a TSH of 0.09 mIU/L (reference range: 0.4-4.5 mIU/L). She was referred to endocrinology who performed additional testing, including thyroid peroxidase antibody and thyroid stimulating immunoglobulin, all of which were unremarkable. The endocrinologist then initiated treatment with methimazole and her TSH achieved normal range at 1.05 mIU/L approximately 12 months after the previously abnormal test.

As part of comprehensive testing, a thyroid ultrasound was ordered by endocrinology revealing multiple thyroid nodules, two of which met criteria for fine needle aspiration (FNA) based on ACR TI-RADS [American College of Radiology Thyroid Imaging Reporting and Data System] criteria. Due to the likelihood that these nodules were hyperfunctioning autonomous hot nodules, biopsy was not pursued. An iodine-123 scan was ordered to try and determine if the thyroid nodules were hot or cold, recognizing that the scan may not be able to discern this due to previous amiodarone use. Amiodarone use can suppress iodine uptake on iodine-123 scans due to the large iodine content in amiodarone and can suppress uptakes for many months after discontinuing amiodarone due to the long half-life.[10,11] Amiodarone contains approximately 37% of iodine by weight (75 mg of iodine per 200-mg tablet); standard amiodarone therapy can provide more than 100 times the daily iodine requirement.[10]

Iodine-123 scans were ordered by endocrinology to assess thyroid function. The initial iodine-123 scan was done 5 months after stopping amiodarone but due to the very long half-life of amiodarone, iodine uptake on the scan was still suppressed from amiodarone and unable to determine if the nodules were hot or cold. A repeat iodine-123 scan was completed 9 months after stopping amiodarone but still showed suppressed uptakes from previous amiodarone use. A third iodine-123 scan is scheduled in the future to try and determine if the nodules are hot or cold. The workup process remains ongoing at the time of this writing. It is important to determine if the nodules are cold because this would warrant FNA biopsy of the cold nodules. However, if the nodules are hot, no FNA biopsy is indicated, as hot nodules have a low risk of malignancy.[11] Biopsy of a hot nodule may additionally lead to a false positive biopsy; the cited reference describes in detail the workup of a thyroid nodule and pathology classifications, as well as workup.[12] Clinically, with the addition of methimazole to her medication regimen, her symptoms significantly improved. Of note, when methimazole was held for 5 days per protocol prior to iodine-123 scans, she noted a recurrence and exacerbation of her initial symptoms.

Her active medical problems at the time of the apathetic hyperthyroidism diagnosis were hypertension, morbid obesity, obstructive sleep apnea (on nocturnal continuous positive airway pressure [CPAP]), osteoarthritis, thyroid nodules, and lung nodules. The previous atrial fibrillation and associated systolic heart failure resolved following the ablation and with medical therapy; repeat 2D echo showed restoration of ejection fraction to 55%-60%. Past surgical history included C-section, tonsillectomy, and cardiac catheterization. She smoked intermittently for approximately 40 years with a total of 15 pack-years, infrequently consumes alcohol, and denied any illicit drug use. Family history was unremarkable for any similar symptoms. Medications include apixaban, furosemide, dapagliflozin, spironolactone, atorvastatin, potassium chloride, and sacubitril/valsartan.

DISCUSSION

Apathetic hyperthyroidism is a unique and paradoxical presentation for hyperthyroidism in that the expected adrenergic clinical features are often lacking. Present more predominantly are fatigue, apathy, cognitive impairment (sometimes termed "brain fog"), and cardiovascular symptoms like atrial fibrillation. Whether atrial fibrillation is a presenting symptom or a consequence of adverse drug events (i.e., amiodarone-induced apathetic hyperthyroidism) is not effectively established. The use of amiodarone is increased in the older population (ages 65 years and above) for the treatment of anti-arrhythmias.[13] Recent literature sources note (paraphrasing)8: Amiodarone reduces the peripheral conversion of T4 to T3, resulting in modest reduction in serum concentrations of T3 (often to below the normal range) and modest elevation in serum T4 (often to above the normal range). TSH is typically slightly elevated early after initiation of treatment.[5] Approximately 2-3 months after amiodarone is started, the serum TSH level is an accurate indication of thyroid function. Thyrotoxicosis, of which apathetic hyperthyroidism is but one entity, should only be diagnosed in the presence of significant elevation of free T4, together with elevation in serum T3 and suppression of TSH in addition to the previously described symptoms. Sometimes serum T3 is at the upper range of normal rather than elevated, probably because of associated "nonthyroidal" illness in individuals 65 years of age and older, together with the block of T4 to T3 conversion seen with amiodarone.

TABLE 1: Summary of findings for apathetic hyperthyroidism

History
• Abrupt or recent onset of fatigue, anorexia, weight loss, apathy or depression, agitation, or cognitive impairment • Diagnosis of atrial fibrillation or other dysrhythmias/arrhythmias • Treatment of arrhythmias with amiodarone • Ingestion of excessive amounts of iodine • History of thyroid disease (Hashimoto's thyroiditis, Graves' disease, or others), abnormal thyroid laboratory studies, or abnormal thyroid imaging
Focused physical examination
• Goiter or thyroid enlargement • Proximal muscle weakness • Atrial fibrillation • Lower-extremity edema
Laboratory studies
• Thyroid panel including TSH, free/total T3, and free/total T4 • B12 and folate • Thyroid-stimulating immunoglobulin • Thyroid peroxidase antibody
Imaging/diagnostic studies
• Thyroid ultrasound – assess for nodules • Iodine-123 uptake scan – will see decreased uptake with residual amiodarone
Appropriate referrals
• Physiatry – EMG to rule out nerve damages • Endocrinology – thyroid disease management • Cardiology – arrhythmia management
Treatment
• Stop amiodarone • Initiate treatment with methimazole

Treatment involves thioamides – specifically, methimazole, which is structurally a 5-membered imidazole ring with a methyl group on the tertiary nitrogen in the imidazole and a thione group at position 2 – in addition to laboratory studies and imaging. The patient described in this case report was prescribed methimazole 5 mg daily.

A summary of history, physical examination findings, and workup for apathetic hyperthyroidism for primary care physicians is included in Table 1.

Apathetic hyperthyroidism is a rare syndrome predominantly observed in older adults associated with amiodarone use, though not exclusively. Its impact in this population cannot be understated due to the impact it may have on their functional status. In older adults, functional status is a major predictor of mortality. Two instruments are used to assess functional status in older adults: the Katz Activities of Daily Living (ADLs) and Lawton-Brody Instrumental Activities of Daily Living (IADLs). (Table 2)

TABLE 2: Functional status criteria – ADLs and IADLs[14,15]

Katz Activities of Daily Living	Lawton-Brody Instrumental Activities of Daily Living
• Bathing • Dressing • Toileting • Transferring • Continence • Feeding	• Ability to use the telephone • Shopping • Food preparation • Housekeeping • Laundry • Mode of transportation • Responsibility for own medications • Ability to handle finances

By considering a premorbid and posttreatment functional status, the urgency of identifying and treating this unlikely diagnosis is made apparent. In the case of this patient, she was independent of 6/6 of her ADLs and 8/8 of her IADLs. However, with onset of symptoms as described, she remained independent of both ADLs and IADLs but with considerable effort and occasional assistance. In addition to medical management, physical and occupational therapy were consulted due to concerns of physical deconditioning due to profound fatigue; however, her participation was limited. Upon treatment, her functional status significantly improved to the point where she was able to perform her ADLs and IADLs without any assistance or considerable effort. (Table 3)

TABLE 3: Pre- and Posttreatment functional assessment measurable outcomes

Criteria	Pretreatment	Posttreatment
ADL independence	6/6 independent but required considerable effort	6/6 independent
IADL independence	8/8 independent but required considerable effort	8/8 independent
Patient Health Questionnaire (PHQ) scores	PHQ-2: 4/6 PHQ-9: 11/27	PHQ-2:1/6 PHQ-9: N/A
Montreal Cognitive Assessment	30/30	30/30
Fall risk: timed up and go	17 seconds	10 seconds
Hours sleeping per day	10-12 hours	6 hours

CONCLUSION

The symptoms of apathetic hyperthyroidism are often insidious and lack the typical adrenergic hyperthyroid or thyrotoxicosis presentation. Symptoms may be masked by more likely diagnoses or geriatric syndromes, particularly in medically complex older adults with conditions such as cognitive impairment or depression. Amiodarone-induced apathetic hyperthyroidism, like the classical presentation of amiodarone-induced hyperthyroidism, can be characterized on laboratory studies by decreased

TSH, decreased serum T3, and increased T4 due to amiodarone's effects on the peripheral conversion of T4 to T3. The case presented here illustrates type 1 AIT. Apathetic hyperthyroidism should not be considered a diagnosis of exclusion, but other reversible or organic causes of associated symptoms should be ruled out. There are only a small number of cases reported in the literature as cited previously. The significantly prolonged half-life of amiodarone plays a large part in pathologic progression and the need for prolonged monitoring until resolution or cure of the disease.

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