PULMONARY TOXICITY INDUCED BY AMIODARONE – A DIAGNOSIS CHALLENGE

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Abstract: *The use of Amiodarone as a first-line antiarrhythmic agent in secondary prophylaxis of sudden cardiac death is limited by its well-known toxicity. The side effects depend on the age of the patient, the dosage and the duration of the treatment. We hereby present the case of a 62-year old female patient, with obesity and hypertension, with a history of malignant rhythm disorders and a long and effective, but unsupervised treatment with Amiodarone. After a period of 7 years, the patient is hospitalized with severe acute respiratory insufficiency, initially diagnosed as a high risk pulmonary thromboembolism. Although the specific treatment, including the thrombolytic one, improved the respiratory and hemodynamic status of the patient, it did not have the estimated result. The repeated imaging showed parenchymal aspects, not farmable in the initial diagnosis, corresponding to pulmonary fibrosis. The treatment with Amiodarone was replaced with corticotherapy, resulting in a noticeable alleviation of respiratory status.*

INTRODUCTION

Amiodarone is a powerful antiarrhythmic agent that contains iodine and is widely used in the treatment of supraventricular and / or ventricular arrhythmias.(1) The toxicity of Amiodarone can lead to a number of pulmonary diseases such as: interstitial pneumonia, acute respiratory distress syndrome, diffuse alveolar hemorrhage, pulmonary fibrosis, pulmonary nodules and sometimes pleurisy.(2) Pulmonary toxicity induced by Amiodarone (AIPT) occurs in 2-10% of the treated patients, as the most severe adverse effect. Usually, AIPT is associated with large cumulative doses that have been administrated for years and with high daily doses of over 400 mg.(3) AIPT remains a difficult diagnosis of exclusion due to the lack of specificity of the noninvasive criteria. The specific criteria are the histopathology results, if available.

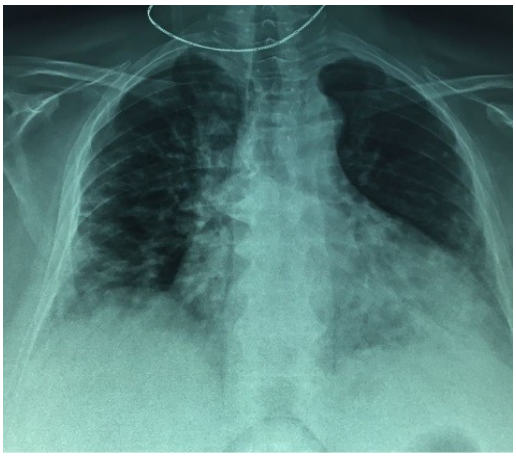
CASE REPORT

We present the case of a 62 year-old female patient, with a history of arterial hypertension and recurrent ventricular arrhythmia (TV) treated with Amiodarone 200 mg/day, for 7 years, Prestarium – 5 mg/day and Lokren – 20 mg/day. After an eventless 7-year period, the patient is hospitalized after two weeks of progressive dyspnea, dry cough and fever. Upon admission in the hospital, the general health state is altered, afebrile, and with a respiratory rate of 28 breaths per minute. The pulmonary stethacoustic showed subcrepitant and bronchial rales present in both lungs. Oxygen saturation was of 66% in atmospheric air and of 77% with oxygen provided through the mask. There could be noticed rhythmic cardiac sounds, slightly blurred, with no murmurs or gallop, the arterial tension was of 180/100 mmHg and the heart rate was of 80 bpm, sinus rhythm.

The laboratory tests indicated neutrophilic leukocytosis, serum electrolytes concentration within normal range, polyglobulia and moderate increase of necrosis markers: myoglobin (MYO)=213 mg/ml, troponin I (TNI)=0,09 ng/ml and brain natriuretic peptide (BNP)=1360 pg/ml, D-Dimer (DDIM)=2960 ng/ml. The ASTRUP test revealed hypoxemia without hypercapnia or modifications of the acid base balance.

The Doppler echocardiography revealed concentric left ventricular hypertrophy with normal systolic function, diastolic dysfunction with delayed relaxation pattern, enlarged right cavities, with super unit ratio of right ventricle/left ventricle (RV/LV), flattened interventricular septum (IVS) (D-shaped) and pulmonary hypertension estimated as medium. The suggested pulmonary CT with contrast exposed filling defects in the upper and lower right lobe arteries (figure no. 1. a,b).

Figure no. 1.a. Upon admission: Rdg. PA-CP: bilateral alveolar opacities, with the tendency for right basal confluence, pleural effusion in the right costodyaphragmatic sinus



Consequently, the diagnosis of the stage was very high risk pulmonary thromboembolism, with a 10%-24,5% of mortality rate estimated at 30 days (according to PESI score - Pulmonary Embolism Severity Index – calculated at 172). Moreover, the presence of pulmonary condensations on

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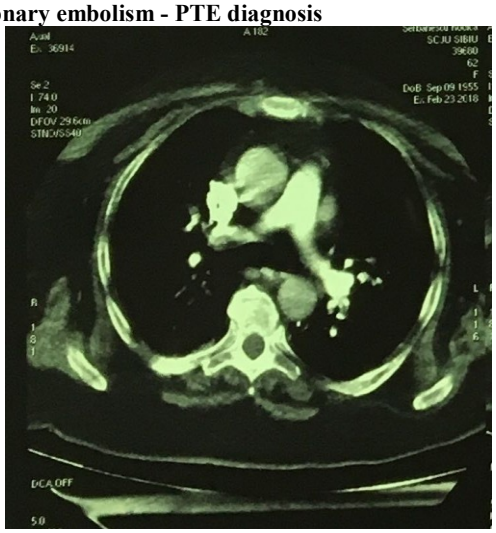
infectious background, clinically and biologically demonstrated, required performing bacteriological tests and non-specific antibiotherapy. Initially, the patient was stable from a hemodynamic point of view, despite the increased tensional values which required a triple antihypertensive association (Carvedilol-2x12,5mg/24h, Olmesartan/Amlodipine-40/5 mg/24h).

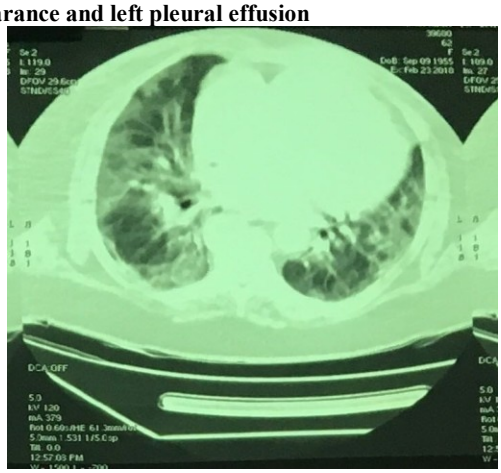
Figure no. 1.b. The Angio CT scan performed upon admission shows the following: filling defects at the upper and lower lobe arteries (the result is compatible to the pulmonary embolism - PTE diagnosis



Consequently, the first option was the IV heparinotherapy at the therapeutically adjusted dosage. Subsequently, under the conditions of deterioration of the respiratory and hemodynamic status, thrombolysis with Actylise is initiated, followed by heparinotherapy according to the protocol. The health status of the patient improved hemodynamically, but the severe respiratory insufficiency persisted, with a high level of desaturation, which made oxygen therapy still compulsory.

The native thoracic CT was repeated, thus revealing important parenchymal changes, unjustified by thromboembolic vascular pathology, but radiologically interpretable as pulmonary fibrosis (figure no. 2).

Figure no. 2. Native thoracic CT, a week after admission: bilateral alveolar condensations with ground glass opacity appearance and left pleural effusion



It is thus necessary to accept a causal relationship between the present pathology and the prolonged treatment with Amiodarone. The diagnosis of pulmonary thromboembolism is supported by Amiodarone Induced Pulmonary Toxicity (AIPT). Starting with the 4th day of admission in the hospital, the Amiodarone treatment was interrupted and Diltiazem HTP was initialized, despite the fact that the patient could not be tested in this respect. From day 5, corticosteroid therapy began, and the respiratory status improved significantly (normal gasometry values, without oxygen demand). After 10 days of corticotherapy, the patient was discharged with indications from the pulmonologist to follow the methylprednisolone therapy with subsequent dose adjustment.

Assessing the patient's ischemic and arrhythmic risk by practicing an antiarrhythmic alternative is an immediate goal.

DISCUSSIONS

Amiodarone was first used in Europe in the '60s for the treatment of angina pectoris. It began to be widely used as an antiarrhythmic agent in the 1970s. Currently, it is one of the most commonly used antiarrhythmic agents for the treatment of tachyarrhythmias. However, the frequent side effects limit its long term use.(5) We often come across situations when Amiodarone is used for an unlimited period of time (over 10 years), with no precautions regarding its side effects.

By analysing 237 cases of AIPT, Leanne Stafford et al. have demonstrated that the main risk factors are the age of the patient and the duration of the treatment.(6) This fact is observable in the case of our patient as well, as she has been treated with Amiodarone for 7years. Other risk factors are the male gender, the preexisting pulmonary disease and supplementary oxygen therapy in high doses, with or without mechanical ventilation.(7)

The exact mechanism of Amiodarone induced pulmonary toxicity is unclear. Some authors have argued that the main mechanisms are represented by the direct cytotoxic pulmonary lesion. A reaction of indirect hypersensitivity is also plausible.(8)

The differential diagnosis of AIPT includes chronic bronchitis, chronic eosinophilic pneumonia, and interstitial pneumonia. In patients with chronic adjacent cardiopulmonary diseases, the diagnosis is even more difficult. In such cases, a temporal relationship regarding the intake of Amiodarone over a few months or years may be a valuable clue.(9)

There is no specific test in order to diagnose the pulmonary toxicity of Amiodarone. The diagnosis is based on the clinic presentation, radiographic imaging and on histopathological results, as it is basically an exclusion diagnosis.(9) Susceptible patients may be at risk for acute pulmonary edema, pulmonary embolism, as in our case, or other acute events that may require differential diagnosis. Within the proper clinical frame, the imaging results described above may be sufficient to endorse the diagnosis and to initiate the treatment.(7)

Gallium scanning with the increase of gallium absorption may predict an inflammatory process, but this is nonetheless a non-specific result. The functional pulmonary tests usually represent a restrictive pattern with a low diffusion capacity. The bronchoalveolar lavage may indicate an inflammatory process or an immune response.(10) In the case of an unclear diagnosis, pulmonary biopsy may be needed, otherwise an avoidable procedure due to the high risk of aggravating the respiratory symptoms after a thoracic surgical intervention.(7)

The main treatment in AIPT is the interruption of Amiodarone administration. In the beginning, disease progression can occur due to accumulation of the drug in the adipose tissue and prolonged half-life.

Okayasu et al. have shown that patients with increased

adipose tissue (measured through an increased body mass index) are more susceptible to recurrences due to high concentration of lipophilic Amiodarone in adipocytes.(11)

Additional therapy involves corticotherapy (prednisone 40-60 mg daily) that can be administrated for prolonged periods.

In our case, the patient discontinued the treatment with Amiodarone on the 4th day of hospitalization, and then corticotherapy was initiated, which indicated a significant improvement in the respiratory status. She was discharged with the indication of treatment with methylprednisolone 30 mg/24h, for at least three months.

Approximately 75% of the Amiodarone induced pulmonary toxicity cases have a favourable outcome after discontinuing the treatment, with or without the addition of corticosteroids.(12)

CONCLUSIONS

Amiodarone induced pulmonary toxicity is a rare and difficult diagnosis. We are looking at a primarily exclusion diagnosis, because the pulmonary fibrosis on Amiodarone cannot be tested with specific methods.

AIPT should be on the differential diagnosis list for any patient suffering from an acute impairment of respiratory function with the current or recent use of Amiodarone.

The therapeutic routine consisting in discontinuing the Amiodarone treatment and in introducing the corticosteroids proved to be beneficial as the long-term prognosis was favourable.

We have chosen this first case to be published mainly to bring to spot light the possible severe side effects of Amiodarone, as the most used antiarrhythmic drug. We wish to emphasize the difficulty of the primary diagnosis in a female patient with multiple causes of severe respiratory insufficiency. The patient has followed this justified treatment for the secondary prophylaxis of sudden death, by maintaining apparently safe daily doses, administrated over a long period of time.

Regular check-ups, mainly cardiologic ones, with the assessment of the arrhythmic and ischemic risks, as well as the implication of the pulmonologist, endocrinologist and ophthalmologist are absolutely compulsory in the management of these patients. Early stage detection of Amiodarone toxicity is valuable in avoiding extremely severe, possibly life-threatening complications.

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