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UNUSUAL SCINTIGRAPHIC FINDING IN A PATIENT WITH AMIODARONE-INDUCED THYROTOXICOSIS: A CASE REPORT

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Abstract

Amiodarone, an antiarrhythmic drug with 37% iodine of its weight, is often used for treatment of severe cardiac arrhythmias. Enormous iodine content and structural similarity to thyroxine leads to thyroid dysfunction in 14-18% of patients.

A 64-year-old man presented at our department with signs of thyrotoxicosis for further work up. He reported taking amiodarone for treatment of atrial fibrillation for two years. The patient denied any thyroid dysfunctions in the past. Full thyroid examination revealed elevated FT4 and suppressed TSH, with undetectable level of thyroid antibodies, increased iodine urinary concentration and normal thyroid ultrasound features. Although the above mentioned was indicative for amiodarone-induced thyrotoxicosis (AIT) type 2, 99mTc-pertechnetate scan showed normal thyroid uptake, highly unusual for iodine contamination and destructive thyroiditis. We presumed that this was a mixed form of AIT. Amiodarone administration was stopped and the patient was put on antithyroid drug therapy with thiamazole. During the follow up period he became clinically and biochemically euthyroid and thiamazole was discontinued.

Thyroid screening should be performed in all patients undergoing amiodarone treatment. The presented case highlights the challenge of differentiation and management of a form of AIT with mixed features of both types.

***Keywords*:** iodine excess, amiodarone induced thyrotoxicosis, mixed form.

Introduction

Amiodarone, an iodine-rich benzofuran derivative, is the most commonly prescribed antiarrhythmic drug for treatment of severe cardiac arrhythmias [1].

The concentration of iodine in amiodarone is approximately 37 % of its weight. In this regard, the treatment with amiodarone can affect thyroid hormone production leading to changes in thyroid functional tests [2].

Amiodarone also inhibits D1 and D2 deiodinase activity and therefore decreases peripheral monodeiodination of thyroxine (T4) in triiodothyronine (T3).

Patients on amiodarone therapy present with alterations in serum T4, T3, reverse T3 (rT3) and thyroid stimulating hormone (TSH) levels [3]. As a therapy adverse effect, thyroid dysfunction can be present as amiodarone-induced hypothyroidism (AIH) or amiodarone-induced thyrotoxicosis (AIT).

Patients with autoimmune disorder or goiter have increased risk for developing a disease, although both entities may occur in normal thyroid gland. AIT can be present in 2 main forms, type 1 and type 2. Type 1 AIT usually develops in patients with goiter or latent Graves' disease, followed by autonomous thyroid hormone production. Type 2 AIT develops in normal thyroid glands resulting in tissue destruction and thyroid hormone release. Mixed forms have both pathophysiological mechanisms [4, 5].

Distinguishing between different forms of AIT is very important for choosing the right treatment option. Treatment of AIT type 1 consists of antithyroid drugs, while type 2 is usually treated with oral glucocorticoids due to their anti-inflammatory effects [6,7]. Differential diagnosis and treatment of type 1 and 2 still remains a dilemma between clinicians. Here, we present a case of amiodarone induced thyrotoxicosis and the challenge of managing a patient with overlapping features of both types.

Case presentation

A 64-year-old man was referred to the Institute of Pathophysiology and Nuclear medicine with suspicion of amiodarone induced hyperthyroidism for further workup. He reported taking amiodarone for treatment of atrial fibrillation for two years.

The patient's condition was stable until October 2018 when he noticed increased sweating, weight loss to a normal calorie intake and tiredness.

Thyroid function was assessed and the test revealed thyrotoxic state.

Thyroid pertechnetate scan showed normal thyroid uptake with homogeneous accumulation of the tracer in the right lobe, while inhomogeneous accumulation was noticed in the left thyroid lobe (Figure 1).

Amiodarone administration was stopped and the patient was put on antithyroid drug therapy with thiamazole with a daily dose of 20 mg. Four months later he presented at our department for further evaluation of thyroid status and appropriate management. He presented only with a continuous weight loss, while other symptoms were normalized due to thiamazole therapy.

On examination there was no tremor, nor sweating or tachycardia. The patient denied any thyroid dysfunctions in the past or family history of thyroid disorder. His other medical history included hypertension and heart failure.

Thyroid function and morphology evaluation was performed which included repeat laboratory tests for thyroid function and autoimmunity, neck palpation, ultrasonography with color doppler flow and iodine urine excretion.

Thyroid hormones were within normal range, with TSH slightly decreased under antithyroid treatment. Antibodies against TSH receptor (TRAb) and thyroid peroxidase antibodies (aTPO) were negative.

Thyroid ultrasonography showed normal sized thyroid gland with isoechoic, homogeneous structure and normal vascularity on Color doppler. Iodine urine excretion was increased suggestive of iodine contamination. No previous thyroid disorders, absence of goiter, negative thyroid antibodies and normal thyroid ultrasound with absence of hypervascularity were indicative for AIT type 2.

However, previously performed scintigraphy with 99mTc-pertechnetate had revealed normal thyroid uptake, which is highly unlikely for destructive thyroiditis.

Diagnosis of an indefinite type of AIT was made based on these results and thiamazole therapy was continued, with a plan to add oral steroids in the treatment if there is no improvement. On checkup one month later, the patient had reported stabilization of his weight.

Laboratory tests showed euthyroid state and thiamazole therapy was reduced to 10 mg per day. Afterwards, the patient did not show on his regular appointment and presented five months later with an increased TSH value of 48,01 mg/l. Antithyroid therapy was stopped and he was reviewed one month later. Laboratory tests showed a decrease in TSH value which was normalized 11 months later. Iodine urine excretion was still increased above 1000 μg/L.

The patient was followed every three months. Iodine urine secretion normalized two years after discontinuation of therapy. On his last two checkups, the patient was clinically and biochemically euthyroid. His weight remained stable during the follow up period.

Considering previous laboratory and radiological examination and the fast response to thiamazole, the final diagnosis was a mixed type of AIT.

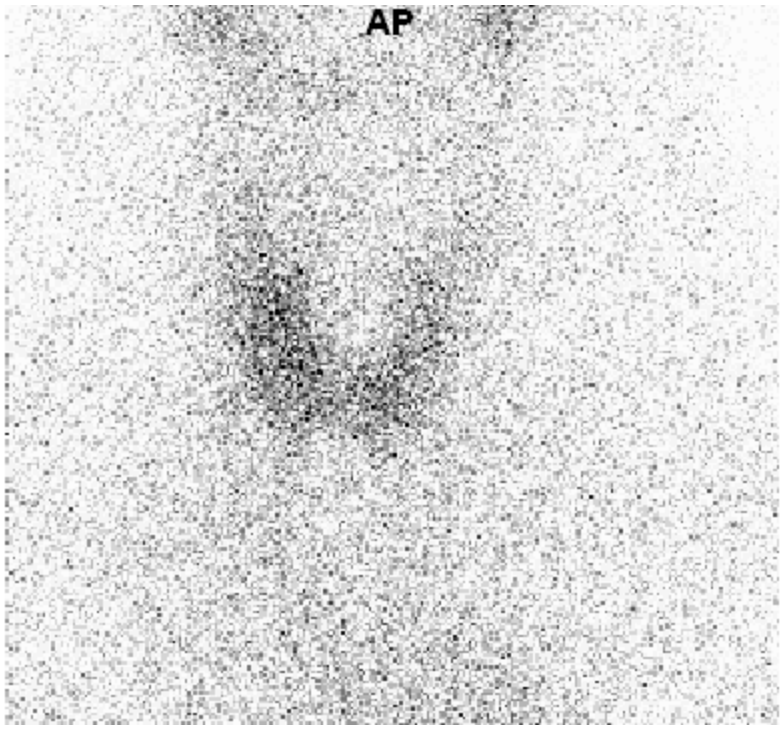

Figure 1: 99mTc-pertechnetate thyroid scan revealed a normal sized thyroid gland with homogeneous accumulation of the tracer in the right lobe and inhomogeneous accumulation of the tracer in the left thyroid lobe.

Discussion

Iodine is an essential micronutrient for thyroid hormone synthesis with a recommended daily intake of 150 μg in adults. Tolerable upper intake level, which will pose no adverse health effects is 1100 μg of iodine per day [8].

Acute or chronic iodine overload usually occurs by ingestion of iodine-rich medications or dietary supplements and exposure of iodinated contrast agents in radiologic studies.

Thyroid gland responds to iodine overload with the Wolff–Chaikoff effect- an acute and transient mechanism which involves inhibition of thyroid peroxidase activity by production of iodolactones, iodoaldehydes, or iodolipids. This reaction prevents synthesis of large amounts of thyroid hormones.

The effect lasts several days, then a marked decrease in sodium/iodine symporter is seen, with decreased in intrafollicular iodine concentration, resumption in iodine organification and normalization in thyroid hormone synthesis-phenomenon known as the escape of Wolff–Chaikoff effect [9-11].

Although iodine excess is well tolerated in most cases, some individuals develop subclinical to overt thyroid dysfunction [10].

The variability in personal response to high iodine intake is probably related to factors such as age, sex, body size, previous iodine intake, route and duration of intake, thyroid health and general health [1].

Underlying pathophysiological mechanism for iodine-induced hypothyroidism is thyroid failure to escape from the acute Wolff–Chaikoff effect, while Jod–Basedow phenomenon is associated with iodine-induced hyperthyroidism in patients with impaired thyroid autoregulation [10].

Excess of iodine reduces activity of glutathione peroxidase (GPx) resulting in thyroid oxidative damage that may lead to impaired production of thyroid hormones [12].

Furthermore, it has an impact on T cell differentiation into Th17 and Th1, with inhibition on regulatory T cell development, inducing autoimmune thyroid disorders [13].

Our patient probably had some form of destructive thyroiditis that led to thyroid hormone release due to iodine overload from amiodarone therapy.

The presence of 99mTc-pertechnetate uptake on scintigraphy, regardless of high systemic iodine level, was highly unusual.

Amiodarone is a class III antiarrhythmic drug with high effectiveness in maintaining sinus rhythm in patients with ventricular and supraventricular arrhythmias, especially atrial fibrillation. Structurally represents iodinated benzofuran derivative, with 2 atoms of iodine radical in the external part of the aromatic ring which gives stability and increases its potency [14].

It contains about 37% iodine by weight. Moreover, even a daily dose of 200 mg amiodarone raises daily iodine intake by 40 times [15].

Because of his huge iodine content and structural similarity to thyroid hormones, the drug has an impact on thyroid function causing thyroid abnormalities in 14-18% of patients [16].

The older population has a higher incidence of cardiopulmonary comorbidities. As a result, iodine induced hyperthyroidism can be overlooked in this age group, as they tend to have less typical symptoms [17].

Also, the management of this population is more complex, with slow recovery and increased risk of damaging consequences.

Foppiani et al. reported a case of an 80-year-old man who developed hyperthyroidism after receiving amiodarone therapy and iodine contrast that proved to be challenging to manage [18].

Two types of amiodarone-induced thyrotoxicosis are recognized, defined as type 1 and type 2, based on patient' previous thyroid status. Differential diagnosis is made on the basis of several factors such as presence of anti-thyroid antibodies, thyroid ultrasound and nuclear medicine imaging with radioiodine, 99mTc-pertechnetate or 99mTc-MIBI. High serum level of anti-thyroid antibodies, presence of goitre with hypervascularity on ultrasonography and intensive thyroid uptake on scintigraphy are indicative of AIT 1, while combination of decreased or no thyroid uptake with absent hypervascularity are suggestive of AIT 2 [6, 19].

We reported a case of AIT with normal ultrasound features for thyroid and negative TRAb and aTPO pathognomonic for AIT type 2; however, the presence of thyroid uptake on 99mTc-pertechnetate scintigraphy despite the iodine load was suggestive for AIT type1. Therefore, this probably was a patient with a mixed form of AIT.

Distinction between the two types is important as specific medical treatment exists for both forms. Choosing the wrong treatment will lead to prolonged response increasing cardiovascular risk. When response to conventional treatment with antithyroid drugs and glucocorticoid is poor, or rapid restoration of euthyroidism is needed due to severe cardiac dysfunction, thyroidectomy is the method of choice [6, 20].

To reduce thyroid hormone level other therapeutic options before definitive surgical treatment had been proposed. Iodine saturated solutions such as lugol's solutions inhibit the enzyme thyroid peroxidase, block hormone release and decrease thyroid vascularity [21].

Plasmapheresis is also described as a useful procedure for decreasing thyroid hormone levels by removing them from the circulation in severe thyrotoxicosis prior thyroidectomy [22, 23].

Radioiodine therapy is recommended as safe and cost-effective first-line treatment in patients with toxic thyroid adenoma or multinodular goiter and secondary therapy in patients with Graves' disease who cannot achieve remission with antithyroid drugs [17,24].

Iodine contamination in patients with AIT makes the treatment controversial in this subgroup, especially in individuals with low uptake values on scintigraphy [6].

However, Czarnywojtek et al. found treatment with radioiodine to be rational, when amiodarone is the only effective antiarrhythmic drug and should be continued or reintroduced [25].

In a retrospective study of 64 patients with AIT, a modest response to medical treatment was found with the poorest response rate to combinate therapy (thionamides + glucocorticoids) in patients with higher fT4. Usage of thionamides was associated with highest response but longer treatment [26].

However, other authors concluded that combination of antithyroid drugs and oral steroids is the best choice for treating amiodarone-induced thyroiditis [27, 28].

Amiodarone is a lipophilic agent with strong affinity to the skin, liver, lung, eyes, adipose tissue, muscle and thyroid gland [15].

The drug also has a long elimination half-life of approximately 50-100 days. Moreover, it continues to remain in the body for an extended period of time after withdrawal, causing iodine excess during its administration and several months later [10, 14].

Our patient had persistent high iodine urine excretion for two years after discontinuation of amiodarone.

In view of this, patients should undergo a thyroid screening before initiating therapy with amiodarone. Additionally, patients on continuous amiodarone therapy should be checked for signs of thyroid dysfunction with regular thyroid function tests every 6 months [15, 17, 29].

In conclusion, the presented case illustrates the complexity of managing mixed forms of AIT. Differing between AIT types is often imprecise and leads to prolonged therapeutic response. Awareness of disease pathogenesis and diagnostic algorithms is crucial in the therapeutic management of these patients.

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