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INTERSTITIAL PNEUMOPATHY INDUCED BY AMIODARONONE, A DIAGNOSIS THAT MUST BE REMEMBERED

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Abstract: Organizing pneumonia secondary to the use of amiodarone is rare, with an interstitial pattern mostly of subacute or chronic clinical onset, with less than 10 cases described in the literature. The initial clinical suspicion is usually suggested as a respiratory tract infection, with persistent cough and progressive dyspnea. Usually, the disease is idiopathic, however, it can be associated with connective tissue diseases, radiation, drug toxicity (in addition to amiodarone, gold, cocaine and crack) and infections. In the complementary exams, moderate hypoxemia, radiography with interstitial-alveolar infiltrate, mainly in the lung bases, pulmonary function test with restrictive ventilatory disorder and decreased diffusion are found. Amiodarone is a drug widely used for the treatment of cardiac arrhythmias, and its mechanism of drug toxicity is not well known, but there are indications that it is dose-dependent, with an increased risk being well reported in doses above 400mg/day, or even low doses (100 mg/day) for prolonged periods. Its half-life is long, from 40 to 70 days, which means that improvement will be seen after discontinuation within months. Most with a good prognosis, all treated with corticosteroids have marked improvement after two to six weeks, and recurrences are rare. In the present report, an 86-year-old female patient, with cumulative use of this medication, had a chest tomography showing areas of mosaic paving with parenchymal retraction. After discontinuing the medication, the clinical picture was stabilized and the lung parenchyma recovered, in addition, she was treated with systemic corticosteroids – prednisone and inhaled – budesonide due to her pulmonary comorbidity, COPD.
Keywords: Organizational pneumonia. Amiodarone. drug toxicity.

INTRODUCTION

Organizing pneumonia is a rare, usually idiopathic, disease; in other cases, the etiology can be associated with connective tissue diseases, inhalation of toxic gases, infections (viral, Legionella, Mycoplasma) and drugs (amiodarone, bleomycin, methotrexate, cocaine, crack, etc). Amiodarone is a drug used to treat some cardiac arrhythmias, but it can cause serious lung damage. Amiodarone accumulates in the lung largely in macrophages and type 2 pneumocytes. treatment, the total cumulative dose is more important than the daily dose.

Pulmonary manifestations of its toxic effects include: 1) Histological pattern of usual interstitial pneumonitis with xanthomized macrophages in the alveolar lumen; 2) Diffuse alveolar damage; 3) Organizing pneumonia or bronchiolitis obliterans with organizing pneumonia. The clinical picture can range from dry and mild cough, dyspnea to classic respiratory failure, with fatigue on exertion being the predominant clinical picture. Progression to irreversible pulmonary fibrosis occurs in 30% of cases.

GOAL

To report a case with marked regression after discontinuation of medication and include amiodarone-induced organizing pneumonia in the differential diagnoses of patients presenting with dyspnea.

CASE REPORT

Patient, 86 years old, female, with chronic obstructive pulmonary disease (COPD), former smoker and with paroxysmal atrial fibrillation (AF). She was on regular use of: captopril (25 mg 8/8 hours), propranolol (40 mg 12/12 hours), amiodarone (200 mg once a day) and levothyroxine (75 mcg once a day). Admitted to the Emergency Room

with a report of dry cough and progressive dyspnea for 3 days with evolution to minimal exertion; she denied fever and other associated symptoms. Treatment with Ceftriaxone and Azithromycin was started due to the hypothesis of Pneumonia, but without improvement. After 5 days of hospitalization, the patient presented, in addition to the condition already described, retrosternal chest pain, tightness, of strong intensity (10/10) radiating to the cervical region and left upper limb, with sudden onset and duration of 20 minutes. An electrocardiogram was performed, which showed atrial fibrillation and ST-segment depression in the precordial leads (v1 to v6). , but with persistent depression in V5 and V6 on electrocardiogram. On physical examination, he presented agitation and disorientation, blood pressure (BP) 140/90 mmHg, heart rate 132bpm in AF rhythm, respiratory rate 26 IRPM and SatO2 95% on room air, without murmurs, decreased breath sounds with diffuse wheezing and snoring in upper third of the right hemithorax, with prolonged expiratory time, without pathological jugular distension and other congestive signs. Other items of the physical examination were unchanged. About past pathological history, previous comorbidities: paroxysmal AF, Systemic Arterial Hypertension (SAH), COPD, former smoking (48 pack-years, stopped 30 years ago) and Hypothyroidism. She has a positive family history of cardiovascular diseases, the two sisters died of Acute Myocardial Infarction (AMI) at 54 and 62 years of age.

During hospitalization, she persisted with difficult-to-control bronchospasms, even with the use of systemic corticosteroids, inhaled bronchodilators and antimicrobials – tazobactan / piperacillin. Paroxysmal AF was always reversed with the use of intravenous amiodarone, the episodes started approximately every 2 days, in the use of rivaroxaban due to CHA_2DS_2-VASc equal to 5.

Chest radiography with elevation of the right hemidiaphragm and diffuse heterogeneous opacities. There was no change in laboratory tests, including thyroid function, infectious screening and NT-proBNP (108 pg/ml / Reference value: <125 pg/ml), except for a mildly elevated troponin curve (111 - 0h, 109 - 6h and 103 - 9h / Reference value: 19 ng/ml) which suggests only myocardial injury not characterizing acute coronary syndrome. The transthoracic echocardiogram showed preserved ventricular ejection fraction (65%), moderately enlarged left atrium, mild concentric ventricular hypertrophy, grade 2 diastolic dysfunction and PASP 42 mmHg, without akinesias and hypokinesias of the ventricular walls. High resolution chest tomography showed chronic obstructive bronchopulmonary disease with centrilobular emphysema, consolidation in the posterior segment of the lower and middle lobes of the right lung, in addition to areas of ground-glass opacification - in mosaic, accentuation of bronchovascular marks, especially central, with parenchymal retraction and bronchial ectasia suggestive of organizing pneumonia (Figure 1).

Considering the suspicion of amiodarone-induced pneumopathy, amiodarone (200 mg 8/8 hours) was replaced by bisoprolol (10mg once a day) to control heart rate, maintaining prednisone (40mg daily) and starting inhaled corticosteroids. The patient then showed a dramatic clinical and radiological response to the treatment instituted after 11 days of hospitalization. A new CT scan of the chest was performed after 3 months (Figure 2), which showed complete resolution of pulmonary consolidation, complete reduction of areas of ground-glass attenuation and other findings that were evolutionarily unaltered.

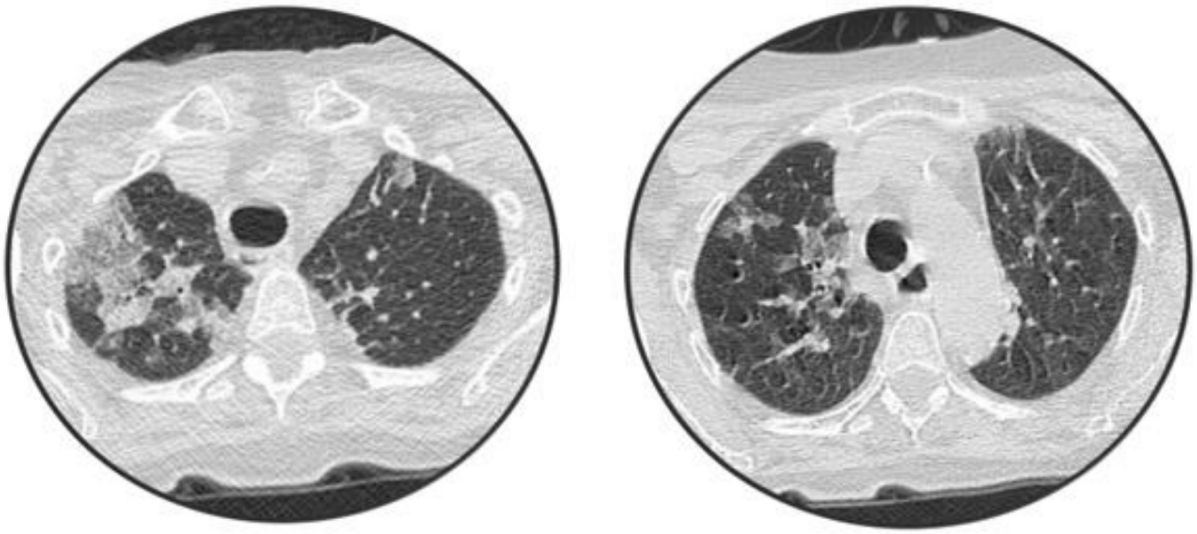

Figure 1: Computed tomography of the chest without contrast, with signs of PID.

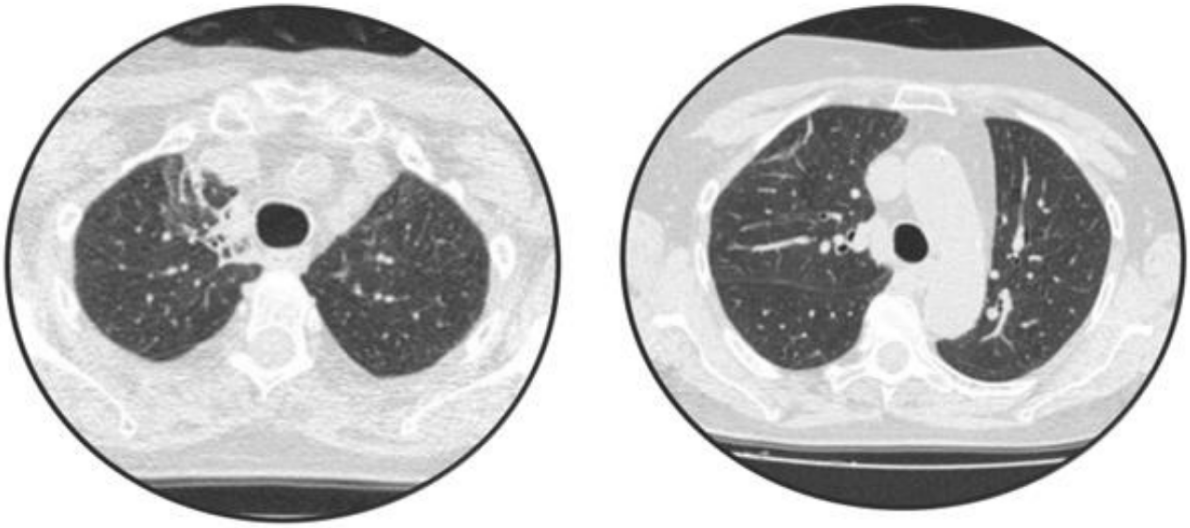

Figure 2: Computed tomography of the chest without contrast, showing an improvement after 3 months.

DISCUSSION

Organizing pneumonia is an uncommon disease, with a subacute or chronic clinical form, with an initial condition suggestive of an upper respiratory tract infection, with persistent cough and progressive dyspnea. Generally, the disease is idiopathic or cryptogenetic, however it can be associated with connective tissue diseases, radiation, drug toxicity (amiodarone, gold and cocaine) and infections (viruses, Legionella, Mycoplasma). Histologically, it is characterized by the presence of intrabronchiolar polypoid formations composed of fibroblasts and rare inflammatory cells, generally extending through the ducts and alveolar sacs (organizing pneumonia). {1,2}

Amiodarone is a drug widely used as an antiarrhythmic agent, acting by interfering with the activity of calcium and sodium channels and also with beta-adrenergic receptors (class IV, II and I of antiarrhythmic drugs). One of the possible side effects, and also one of the most serious, of the chronic use of amiodarone is the pulmonary and thyroid toxicity that the drug has. Factors such as higher plasma concentrations, time of exposure to therapy (more than two months), advanced age of the patient, preexisting lung disease seem to have a great influence on the development of lung injury from the use of the drug. The mechanism of drug toxicity is not well known, but there are indications that it is dose-dependent, with an increased risk being well reported at doses above 400mg/day, or even at low doses (100mg/day) for prolonged periods. Its half-life is long, from 40 to 70 days, which means that improvement will be seen after discontinuation within months. In reported cases of organizing pneumonia or bronchiolitis obliterans with organizing pneumonia, the dose ranged from 9.9 to 370mg, which suggests individual sensitivity. Because the drug is used in patients with heart disease, the initial diagnosis can be made as a complication of heart disease with a phenotype of heart failure or pulmonary embolism, as occurred in two published cases. {1,2,3,7}

Pulmonary involvement is very varied, and may present varying degrees of pulmonary fibrosis, hemorrhages, pulmonary nodules or masses, pleural disease (more rarely). Interstitial pneumonitis is the most common presentation of amiodarone toxicity. Amiodarone-induced lung lesions occur through several mechanisms such as direct toxicity to lung epithelial cells leading to type II alveolar cell hyperplasia and the presence of foamy macrophages, the most common features of amiodarone pulmonary fibrosis. Other existing mechanisms are: imbalances between Th1 and Th2 cells; increased production of necrosis and growth factors (TNF-α and TGF-β) and apoptosis. Due to these factors, tissue inflammation begins and spreads. {1.8}

The patient with interstitial pneumonia can be either asymptomatic or symptomatic. In symptomatic cases, the main clinical manifestations include non-specific symptoms such as non-productive cough, dyspnea or sudden worsening of dyspnea when the patient already has lung disease, pleuritic chest pain, weight loss, low-grade fever and even acute respiratory failure. Physical examination is also nonspecific, and may show fine crackles in one or both lung bases, tachypnea, increased thoracovocal thrill in cases of more advanced pulmonary fibrosis, or even a physical examination without significant changes {1,2,3,4 }.Because both the clinical manifestations and the physical examination are nonspecific, it is necessary to exclude possible differential diagnoses such as malignancy, hemorrhage, exacerbated heart failure and respiratory tract infection. the diagnosis {5}.

In laboratory tests, moderate hypoxemia, increased erythrocyte sedimentation rate, increase in erythrocyte sedimentation and lactate dehydrogenase, leukocytosis and eosinophilia may be found. There is some evidence reporting an increase in KL-6 glycoprotein, since type II pneumocytes and bronchiolar cells express this protein, being used as a marker for detection and evaluation of interstitial pneumonitis. {6}

Imaging tests are essential for diagnosis and exclusion of other pathologies. Chest radiography may show the presence of scattered infiltrates, interstitial thickening, presence of nodules or masses, consolidations, and pleural effusion. These changes can be detected even in asymptomatic or mildly symptomatic patients. A chest X-ray is always indicated when starting treatment with amiodarone and annually thereafter, in order to monitor the emergence of these types of changes. Computed tomography (CT) of the chest may show consolidation, irregular alveolar opacities usually located at lung bases, areas of mosaic flooring, nodules or masses, pleural thickening. Findings must always be interpreted with care and based on the appropriate clinical appearance in order to avoid discontinuing amiodarone without clear reasons. {6,10,11}

Another test that is indicated to be performed when introducing amiodarone to a patient is the pulmonary function test, especially for patients with previous lung disease, since amiodarone toxicity has a restrictive pattern. {6}

In cases in which cardiac causes for the patient's condition have been excluded, bronchoscopy with bronchoalveolar lavage is indicated in order to exclude malignancy or some type of infection; this test acts only for exclusion, since it has no specificity for amiodarone intoxication. In cases of diagnostic doubt, histological analysis can be used through biopsy (transbronchial or open) which is considered the gold standard for diagnosis in the presence of a characteristic radiological clinical picture, with the finding of histological lesions with a localized pattern, associated with other diseases. diffuse. Pathological examination shows foamy macrophages, reactive type II pneumocytes, as well as endothelial cells with cytoplasmic lamellar inclusions containing phospholipids. These findings characterize a pattern called phospholipidosis, very characteristic of the chronic use of amiodarone. Of the cases described in the literature correlated with the use of amiodarone, approximately half were conclusive by transbronchial biopsy, the others, as in the present case, resorted to discontinuation of the drug for clinical stabilization and a non-invasive approach. {2,3,4,6,10,11}

With regard to treatment, from the diagnostic suspicion, the first step is to discontinue the use of amiodarone, in cases where it is possible to substitute another drug or consider inserting an implantable defibrillator depending on the patient. After discontinuation of the drug, in cases of limited disease, most patients begin to present a gradual improvement in the clinical picture, without the need for other drugs. If the suspension is not enough to lead to improvement, the combination of corticosteroids is indicated. The dose and duration of therapy are not well recommended, however, studies show that the use of prednisolone at a dose of 0.5-1mg per day, usually in gradual reduction over a period of 12 months, has good results. The gradual reduction of corticosteroids will depend on the response of each patient, since amiodarone can remain in the lung tissue for up to one year.

If amiodarone is considered essential and cannot be substituted, it is indicated

to maintain a regimen with the lowest tolerable dose possible in combination with the use of corticosteroids, as mentioned above. Situations in which the patient has acute respiratory failure, oxygen therapy and mechanical ventilation are indicated if necessary. In these same cases, administration of broad-spectrum antibiotics is indicated until the hypothesis of pulmonary infection and intravenous corticosteroid therapy is ruled out.{5,6,8,9,12,13}

Thus, every patient who starts therapy with amiodarone must be followed up with a chest X-ray, which will be repeated annually together with an electrocardiogram, thyroid profile and liver profile, other organs that are sensitive to the toxicity of the drug in question. It is essential that the patient is accompanied by a specialist in pulmonology, particularly in cases of chronic lung diseases. Other complaints that arise must be evaluated by a specialist. {5,6,8,11,14}

CONCLUSION

Organizing pneumonia can lead to dyspnea with the potential to progress to acute respiratory distress syndrome. One of the probable etiologies is drug-induced, with amiodarone being responsible for pulmonary toxicity in about 5 to 7% of patients. Because the drug is used in patients with heart disease, the initial diagnosis can be made as a decompensation of heart disease, pulmonary infection or pulmonary embolism, it is known that the possibly harmful dose varies according to individual sensitivity, ranging from 9.9 to 9.9. 370mg (wide variation), in addition, there is a greater correlation with the cumulative dose than with the serum level of the drug, so it must be remembered as an etiology in patients with dyspnea who use this medication.

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