CASE REPORT

Amiodarone induced pneumonitis and hyperthyroidism: case report

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KEY WORDS

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ABSTRACT

Amiodarone is a highly effective antiarrhythmic agent used in life-threatening ventricular and supraventricular arrhythmias. Its long-term use may however lead to several adverse effects, including corneal deposits, liver and thyroid gland dysfunction, lung lesions, bone marrow injury, skin lesions, or neurological abnormalities. The article presents the case of a 56-year-old man with a history of a stroke, who after a few days of amiodarone therapy for an episode of atrial fibrillation was diagnosed with amiodarone-induced hyperthyroidism and interstitial pulmonary lesions. Clinical and laboratory symptoms of hyperthyroidism and radiographic signs of pulmonary involvement did not occur until several weeks after discontinuation of amiodarone therapy. Differential diagnosis of causes of hyperthyroidism and diseases causing nodular pulmonary lesions did not demonstrate any other pathologies. Empirical antibiotic therapy and administration of thiamazole and high doses of propranolol failed to improve the patient's clinical status. It was not until thiamazole was given in combination with glucocorticosteroids, when a slow relief of hyperthyroidism symptoms and resolution of radiographic pulmonary signs were observed.

Based on the presented case, the risk of appearance of 2 serious concomitant adverse effects was demonstrated, even following a short-term amiodarone therapy. This paper also contains an overview of adverse effects which may be encountered during or after therapy with this effective antiarrhythmic agent. It was emphasized how important it is to select patients appropriately, and to monitor potential adverse effects during amiodarone therapy.

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INTRODUCTION The use of medications is always associated with a risk of development of adverse effects, either well known and documented in available data, or completely unexpected. It is estimated that drug-induced adverse effects account for 5–7%, and in the elderly even for 10%, of all hospitalizations and are responsible for 0.15–0.3% of inpatient deaths.[1] Undesirable effects of therapy often cannot be avoided, therefore the risk of their occurrance should be kept in mind, which allows establishing early diagnosis and implementation of the adequate management.

CASE REPORT A 56-year-old locksmith, abusing alcohol and smoking cigarettes, with no previous history of chronic therapy, was admitted to the Department of Neurology with the rapid onset of speech and gait disorders. On admission the patient was in a moderately severe condition. Neurological examination demonstrated mixed sensomotor aphasia, profound right-sided paresis and positive Babiński's sign on the right side. The computed tomography (CT) of the brain showed features of a hemorrhagic stroke of the left hemisphere. The chest X-ray did not reveal any new onset consolidations, and function of the pulmonary circulation was normal. The ECG showed a regular sinus rhythm, with

no signs of recent myocardial ischemia. Laboratory tests were characteristic of macrocytic anemia – hemoglobin 10.3 g/dl (norm: 14–18 g/dl), mean corpuscular volume 102 μm^3, ferritin 673 ng/ml (norm: 13–150), transferrin 169 mg/dl (norm: 200–360), vitamin B_{12} 181 pg/ml (norm: 191–663), folic acid 3 ng/ml (norm: 2.7–3.4), fibrinogen 731 mg/dl (norm: 200–400), mild electrolyte disorders, i.e., sodium 135.5 mmol/l (norm: 137–148), potassium 5.04 mmol/l (norm: 3.6–5.0). A reduced level of albumins was also observed – 2.8 g/dl (norm: 4.3–5.1), with a normal level of total protein (6.5 g/dl). Symptomatic treatment was introduced, nevertheless a general condition of the patient deteriorated during the first days of hospitalization, and ventilatory support and treatment intensification were required. The follow-up cranial CT showed no signs of more extensive central nervous system bleeding. According to the results of additional tests and the ECG recording, recent myocardial infarction was ruled out, and no abnormalities were observed in the follow-up chest X-ray. After stabilization of a general condition of the patient and his return to a general room, the symptoms and signs of hypovolemic shock and acute renal failure developed (elevated levels of creatinine and urea, electrolyte disorders, i.e., potassium 6.21 mmol/l, sodium 155.3 mmol/l), most likely resulting from dehydration of the patient. Intravenous rehydration, dopamine in continuous infusion, and forced diuresis were implemented, and the patient was again monitored in the Neurological Intensive Care Unit (NICU). During intensive therapy in the NICU, atrial fibrillation occurred. Due to ineffectiveness of digoxin (a single dose of 0.5 mg *i.v.*) and a severe general condition of the patient associated with stroke, amiodarone was administered, initially in a bolus injection, and subsequently in continuous infusion, with the resultant decreased heart rate and restoration of the sinus rhythm on the second day of treatment (a total dose of amiodarone was approximately 1200 mg). Because of the need for immediate amiodarone therapy, and the recent stroke, tests recommend before introduction of this drug, i.e. pulmonary function tests and the determination of thyroid stimulating hormone (TSH) level, were not performed.

2 months later, because of tachycardia of unknown origin, levels of thyroid hormones were measured. On the basis of the obtained results, including TSH – 0.001 mIU/ml (norm: 0.350–4.940), free triiodothyronine (fT_3) – 7.06 pmol/l (norm: 2.63–5.70) and free thyroxine (fT_4) –37.57 pmol/l (norm: 9.0–19.0), hyperthyroidism was diagnosed. Thiamazole therapy was started, initially at a dose of 10 mg daily, and because of lack of improvement the dose was gradually increased to 30 mg daily. The chest X-ray, performed due to persistent cough and elevated body temperature (3 months after discontinuation of amiodarone), demonstrated subtle alveolar consolidations, tumor-like pneumonia in the upper lobe of the left lung, and a nodular lesion in the middle field of the left lung. Broad-spectrum antibiotic therapy was used, which did not produce any improvement. The chest CT demonstrated an area of consolidated opacities at the base of the upper lobe of the right lung, disseminated micronodular interstitial lesions in the middle-upper pulmonary fields, and one slightly enlarged (11 mm) mediastinal lymph node. A suspicion of sarcoidosis was formed, and the patient was transferred to the Department of Pneumonology.

On admission the patient was in a moderately good general condition, reported mild cough with expectoration of white sputum, and exertional dyspnea. Cachexia and right-sided paresis were noticed during the physical examination. On auscultation, the vesicular sound was normal, and no additional sounds were heard. Laboratory tests revealed anemia (hemoglobin 11.2 g/dl) and slightly elevated erythrocyte sedimentation rate (ESR) – 25 mm/h. Diagnostic procedures for sarcoidosis failed to demonstrate abnormalities specific to this disease including angiotensin-converting enzyme (ACE) activity of 4.6 U/l (norm: <35.5 U/l), Ca^{2+} serum level of 2.09 mmol/l, and tuberculin skin test of 10 mm. Pulmonary function tests demonstrated slight elevation of airway resistance, 3.19 cm $H_2O/l \times s^{-1}$ (norm: <3.06) and residual volume (155% of the predicted value). Because of marked tachycardia and elevated arterial blood pressure during an attempt of bronchoscopy, invasive diagnostic procedures were postponed until the resolution of thyrotoxicosis symptoms. Despite a 2-month thiamazole therapy at the dose increased to 60 mg/24 h and a 2-week propranolol therapy at the dose of 120 mg/24 h, clinical and laboratory symptoms and signs of hyperthyroidism persisted (TSH – 0.0 mIU/ml, fT_3 – 5.57 pmol/l, fT_4 – 24.96 pmol/l). The USG demonstrated an enlarged thyroid gland of a heterogeneous ultrasonographic structure with scarce areas of hypoechoic reflections in both lobes. Serum assays did not detect any antithyroid antibodies (against thyroperoxidase, thyroglobulin and TSH receptor). Amiodarone-induced hyperthyroidism was diagnosed, prednisone was administered (20 mg/24 h), the thiamazole dose was reduced to 30 mg/24 h and the propranolol dose was reduced gradually, which resulted in a slow return of free thyroid hormone levels to normal values (fT_3 4.22 pmol/l, fT_4 16.30 pmol/l) and in a gradual increase in the TSH level (0.002 μIU/ml).

The patient was referred to a rehabilitation centre, where he underwent a 2-month treatment and motor rehabilitation, and was then readmitted to the Department of Pneumonology for completion of diagnostic evaluation. On admission the patient was in a good general condition, with significantly improved motor function, and he reported no respiratory complaints. The chest X-ray performed at that time demonstrated only a small shadow (about 10 mm)

in the middle-upper field of the left lung. Marked regression of interstitial lesions was demonstrated in the high-resolution computed tomography (HRCT) of the lungs. The flexible bronchoscopy did not reveal any abnormalities in the bronchial tree, however bronchoalveolar lavage demonstrated an increased cell count (25.8×10^6), particularly with regard to eosinophil population (23%). Foam macrophages and eosinophilic amorphous deposits could also be observed. The histologic examination of bronchial mucous membrane biopsy samples, taken during bronchoscopy, demonstrated only mild inflammatory lesions. According to the 5-point criteria for drug-induced lung injury by Camus[2], on the basis of clinical symptoms, the course of the disease and negative results of immunological tests (malignancy markers, perinuclear-staining anti-neutrophil cytoplasmic antibodies, cytoplasmic-staining anti-neutrophil cytoplasmic antibodies, latex and Waaler-Rose tests) which did not indicate connective tissue disease, vasculitis or cancer, amiodarone-induced interstitial pneumonia was diagnosed. The patient in a good general condition, without dyspnea, with a good cardiorespiratory function, ambulating with a walker, was discharged home with recommendations to continue the previous therapy (thiamazole 10 mg/24 h, prednisone 10 mg/24 h, propranolol 30 mg/24 h, furosemide, potassium, magnesium) and outpatient follow-up. Nevertheless, the patient was lost to follow-up in the outpatient clinic at the Department due to his noncompliance.

DISCUSSION Amiodarone is a effective antiarrhythmic agent in prevention and treatment of both supraventricular and ventricular arrhythmias.[3] However, its use is significantly limited by numerous undesirable effects. Liver and thyroid gland abnormalities are most commonly observed, with lower prevalence of lung or bone marrow injury, skin lesions, or neurological abnormalities. Up to 90% of patients taking this drug are diagnosed with corneal deposits.[4] Amiodarone toxicity is associated with its very long (58 days) half-life, resulting from its lipophilicity and accumulation in the adipose tissue, muscles and many other organs.[5] Therefore, this medication can cause adverse effects up to several months after its discontinuation. It is thus not surprising that the pulmonary lesions and hormonal disorders, described above, were detected within several weeks after short-term amiodarone treatment.

Amiodarone therapy requires TSH, fT_3 and fT_4 levels monitoring, anti-thyroperoxidase antibody titer determining, and performing the USG of the thyroid gland. The effect of amiodarone on the thyroid gland is diverse, and is associated with structural similarity to thyroxine and high iodine content in a molecule of the drug. It blocks the activity of 5' deiodinase in the liver and other tissues, which results in the increased T_4 and decreased T_3 levels caused by inhibition of T_4 to T_3 conversion.[6] A direct toxic effect of amiodarone on the thyroid gland can also occur. Administration of this medication may produce both hyperthyroidism and hypothyroidism, however the symptoms of hypothyroidism are more commonly observed.[5] Amiodarone-induced hypothyroidism develops mainly in women, the elderly, and also in regions with no iodine deficiency.[6] Autoimmune thyroiditis (Hashimoto goiter) and positive results of anti-thyroperoxidase antibodies are also listed among risk factors.[7,8] If antiarrhythmic therapy is necessary, amiodarone can be continued with L-thyroxine. Sometimes euthyroidism may be restored spontaneously.[8]

The reported prevalence of hyperthyroidism is highly variable ranging 1–23%.[6] Characteristically, amiodarone-induced hyperthyroidism is more prevalent in areas with dietary iodine deficiency. This complication is observed 3 times more often in men than in women.[6] Antiadrenergic effect of amiodarone may be responsible for absence of clinical symptoms typical of hyperthyroidism. 2 types of amiodarone-induced hyperthyroidism are distinguished, and each of them requires different therapy. Type 1 is associated with increased synthesis of thyroid hormones due to iodine excess, with normal or excessive accumulation of ^{131}I. This form of the disease requires a combination treatment with high doses of thyrostatic agents and potassium perchlorate. Type 2 of amiodarone-induced hyperthyroidism, which was diagnosed in the current case, is characterized by acute thyreoiditis and release of thyroid hormones from damaged alveolar cells. It is associated with reduced ^{131}I accumulation. In this situation, as in this case, treatment with glucocorticosteroids is helpful.[6] In contrast, even high doses of thyrostatic agents (60 mg of thiamazole daily in the presented case) do not reduce thyroid hormone levels in peripheral blood. In some cases, administration of glucocorticosteroids likewise does not result in clinical improvement, and thyroidectomy is necessary. It seems that there is no association between the daily or total dose of amiodarone and the risk of amiodarone-induced hyperthyroidism.[6] However, if it develops, discontinuation of the drug is recommended.

Available data provide inconsistent information about prevalence of pulmonary lesions in patients treated with amiodarone, but at present it is estimated that they may appear in 5–7% of the treated patients, resulting in death in 5–10% of patients from this group.[4] It is believed that pulmonary lesions may occur even during administration of a daily dose of 200 mg.[9,10] They develop in the course of hypersensitivity reactions or due to damaging effects of iodine. Different amiodarone-induced pulmonary lesions were reported, with lung fibrosis being most prevalent, and organizing pneumonia and acute respiratory distress syndrome occurring less frequently.[11] Dry cough is the main symptom of pulmonary manifestation of undesirable effects of amiodarone, and it may be accompanied by dyspnea, weight

loss and fever.[4] Physical examination may reveal crepitations over the lungs. However, radiographic changes in the lungs are frequently not accompanied by apparent clinical symptoms. Disseminated interstitial lesions are seen on the lung X-ray. The HRCT imaging plays a special role, because it allows visualization of pulmonary lesions even in asymptomatic patients.[12] Most commonly it shows disseminated thickening of alveolar septa, and less frequently subpleural nodules, similar to these observed in the reported patient. Parenchymal consolidations are even less commonly observed.

It is difficult to give a clear reason for mediastinal lymphadenopathy visualized on the chest CT scans. Some agents, including phenytoin, bleomycin, or penicillins, can be responsible for mediastinal lymphadenopathy.[2] A size of the lymph node (11 mm) did not justify invasive diagnostic approach. Patients with amiodarone-induced pulmonary lesions demonstrate non-specific elevation ESR, leucocytosis and lactate dehydrogenase activity. Increased peripheral blood eosinophilia is reported in few cases, and an increased eosinophil count in bronchoalveolar lavage fluid (BALF) is much more frequent, as it was in the reported case.[13] BALF may demonstrate diverse abnormalities in the cell count, and an increased count of not only eosinophils, but also lymphocytes and neutrophils was observed.[13] Pulmonary function tests may demonstrate restrictive ventilation disorders, but it is the examination of diffusing capacity for carbon monoxide that is especially recommended in patients treated with amiodarone.[11] This value was normal in the reported patient, however the test was performed after initiation of glucocorticosteroid therapy. In many patients, discontinuation of amiodarone is sufficient for slow and spontaneous regression of pulmonary lesions.[4] In case of clinical symptoms and advanced radiographic-functional abnormalities, glucocorticosteroids are recommended, which brings improvement and slow regression of interstitial pulmonary lesions, like in this patient. In the current report, interstitial lesions had a pattern of nodules and organizing pneumonia, which are associated with a much better prognosis than amiodarone-induced lung fibrosis. Discontinuation of the drug and administration of glucocorticosteroids usually result in regression of lesions. Lung fibrosis, developing with chronic administration of amiodarone, is irreversible.[11]

Amiodarone-induced lung injury was diagnosed based on clinical symptoms and the course of the disease, after the elimination of other pathologies.[15] Infectious etiology seemed rather unlikely, because of effectiveness of glucocorticosteroids and lack of improvement after the administration of broad spectrum antibiotic therapy. Both radiographic and clinical symptoms and signs were not typical of heart failure. No features of malignancy were found (bronchoscopic picture was normal, neither suspected cells in BALF, nor cancer markers in blood were identified). At the same time the suspicion of sarcoidosis could not be confirmed, because of the very low ACE level, the positive tuberculin test, and the high eosinophil count in the BALF. There were also no grounds to diagnose pulmonary lesions in the course of connective tissue diseases, because serologic tests were negative, and no abnormalities were observed in other systems or organs. The development of complaints during hospitalization, with no clear exposure to any allergens, and the pattern of pulmonary lesions on the X-ray weighed against the diagnosis of allergic alveolitis. It is not possible to rule out eosinophilic pneumonia, although no eosinophilia in peripheral blood was observed, and the disease ran a chronic course. However, the most difficult task is to distinguish between amiodarone-induced lung injury and cryptogenic organizing pneumonia (COP), which can be idiopathic or secondary (in the course of other diseases, including drug-induced reactions). Among drugs taken by the patient, only amiodarone is listed among potential causes of COP-like pathologies. The radiographic picture of COP can have the pattern of nodules or consolidating peripheral opacities; BALF demonstrates polymorphic abnormalities, however the eosinophil count is not as high as in the reported case. Initially, the condition of the patient precluded lung biopsy, and because pulmonary lesions regressed after the administered treatment, the biopsy was abandoned, which made it impossible to distinguish between these diseases.

It is estimated that 34–93% of patients treated with amiodarone will develop an adverse effect, usually within the first year of therapy, and in 2–26% of cases discontinuation of amiodarone will be necessary because of undesirable effects.[14] In the presented case, the several-day amiodarone therapy was followed by pulmonary and thyroid side effects. Both of these complications has been reported in the literature in detail separately, however the authors of the present article could not identify any reports showing their concurrent occurrance.

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