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Case Report

# Amiodarone Induced Thyrotoxicosis in Previously Sub clinically Hypothyroid Patient on Amiodarone – Case Report

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**Abstract**

Amiodarone (AMD) is a potent antiarrhythmic iodine rich agent, which may induce clinical and subclinical thyroid dysfunction (TD). We describe a male patient with the rare phenomenon of amiodarone-induced thyrotoxicosis (AIT) after subclinical hypothyroidism on AMD therapy, which was recovered after AMD with drawl alone. Normal thyroid grey scale echosonography, absent pertechnetate and MIBI uptake, along with suppressed serum TSH and elevated serum free T4 and free T3 were diagnostic criteria for the AIT type 2 and the treatment choice.

## INTRODUCTION

Amiodarone (AMD) is a potent antiarrhythmic iodine rich agent, which may induce clinical and subclinical thyroid dysfunction (TD). The mechanism of TD could be the iodine overload with antiarrhythmic drug and/or direct cytotoxic effect of the drug on the thyrocytes [1-3].

## CASE REPORT

We describe a male patient with the rare phenomenon of amiodarone-induced thyrotoxicosis (AIT) after subclinical hypothyroidism on AMD therapy.

Patient, J J, 66 years old male, came in the clinic for thyroid status check due to chronic amiodarone therapy. He has a history of 12 months at AMD therapy, 1 tablet / day, 5 days a week - asymptomatic. There are hypertension and angina pectoris among comorbid states - under treatment with ACE inhibitor, β blocking agent, double diuretic, including K saving one, H2 blocking agent and vasodilator. Eight years before he underwent aorto-coronary bypass. Family history was negative in terms of thyroid diseases. In clinical status: obesity (BMI 31), warm and dry skin, pulse 52/min, no tremor, no goiter, without signs of thyroid ophthalmopathy, were found. Blood tests in the first visit indicated subclinical hypothyroidism: TSH = 5.1 m IU / L (normal range 0.3-4 m IU / L), FT4 = 16 pmol / L (normal range 9.25-25 pmol / L) = 4.7 pmol FT3 / L (normal range 3.5-9 pmol / L), TgAb = 30 IU / ml (normal < 60 IU / ml), TRAB = 0.1 U / L (normal < 1.5 IU / L). AMD remained in therapy. On follow-up visit after 3 months, clinical findings were without changes and blood tests indicated a normalization of TSH: TSH = 2.8 m IU / L, FT4 = 19.7 pmol / L. After two years of the commencement of AMD therapy, or after 12 months from the first control of thyroid status, when patient was subclinically hypothyroid, but all the time without symptoms and without clinical signs of thyroid dysfunction, blood tests indicates the AIT: TSH = 0.01 m IU / L, FT4 = 34.4 pmol / L, FT3 = 12 pmol / L. AIT was considered as destructive thyroiditis induced by AMD (AIT type 2) after performing additional diagnostic methods: echo sonographically finding normal; pertechnetate scintigraphy and MIBI scan - showed absent uptake of both radiotracers. AMD therapy was discontinued and monitoring of thyroid status continued, without introducing therapy for AIT. Two months after cessation of AMD therapy, the patient remains clinically eumetabolic with the blood tests indicating subclinical hypothyroidism - recovery phase of type 2 AIT: TSH = 9 m IU / L, and in the coming months there is a normalization of biochemical indicators of functional thyroid status.

## DISCUSSION AND CONCLUSION

Amiodarone is a lipophilic benzofuran derivative classified as a class III antiarrhythmic agent. It has high iodine content and structural similarity with thyroid hormones. High iodine

content along with other amiodarone intrinsic properties, makes it toxic to thyroid gland, causing various changes in thyroid function, from subclinical to overt clinical dysfunction, both hypothyroidism and thyrotoxicosis [4-6].

AIT is more frequent in iodine deficient areas. According to the mechanism of occurrence there are three types of AIT. The AIT type 1 usually occurs in patients with known or previously undiagnosed thyroid dysfunction or goiter as the result of iodine induced thyroid hormone overproduction in latent autonomous or autoimmune thyroid disorder. The AIT type 2 usually occurs in normal thyroid glands and results in destruction of thyroid tissue caused by thyroiditis which is an intrinsic cytotoxic drug effect from the amiodarone itself. There are also mixed types of AIT which have features of both, type 1 and type 2 AIT. Treatment choice depends on the type of AIT. Treatment include thionamides in AIT type 1 with or without sodium/potassium perchlorate (which by inhibiting thyroidal iodine uptake, may increase the response to thioamides), glucocorticoids in type AIT type 2, or both, thyonamides and glucocorticoides in mixed type AIT [5,7-9].

Bogazzi and co-authors suggest that amiodarone should be discontinued, if feasible from a cardiac standpoint because continuation of amiodarone is sociated with a delayed restoration of euthyroidism and a higher chance of recurrence after glucocorticoid withdrawal. Whether amiodarone treatment can be safely reinstituted after restoration of euthyroidism is still unknown. In rare cases of AIT resistance to standard treatments, or when a rapid restoration of euthyroidism is advisable, total thyroidectomy represents a valid alternative. Radioiodine treatment is usually not feasible due to the low thyroidal iodine uptake [10].

In our previous investigation the aim was to determine the incidence of amiodarone-induced thyroid dysfunctions and the influence of gender, age, treatment duration, goiter, thyroid antibodies, thyroid echogenicity and family history on their appearance. Of 248 consecutive patients from the iodine sufficient area (TimočkaKrajina Region, Serbia), 144 males and 104 females, referred to thyroid status screening, 16% were with clinical dysfunction, 6% with AIT, 10% with AIH, 21% with subclinical dysfunction, 6% with subclinical AIT and 15% with subclinical AIH and 63% were euthyroid. The presence of goiter and thyroid peroxidase antibodies were the significant individual predictive factors for the occurrence of clinical dysfunction, and in the multivariate regression model, the presence of goiter was a significant predictive factor with the prognostic value of 80%. For subclinical dysfunction, the significant individual predictive factors were female gender and the presence of goiter, as well as in the multivariate regression model, with the prognostic value of 74.5% for female gender and 77.5 % for the presence of goiter [11].

The differential diagnosis between AIT type 1 and AIT type 2 is important for the choice of the appropriate treatment. Radioiodine uptake (RAIU), may be high, normal or low but detectable in AIT type 1 and very low or undetectable in AIT type 2. Colour-flow Doppler sonography (CFDS) shows normal or increased vascularity in AIT type 1 and absent vascularity in AIT type 2. MIBI thyroid scintigraphy may differentiate AIT type 1 and AIT type 2 and represent the best single test. In AIT type 1 there is increased MIBI retention, and in AIT type 2 there is no significant uptake [12,13].

Loy and co-authors evaluated the utility of CFDS in the differential diagnosis and management of AIT. They analyzed clinical and laboratory data, sonography (grayscale), thyroid radioiodine uptake (RAIU) and thyroid scintigraphy, along with treatment and clinical outcome retrospectively in 21 AIT patients. CFDS was separately described for nodule and for the perinodular parenchyma, and AIT was classified as type 1 (increased blood flow) or type 2 (low/no blood flow). The treatment of AIT was with methimazole (alone or with potassium perchlorate) in AIT type 1 and prednisone, or amiodarone withdrawal alone in AIT type 2. Eleven of 21 patients had increased blood flow on CFDS, 10 of them had hyper vascular nodular pattern (amiodarone/iodine induced toxic nodular goiter), while one showed a hyper vascular parenchymal pattern (amiodarone/iodine induced Graves' disease) and were considered AIT type 1. In the remaining 10 patients with low or no blood flow, six had normal thyroid volume, three small diffuse goiters, and one small multinodular goiter and were considered AIT type 2. The clinical outcome showed that 20 of the 21 patients were treatment responsive. The authors concluded that CFDS is useful diagnostic tool in the differential diagnosis of AIT helping in the treatment choice [14].

We reported the value of in vivo diagnostic tests in amiodarone induced thyroid disorders diagnosis. In 42 patients treated with AMD, 20 euthyroid and 22 with subclinical or clinical amiodarone induced thyroid dysfunction, we have performed one or more "*in vivo*" thyroid tests - 99mTcO4- static scintigraphy, 99mTcO4-uptake test (TcU) and radioiodine uptake test. In all but two euthyroid patient's thyroid was "blocked". Remaining two had functional nodes well visualized despite of iodine overload. Amiodarone induced thyrotoxicosis showed either preserved or increased accumulation of tracer, AIT type 1, or reduced accumulation, AIT type 2 [15].

In our case, thyroid gray scale echosonography finding was normal; pertechnetate scintigraphy and MIBI scan showed absent uptake of both radiotracers, suggesting destructive thyroiditis i.e. AIT type 2. Two months after cessation of AMD therapy, the patient remained clinically eumetabolic with the blood tests indicating subclinical hypothyroidism which proved recovery phase of type 2 AIT. In the coming months there was a normalization of biochemical indicators of functional thyroid status, as a complete recovery.

We reported earlier as well a case of a male patient on chronic amiodarone treatment who developed alternating thyroid dysfunction. Nine months after initiation of the AMD therapy he developed distinct biochemical signs of hypothyroidism, which spontaneously resolved after the with drawl of AMD. AMD was administered again after one year due to refractory arrhythmia. After 3 years AMD was ceased when elevated serum TSH was registered. Eight months after withdrawal, worsening of arrhytmia occurs, serum levels of functional thyroid parameters showed hyperthyroidism, scintigraphicaly thyroid was "blocked", and semi quantitative uroiodine test revealed increased levels

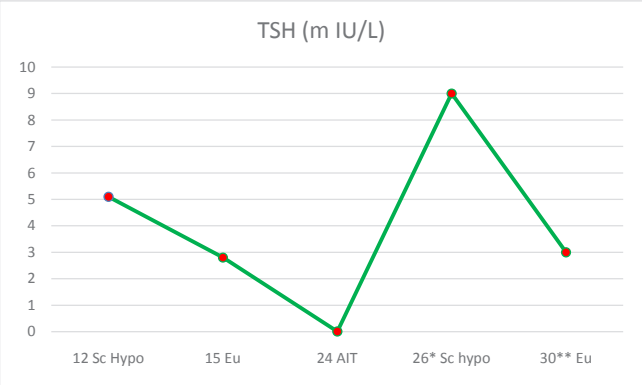


**Figure 1** TSH level during AMD therapy.
X axes: duration of AMD therapy (months) and thyroid status; *- ex AMD 2 months; ** - ex AMD 6 months; sc HYPO - subclinically hypothyroid; EU - euthyroid; AIT - amiodarone induced thyrotoxicosis

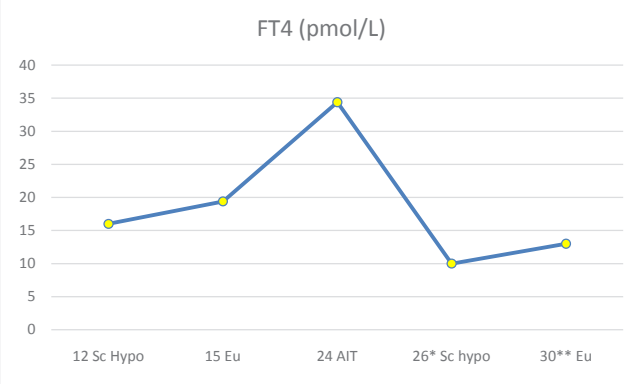


**Figure 2** FT4 level during AMD therapy.
X axes - duration of AMD therapy (months) and thyroid status; *- ex AMD 2 months; ** - ex AMD 6 months; sc HYPO - subclinically hypothyroid; EU - euthyroid; AIT - amiodarone induced thyrotoxicosis

of iodine in urine. We presumed findings as AIT type 2, and the results have normalized during the glucocorticoid therapy. Currently, patient is eumetabolic with no therapy [16].

We have to bear in mind that AMD induced subclinical hypothyroidism can progress to AIT during AMD therapy. AIT can be asymptomatic, discovered in routine periodic thyroid checking. AIT type 2 is self-limiting condition with restitution of euthyroid state in a few months, passing through a phase of subclinical hypothyroidism, and AMD therapy withdrawal could be the only therapeutic measure [Figure 1,2].

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