CLINICAL VIGNETTE

A Patient with Amiodarone-Induced Hyperthyroidism

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Case Presentation

A 76-year-old man with history of hypertension and hyperlipidemia was taken to the emergency room after falling at home and sustaining a head injury. On admission he was alert and oriented without any gross neurological deficits. He was noted to be tachycardic. Computerized tomography (CT) without contrast of the head showed no intracranial bleeding. Further evaluation of his tachycardia showed that the patient was in atrial fibrillation with a ventricular rate of 185. Patient was ruled out for myocardial infarction, given intravenous amiodarone along with beta blockers and admitted for further management.

About 36 hours after admission, patient was noted to be diaphoretic and tremulous. Patient remained tachycardic and repeat 12-lead electrocardiogram (EKG) showed persistent atrial fibrillation. Troponin levels were mildly elevated but did not progressively rise. The cardiologist did not feel that this was representative of an evolving cardiac event. Hyperthyroidism was suspected and a suppressed thyroid stimulating hormone (TSH) prompted endocrine consultation.

At time of consultation, patient denied any prior history of thyroid disease or taking thyroid medication or any supplements. He also denied having any recent imaging involving contrast. Review of systems (ROS) was significant for diaphoresis, a sense of nervousness, and palpitations. There was no eye pain, vision changes, sudden weight loss, or throat discomfort. On exam, patient was diaphoretic and mildly tachypneic but otherwise in no distress. Temperature was 98.4° F with a blood pressure (BP) of 154/89 and a heart rate of 134 beats per minute (bpm). Respiratory rate was 16. Body mass index (BMI) was 23.6. No exophthalmos was appreciated, and eyes had a full range of motion bilaterally. Mild lid lag was present. The thyroid was approximately 2 times enlarged, without masses, and was not tender. No thyroid bruit was heard. The skin was warm and moist to touch and he had hand tremors bilaterally. Heart had an irregular rhythm with a rapid rate with a grade 2 systolic ejection murmur loudest over the right 2nd intercostal space. Pretibial myxedema was not present. The rest of the exam was normal.

Further testing included undetectable TSH. Free thyroxine (Free T4) was greater than 8 ng/dL (which was the lab's limit of detection). Total triiodothyronine (Total T3) was 247 ng/dL (60-181 ng/dL). Thyroid stimulating immunoglobulin (TSI) levels were undetectable. Thyroid peroxidase antibodies were not present (< 9 IU/mL). Thyroid ultrasound showed a right lobe measuring 6.5 cm x 3.0 cm and the left lobe measuring 6.1 x 3.3 cm. The isthmus was 0.8 cm. A sub-centimeter cystic nodule was seen in each lobe. Parenchyma was heterogenous with mention of increased blood flow.

A diagnosis of (Type II) amiodarone induced hyperthyroidism was made but Type I could not be excluded. The patient was started on prednisone 60mg daily. Although he did not have any physical exam findings to suggest Grave's disease and his TSI levels were undetectable, methimazole 15mg twice a day was also started due to concerns of the patient's ongoing cardiac issues. Over 48 hours, his atrial fibrillation converted to sinus rhythm and his pulse decreased to 68 bpm. He reported feeling better and was no longer diaphoretic. Hand tremors persisted but were improved. The patient was discharged from the hospital on amiodarone 200 mg twice a day, prednisone 40 mg daily, and methimazole 20 mg daily. He will be followed by endocrine as well as with his primary care physician.

Discussion

The thyroid gland is susceptible to the effects of various medications. One of the most common of these is amiodarone, which is a widely used class III antiarrhythmic known for its efficacy in managing atrial fibrillation. It has been associated with both hypothyroidism and hyperthyroidism with direct and indirect effects on thyroid function.

Amiodarone's direct effects on thyroid function include inhibition of conversion of thyroxine (T4) into the active thyroid hormone, triiodothyronine (T3).[1] It can also block T3 nuclear receptors.[2]

Amiodarone contains two iodine atoms and the negative effects on the thyroid are predominantly due to this fact. Iodine is an element essential to thyroid hormone synthesis. The approximate minimum daily iodine requirements are 100 mcg for children (up to 13 years of age), 150 mcg for non-pregnant adults, 250 mcg for pregnant women, and 300 mcg for lactating women.[3] The average American diet typically contains 300 mcg of iodine daily – primarily due to iodinated table salt. Given that 100 mg of amiodarone contains about 3000 mcg of organic iodine, amiodarone treatment provides an excess amount of iodine – since total daily treatment doses of amiodarone range from 100 mg to 600 mg. The toxic effects of amiodarone can

occur months after stopping treatment because of its long half-life of 100 days.

Since iodine is the main element in thyroid hormone production, excess iodine substrate, could be expected to produce an excess of thyroid hormone synthesis leading to hyperthyroidism. Luckily, there is a physiologic safety-mechanism in place to prevent this. Known as the Wolff-Chaikoff effect, normally iodine cellular uptake as well as thyroid hormone production are inhibited when iodine concentrations reach a critical level. After about a month, thyroid hormone synthesis returns to normal despite continued exposure to excess iodine.

Unfortunately, in patients with underlying thyroid disease, this self-regulation is hampered. For example, patients with autoimmune thyroid disease, such as Hashimoto's thyroiditis, the Wolff-Chaikoff effect persists and these patients do not resume normal thyroid hormone levels. Instead, they remain in a state of decreased thyroid hormone production, and thus are hypothyroid.

In contrast, patients with nodular thyroid glands may never undergo this inhibitory process and, in the setting of excess iodine substrate, progress to hyperthyroidism – attributed mostly to autonomously functioning regions within the thyroid. This is known as the Jod-Basedow effect.[4]

The risk of amiodarone-induced thyroid dysfunction varies with one meta-analysis noting a prevalence rate of about 4%.[5] In the United States, where dietary iodine content is sufficient, hypothyroidism from amiodarone appears to be more common than hyperthyroidism as opposed to other regions with endemic iodine deficiency where hyperthyroidism from amiodarone seems to be more prevalent.

As mentioned, amiodarone treatment has been associated with hypothyroidism – particularly in patients with underlying autoimmune thyroid disease. Some euthyroid patients on amiodarone may develop a transient subclinical form of hypothyroidism with a temporary rise in TSH and maintenance of T4 and T3 levels. Treatment with levothyroxine is reserved for those patients whose TSH is significantly elevated (over 10 mU/L) along with below reference range levels of T4. It is not usually recommended to stop amiodarone in these cases as thyroid hormone replacement is a relatively simple solution. If a patient is taken off amiodarone for other reasons, monitoring to see if levothyroxine can be tapered off over the next months is recommended.

Amiodarone may also induce hyperthyroidism via two separate mechanisms – categorized as Type I and Type II amiodarone-induced thyrotoxicosis (AIT). In Type I AIT, there is an increase in thyroid hormone production as the amiodarone provides excess amount of iodine substrate. Patients with Type I AIT tend to have autonomously functioning thyroid nodules or latent Graves disease that becomes prominent due to increased iodine concentrations. Type II AIT is associated with direct toxic effects of amiodarone on the thyroid follicular cells leading to their destruction. This, in turn, results in intravascular release of stored T4 and T3.

Clinical manifestations of Type I and II AIT are similar to other forms of hyperthyroidism and can include palpitations, development or lack of resolution of atrial arrythmias, heart failure, exacerbation of myocardial infarct, heat intolerance, diaphoresis, or nervousness.

However, it is imperative that the clinician differentiate between Type I and II AIT as their treatments are different. Thyroid function tests are not useful in making that distinction. There are some clues that may help. Hyperthyroid patients presenting with exophthalmos and/or large diffuse goiters would be suggestive of a developing Graves disease, which is consistent with Type I AIT. A nodular thyroid on exam could also direct toward Type I AIT whereas an unremarkable thyroid exam would steer thinking to Type II AIT. Detectable levels of TSI would suggest Type I AIT as TSI levels are associated with Grave's disease. Thyroglobulin levels, sometimes used as markers of intrinsic thyroid activity, in the serum may be higher in Type I AIT due to the increase in thyroid hormone production. Imaging with AIT may be inconclusive. 24-hour iodine uptake may not be useful due to already excessive amounts of iodine competing with the radiotracer iodine but an increased uptake would be suggestive of Type I AIT. Thyroid gland sonography with color flow Doppler may help. A presence of color flow on Doppler would suggest increased vascularity within the thyroid gland due to increased thyroid activity and guide toward Type I AIT. A lack of flow would mean decreased vascularity within the thyroid gland – a phenomenon seen in thyroiditis and, hence, Type II AIT would be suspected. Doppler flow ultrasounds are limited by the experience of the sonographer and lack of standards as to what is considered increased vascularity. Making the diagnosis more difficult is that some patients may present with a mixed clinical picture suggestive of both Type I and Type II AIT.

In discussing treatment, regardless of type of AIT, stopping amiodarone is not generally recommended. For one, due to amiodarone's long half-life (100 days), stopping treatment would provide no immediate resolution. Second, as mentioned, amiodarone blocks T4 conversion to T3 as well as T3 receptors. Thus, amiodarone may provide some protection against hyperthyroidism and stopping treatment could potentially worsen the situation.

If suspecting type I AIT, anti-thyroid drugs (ATDs), such as methimazole or propylthiouracil (PTU), should be started. ATDs inhibit thyroid hormone synthesis. Methimazole is preferable over PTU due to lower prevalence of toxic effects, such as vasculitis, skin itchiness, agranulocytosis, and hepatotoxicity. Once a euthyroid state is achieved, a slow taper of ATDs is recommended. A rapid taper may lead to recurrence of hyperthyroidism. Some endocrinologists will even add levothyroxine to ATDs therapy if tapering leads to signs of recurrent hyperthyroidism. If the amiodarone is eventually discontinued, ATDs are continued for a prolonged period until the patient's

urinary iodine content is normalized, a sign that the amiodarone has been cleared from the system. For those patients who do not respond to ATDs or develop adverse reactions to ATDs, a total thyroidectomy may be considered after considering patient's cardiovascular risk factors.

For those patients believed to have Type II AIT, ATDs provide no benefit as, in this case, the thyroiditis results in the release of already synthesized thyroid hormone. Instead, patients could respond to high doses of glucocorticoids, such as prednisone. As with Type I AIT, rapid withdrawal of treatment could exacerbate the hyperthyroidism. And so, treatment is usually maintained for up to 3 months. Surgery is an option for those patients who do not respond to glucocorticoids.

Some patients may have findings consistent with both Type I and Type II AIT. Our patient was suspected to have Type II AIT but Type I could not be completely excluded. In such cases, both ATDs and glucocorticoids should be started – especially in the setting of cardiovascular risk uncertainty. A rapid normalization of thyroid function with continued tapering of ATDs would be suggestive of Type II AIT.

In summary, amiodarone is commonly used and may lead to either hypothyroidism or hyperthyroidism. In the case of the latter, hyperthyroidism presents in two distinct pathophysiological forms and it may be difficult to clinically distinguish between the two. Luckily, the majority of patients respond to treatment in amiodarone-induced thyroid dysfunction. Nonetheless, it is recommended to monitor all patients during amiodarone therapy with thyroid function testing every 3-6 months. And given amiodarone's long half-life monitoring should be extended for at least 1 year after discontinuation of treatment.

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