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CASE REPORT
Arrhythmias/Electrophysiology

Frequent ventricular extrasystoles after heart transplantation: a late presentation of amiodarone-induced thyrotoxicosis: a case report

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Background There is a lack of information about a mixed type of amiodarone-induced thyrotoxicosis (AIT) after heart transplantation (HTx) with no amiodarone treatment in almost 1 year. Frequent ventricular extrasystoles (VES) associated with a mixed type of AIT can often be treated using thiamazole and prednisolone, without the need for specific antiarrhythmic treatment.

Case summary We present a clinical case of a 65-year-old heart transplanted male patient with frequent VES associated with mixed type of AIT. Recipient had managed with amiodarone prior to HTx but there were no indications for it after the surgery. One year after antiarrhythmic treatment was discontinued, monomorphic VES (total amount: 27 472/day) were diagnosed. In addition, our investigation revealed that thyrotoxicosis developed. Prednisolone and thiamazole were added to the treatment with positive outcomes. The antithyroid treatment had been discontinued after 9 months and results of the 24-h Holter electrocardiogram monitoring showed only two VES/24 h.

Discussion The case highlights the association of amiodarone, thyroid disorders, and VES. In mixed type AIT or if diagnosis is uncertain, it is reasonable to use mixed therapy. Next is to decide whether you need special treatment for VES. There was no evidence of ventricular tachycardia. Thyroid function tests remained normal off antithyroid medications and the total amount of VES significantly decreased. There were no indications for any antiarrhythmic treatment or ablation.

Keywords Heart transplantation • Thyrotoxicosis • Ventricular extrasystoles • Heart failure • Amiodarone • Case report

Learning points

- In patients who have been treated with amiodarone prior to heart transplantation, should be periodically screened for thyroid disorders to promptly diagnosed delayed onset amiodarone-induced thyroid dysfunction.
- It is important to consider the mixed type of amiodarone-induced thyrotoxicosis in borderline cases.

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Introduction

Amiodarone-induced thyroid dysfunction develops in 15–20% of patients under amiodarone therapy.[1] Two main forms of amiodarone-induced thyrotoxicosis (AIT) may occur: Type 1 is a form of iodine-induced hyperthyroidism occurring in patients with underlying thyroid abnormalities, and Type 2 is a destructive thyroiditis mainly due to direct cytotoxic effects of amiodarone on thyroid follicular cells of a normal thyroid gland.[2] At the same time, AIT Type 2 generally develops in patients without clinical, biochemical, and morphological evidence of thyroid disease.[3] One study showed that despite discontinuation of amiodarone treatment at the time of the heart transplantation (HTx) procedure, patients remain at risk for developing mixed thyroid disease. Heart transplanted recipients treated with amiodarone before HTx should, therefore, be monitored carefully for a development of thyroid dysfunction, especially within the first post-transplant year.[4]

Timeline

Heart transplantation (HTx)	A 64-year-old male patient prior HTx was managed with Amiodarone for atrial arrhythmias and it was discontinued after the surgery.	• Thyroid function tests were normal • Thyroid-stimulating hormone (TSH): 1.35 mIU/L
11 months after HTx, treatment for amiodarone-induced thyrotoxicosis (AIT) Type 2 started	• A complaint about a feeling of sinking heart, tachycardia, and dyspnoea • Frequent ventricular extrasystoles (VES; total amount: 27 472/day) • Oral prednisone treatment (30 mg/day)	• TSH: 0.003 mIU/L • Free thyroxine (FT4): 34 pmol/L • Free triiodothyronine (FT3): 6.99 pmol/L
1.5 months after treatment for AIT started	• A complaint about a feeling of sinking heart, tachycardia, and dyspnoea/breathlessness • Oral prednisone treatment (30 mg/day)	• TSH: 0.004 mIU/L • FT3: 4.16 pmol/L • FT4: 25.4 pmol/L
3 months after treatment for AIT started	• A complaint about tachycardia, breathlessness, and reduced exercise tolerance • Frequent VES (total amount: 26 768/day) • Oral prednisone plus thiamazole (10 mg/three times a day)	• TSH: 0.014 mIU/L • FT4: 46.6 pmol/L • FT3: 6.62 pmol/L
4.5 months after treatment for AIT started	• Less episodes of tachycardia and breathlessness, reduced exercise tolerance on the same level • Frequent VES (total amount: 9901/day) • Oral prednisone (15 mg/day) plus thiamazole (15 mg/day)	• FT4: 21.2 pmol/L • FT3: 3.4 pmol/L
9 months after treatment for AIT started	• Increase of exercise tolerance, no episodes of tachycardia or arrhythmia • VES (total amount: 2/day) • Prednisone and thiamazole discontinued	• TSH: 2.277 mIU/L • FT4: 11.3 pmol/L • FT3: 3.90 pmol/L

Case presentation

A 65-year-old male patient with atrial fibrillation prior HTx 1 year ago for end-stage ischaemic cardiomyopathy, presented with a sensation of feeling his 'heart sink'. There was no prior history of autoimmune disease or thyroid dysfunction and Type 2 diabetes was diagnosed ages prior HTx. The level of patient's thyroid-stimulating hormone (TSH) prior HTx was 1.35 mIU/L (normal values: 0.35–4.94 mU/L). Before HTx recipient was managed with antiarrhythmic treatment with amiodarone (200 mg/day) for atrial arrhythmias. But there were no indications to continue antiarrhythmic treatment after HTx. Recipient was treated with triple-drug therapy (steroids, tacrolimus, and mycophenolic acid), and basiliximab was used as an induction. Through the months we slowly tapered the dose of steroids that was at 8 mg/day. In fact, there were no associations between changes of doses of immunosuppressive agents and development of patient's complaints.

On cardiac examination, patient's heart rate (HR) and rhythm (108 b.p.m.) were regular with frequent extrasystoles. During auscultation heart sounds were clear and no cardiac murmurs have been heard. His 24-h Holter demonstrated sinus rhythm with a HR of 107 b.p.m. (from 93 to 131 b.p.m.), monomorphic ventricular extrasystoles (VES) (total amount: 27 472/day) were diagnosed (*Figure 1*). There was no evidence of atrial fibrillation and no other specific features have been found. According to trans-thoracic echocardiogram (TTE) results, the left ventricle function was normal and left ventricular ejection fraction (LVEF) was above 60%. There were no signs of diastolic dysfunction. N-terminal prohormone of brain natriuretic peptide, D-dimer, and troponin levels were fine.

Patient had no history of thyroid disorders but due to a development of VES we performed an extra investigation. Thyroid function

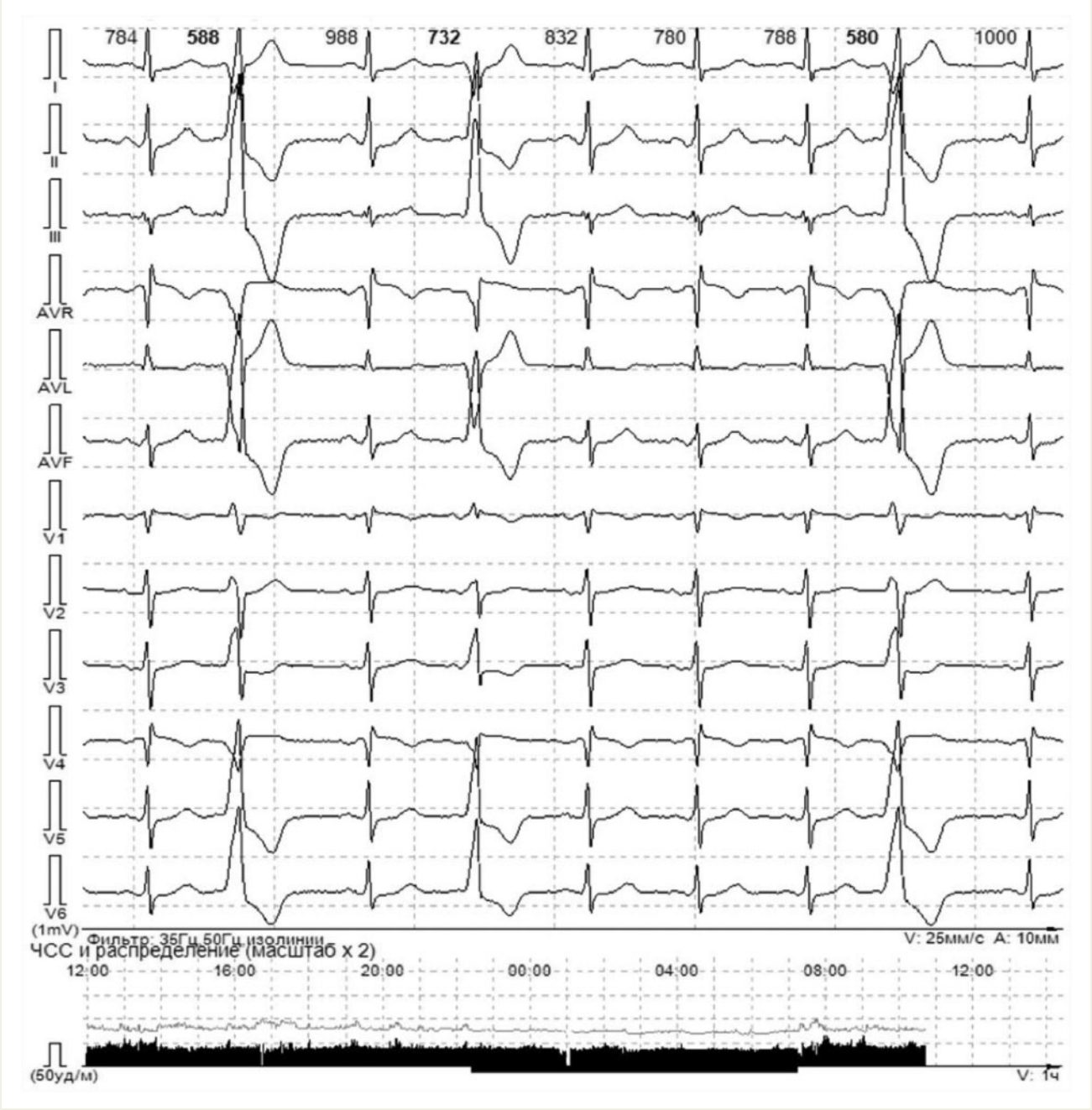

Figure 1 A 24-h Holter monitoring: ventricular extrasystoles diagnosed (total amount: 27 473 ventricular extrasystoles/24 h).

tests (TFTs) were as follows: free thyroxine (FT4)—34 (normal values: 9.0–19.0 pmol/L); free triiodothyronine (FT3)—6.99 (normal values: 2.63–5.69 pmol/L); and TSH <0.003 mIU/L. The level of anti-TSH-receptor antibodies was 0.67 ME/L (normal values: <1.00 ME/L) and antithyroid peroxidase (antithyroperoxidase)—0.0 ME/mL (normal values: 0.0–5.6 ME/mL). Erythrocyte sedimentation rate, C-reactive protein, and cell blood count were normal. Thyroid ultrasonography evidenced a diffusive enlargement of the gland and with no nodules; colour flow Doppler sonography showed a pattern 0 (absent hypervascularity). Our investigation revealed that patient had thyrotoxicosis. The diagnosis of destructive thyroiditis was based on the absence of hypervascularity in spite of high levels of serum thyroid hormones and antithyroid antibodies negativity. He was consulted with an endocrinologist. Prednisolone (30 mg/day) treatment was initiated. Moreover, endomyocardial biopsy was performed. There were no histological signs of cellular and/or antibody-mediated rejection.

A timeline of the patient's outpatient and inpatient follow-up was outlined: blood tests every 2 weeks to estimate levels of thyroid hormones and to fix doses of antithyroid treatment and 24-h Holter

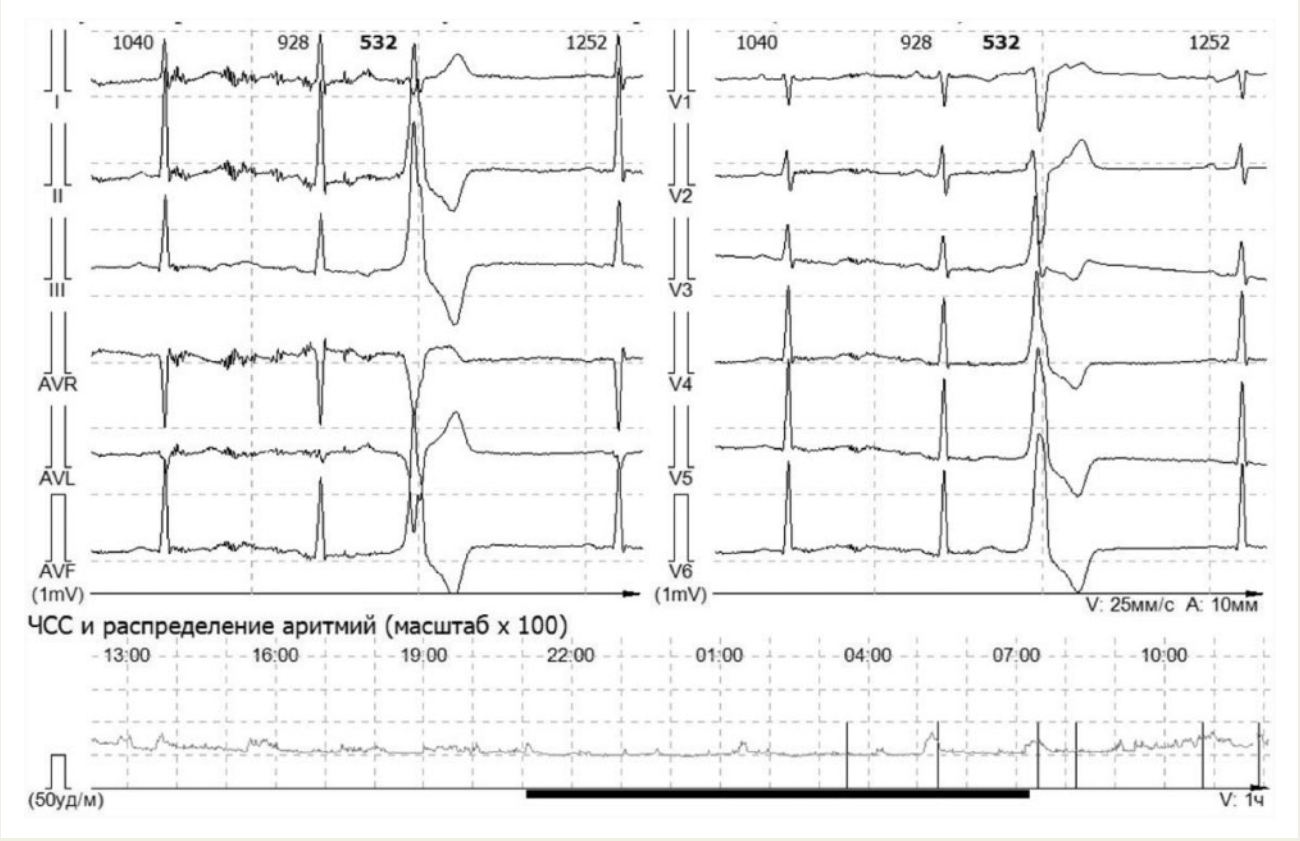

Figure 2 A 24-h Holter monitoring 9 months after initiated antithyroid treatment: ventricular extrasystoles (total amount: two ventricular extrasystoles/24 h).

monitoring every 2–3 months. Two months after initiated treatment recipient was studied with an ambulatory 24-h Holter electrocardiogram and results were the same: sinus rhythm with HR: 117 b.p.m. (from 104 to 138 b.p.m.), total amount of VES were 26 768/24 h. On the other side, the level of FT4 increased and mixed type AIT was hypothesized. According to blood results thiamazole was added to treatment (10 mg/three times a day). Furthermore, he had the same complaints, the same as exercise intolerance.

Given the presence of persistent VES, despite therapy for thyroid disease, we decided to consider a VE ablation. However, this was deferred as it was felt appropriate to achieve a euthyroid state in the first instance.

In fact, 5 months after antithyroid treatment was started, the number of VES per day was significantly decreased to 9901. At the same time, there was positive outcome of combined antithyroid treatment: serum free thyroid hormone concentrations (FT3: 2.35 pmol/L and FT4: 10.8 pmol/L, respectively) normalized in 4.5 months after initiated treatment and remained normal forward. After that recipient had been maintained by oral prednisolone (from 30 to 15 mg/day in <2 months) given in association with thiamazole (from 15 to 10 mg/day). In a month after doses had been reduced TSH became 5889 mIU/L, FT3 and FT4 were normal (3.88 and 11.5 pmol/L, respectively).

In addition, TTE remained normal during the whole post-transplant follow-up, LVEF: 61–65%.

Approximately 9 months after commencing antithyroid therapy (3 months post-normalization of TFTs), the patient had no recurrence of frequent VES on Holter monitoring. Also there was no dyspnoea and exercise tolerance increased. The antithyroid treatment (prednisolone plus thiamazole) had to be discontinued after 9 months. Moreover, the 24-h Holter monitoring was performed and results were unremarkable, no monomorphic VES and only two polymorphic VES were found (*Figure 2*). His last follow-up visit confirmed an euthyroid state 3 months after the antithyroid treatment had been stopped. Thyroid function tests remained normal off prednisolone plus thiamazole and the total amount of VES significantly decreased. Furthermore, patient admitted that his well-being improved. So there were no indications for any antiarrhythmic treatment or ablation.[5,6]

Discussion

Amiodarone is a Class III antiarrhythmic drug used in the treatment of recurrent severe ventricular arrhythmias, paroxysmal atrial tachycardia, atrial fibrillation, and maintenance of sinus rhythm after cardioversion of atrial fibrillation.[7] Our patient had been treated with amiodarone prior to HTx due to atrial arrhythmias but antiarrhythmic was discontinued after the surgery. In fact, amiodarone can lead

to hyperthyroidism (AIT) with suppressed TSH <0.1 and raised FT4 and FT3.[8]

In our case, patient did not have history of thyroid disorders, except being on amiodarone for almost 1 year prior to HTx. Overt hyperthyroidism is defined as a subnormal (usually undetectable) TSH with elevated serum levels of FT3 and/or FT4.[9] Patient's initial laboratory results confirmed hyperthyroidism with a FT4 of 34 pmol/L and a TSH of <0.003 mIU/L. Moreover, thyrotoxicosis has multiple aetiologies, manifestations and potential therapies. However, there is a lack of information about association of post-transplant thyrotoxicosis and immunosuppressive drugs. The administration of the calcineurin inhibitor, mycophenolic acid, or azathioprine may probably inhibit functions of CD4+ memory phenotype cells and significantly decrease the frequency of thyroid diseases and thyrotoxicosis recurrence.[10–12] In actual fact, tacrolimus, mycophenolic acid, and prednisolone are known to reduce the risk for thyroid autoimmune disorders, the immunosuppression may impact on the thyroid to turn into hyperfunction in long term after amiodarone was discontinued.[13] There is no proven data that particular immunosuppressive agents can cause or exacerbate thyroid disorders. Prior history of thyroid disorder is not a known contraindication for immunosuppressive therapy.

In mixed type AIT or if diagnosis is uncertain, it is reasonable to use mixed therapy.[8] Combined antithyroid drugs and corticosteroid therapy should be used to treat patients with overt AIT who fail to respond to a single modality therapy or patients in whom the aetiology of thyrotoxicosis cannot be unequivocally determined.[9] In our study, we started on 30 mg of prednisolone daily. But at about 3 months after initiated prednisolone treatment, the levels of FT3 and FT4 increased. That is why we added thiamazole.

About 4.5 months after thyrotoxicosis had been diagnosed, his free FT3 and FT4 normalized, and his thyrotoxic symptoms resolved. His prednisolone therapy was tapered over 9 months and then stopped. In our study, patient was treated with antithyroid drug therapy, i.e. treatment was discontinued as soon as he became euthyroid. Serial tests of thyroid function performed at monthly intervals showed that there was no recurrence of thyrotoxicosis and all indices of thyroid function returned to normal. There was no manifestation of VES after the antithyroid treatment was discontinued.

Although the described case was relatively simple and treatment was successful, AIT remains a diagnostic and therapeutic challenge for the physician. Identification of different AIT subtypes may be difficult and often imprecise. The difficulty in the initial assessment may hamper a correct therapeutic approach as patients can have atypical complaints like we described above. First-line treatment of AIT is generally medical. When a clear-cut diagnosis of mixed type AIT is made, mixed therapy are the best treatment (possibly associated with thiamazole). Next is to decide whether you need special treatment for VES. In fact, there was no evidence of ventricular tachycardia. Recipient's HR remained stable during the whole post-transplant follow-up. According to our heart team, in this clinical case patient did not require beta-blockers due to their low efficiency in a heart transplant population. We decided to perform ablation, but it could not be done until the achievement of euthyroid state. After the treatment there was no indications for any antiarrhythmic treatment or VE ablation.[5,6] Larger studies are needed to address the proper management approach of amiodarone-induced delayed thyroiditis following HTx.

Conclusion

Patients who were treated with amiodarone prior to HTx should be screened for thyroid disorders after the transplantation. No antiarrhythmic treatment including ablation can be required in case of post-heart transplant development of VES associated with thyrotoxicosis.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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