

Pulmonary masses in a patient with blue-gray cutaneous hyperpigmentation

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Abstract. – Authors describe a case of pulmonary masses and extensive skin pigmentation: “blue-gray syndrome” occurred in a patient in amiodarone therapy who presented with progressive dyspnea, cough, and fever. The diagnosis was suspected by detection of a high attenuation of the pulmonary masses on the nonenhanced chest computed tomography (CT) and lots of foamy macrophages in the bronchoalveolar lavage fluid. Relief of respiratory symptoms and radiological improvement was achieved when amiodarone treatment was stopped.

Key Words:

Pulmonary masses, Amiodarone, Blue-gray syndrome.

Introduction

A 74-year-old woman who presented to the Emergency Department with one month history of progressive dyspnea, fever and weight loss was referred to our Pulmonary Division with diagnosis of community-acquired pneumonia. She had a prior history of acute atrial fibrillation, recurrent despite antiarrhythmics and cardioversions, and currently controlled with amiodarone, 200 mg p.o. bid. She was a non-smoker, with no occupational exposures.

Physical examination revealed an elderly woman in mild respiratory distress. Heart rate was 98 beats/min, BP was 110/80 mm Hg, respiratory rate was 20 breaths/min, and temperature was 38.2°C. She had fine inspiratory crackles at both lung bases extending up to the mid zones. There was no finger clubbing. The rest of the physical examination was normal, except for a blue-grey hyperpigmentation of the face (Figure

1). This hyperpigmentation appeared a few months after starting amiodarone therapy but, although this side effect was attributed to the amiodarone, the medication was not discontinued.

Laboratory data were unremarkable, except for a moderate increase in erythrocyte sedimentation rate (38 mm/hour). Arterial blood gas measurements in room air were as follows: pH: 7.404; PCO₂: 38 mm Hg; PO₂: 68.9 mm Hg. Spirometry was not performed because the patient was uncooperative. Chest radiography (Figure 2) revealed hazy opacities in both lung bases, particularly evident in lateral view. The cardiac size was normal. A nonenhanced chest computed tomography (CT) revealed infiltrates in both lung bases (Figure 3 A, B). Tubercoline skin test (PPD 5 IU, 72 hrs) was negative.

Empirical treatment with intravenous cefotaxime (2 g every 8 hours) and levofloxacin (500 mg/day) was started.

On the sixth day, a chest radiograph was unchanged, as well a CT scan of the chest on the tenth day. Despite antimicrobial therapy, the patient remained unwell, with persistent fever, breathlessness and hypoxaemia.

A bronchoscopy was performed, but no abnormalities were observed in the visible range. Bronchoalveolar lavage (BAL) was carried out from the right lower lobe. The BAL fluid was clear and free from bacteria. Bacterial and fungal cultures were also negative. Cytological analysis of BAL fluid showed a marked increase in the number of alveolar macrophages, all characterized by a finely vacuolated cytoplasm at the light microscopy (foamy cells) (Figure 4).

Based on these findings, which should be considered markers of amiodarone exposure, we critically reviewed the initial non-enhanced chest CT and we noted that the pulmonary infiltrates enhanced intensely even though contrast was not given. Because amiodarone contains about 37%



Figure 1. Blue-gray hyperpigmentation of the face (Blue Gray Syndrome).

iodine by weight, we hypothesized that the high attenuation of the pulmonary infiltrates was caused by the incorporation of amiodarone.

These findings were believed to be consistent with a diagnosis of amiodarone induced pulmonary toxicity, presenting as mass-like peripheral opacities. Because the patient had already manifested cutaneous manifestations of amiodarone toxicity (blue-gray syndrome), the drug was discontinued without introducing other therapy. Two weeks later, fever and dyspnea were resolved. The patient was followed up with serial



Figure 2. Chest radiograph showing hazy opacities in both lung bases.

CT scans and three months after stopping the amiodarone, the scans showed a complete resolution of the parenchymal masses. The patient has been followed up for 1 year, with no relaps of symptoms or radiographic changes, while the blue-grey discoloration of the face was attenuated, but not completely resolved.

Discussion

This case represents an unusual presentation of amiodarone pulmonary toxicity, presenting with focal opacities that are mass-like. There

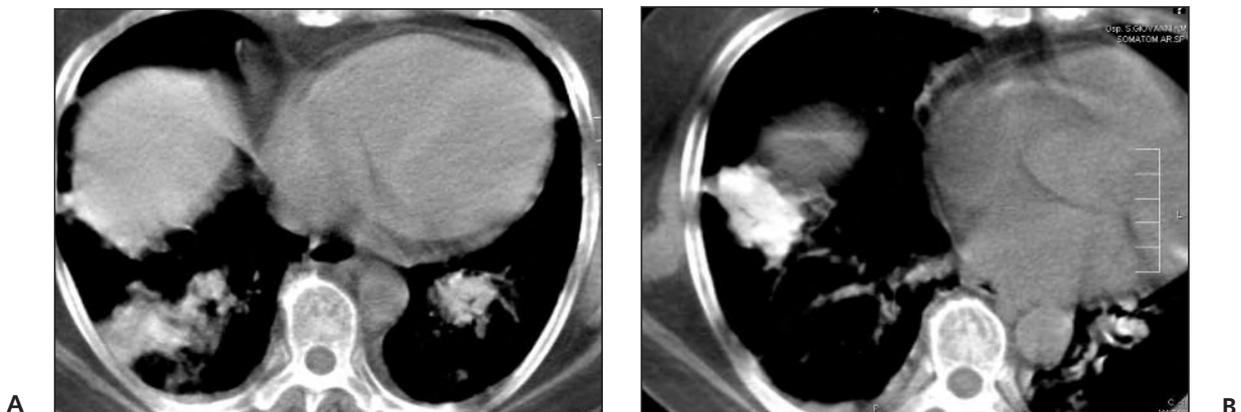


Figure 3. A, B, CT scan of the chest without contrast medium at different levels showing enhanced infiltrates, due to the iodine content in amiodarone. Following radiotherapy.

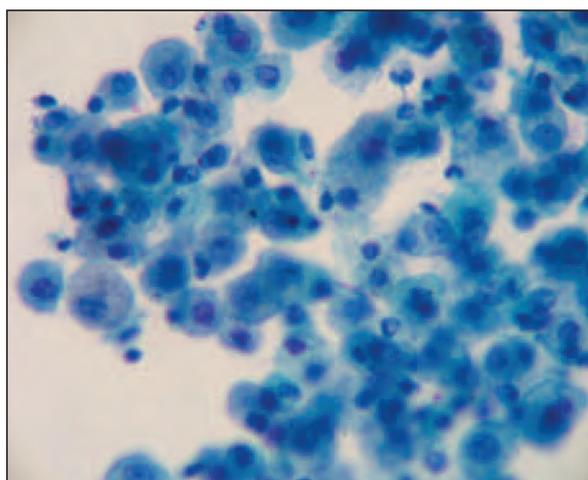


Figure 4. Bronchoalveolar lavage. Marked increase of alveolar macrophages with finely vacuolated cytoplasm at the light microscopy (foamy cells) (haematoxylin and eosin stain; 400 ×).

have been some report on amiodarone induced pulmonary masses or cutaneous vasculitic over the last years¹⁻⁴, but in our report is described a contemporary manifestation of pulmonary masses and cutaneous toxicity under the form of blue-gray syndrome and not to vasculitis.

Amiodarone is an iodinated benzofuran derivative used in the treatment of supraventricular and ventricular arrhythmias. This drug, however, has a variety of side effects⁵. Lung involvement is the most serious, with amiodarone-induced pulmonary toxicity (AIPT) occurring in 5 to 10% of patients. Although AIPT develops more commonly in patients treated with high doses (> 400 mg/d), it is not uncommon at low doses (200 mg/d) or after a short treatment⁶.

Amiodarone can damage the lung through an indirect immune reaction or direct cytotoxic damage. The different mechanism of injury contribute to the variability of symptoms onset, ranging from 1 to 6 months. The presenting signs and symptoms are often aspecific and include cough, dyspnea, fever and weight loss. Leukocytosis and an elevated erythrocyte sedimentation rate are frequent, but sometimes are absent. Pulmonary function tests usually reveal a restrictive pattern and a decreased diffusion capacity. The symptoms and the imaging findings are often attributed to heart failure, pneumonia, or malignancy. The radiographic manifestations of AIPT are protean^{7,8}, reflecting the different mechanisms of injury. Frequently, AIPT presents as nonspecific interstitial pneumonia (NSIP) with infiltration of

the pulmonary interstitium with inflammatory cells, interstitial fibrosis, and hyperplasia of type II pneumocytes. High-resolution CT reveal regions of ground-glass opacity and interlobular septal thickening with minimal architectural distortion. This radiological picture can progress to predominant fibrosis with honeycombing and traction bronchiectasis. Less commonly, AIPT can manifest as bronchiolitis obliterans organizing pneumonia (BOOP) with more patchy interstitial inflammation and fibrotic plugs that occlude terminal bronchioles, alveolar ducts and alveoli. In rare cases AIPT can manifest as one or more focal peripheral opacities that are mass-like. These opacities usually show an elevated attenuation because of the incorporation of iodine-rich amiodarone. High attenuation is noted not only in the lungs, but also in the liver and spleen because of the incorporation of metabolites into the reticuloendothelial system. AIPT presenting as a pulmonary mass in association with cutaneous vasculitis has also been reported⁸, with complete resolution of the lung and skin abnormalities after cessation of the drug. In our case, however, the cutaneous side effects was due to skin hyperpigmentation by amiodarone and not to vasculitis. Skin pigmentation is produced by solar elastosis, increase in melanin and accumulation of the amiodarone pigment in the upper dermis⁹. The degree of solar elastosis and the amount of amiodarone pigment is related to total doses of amiodarone. The pathogenesis of amiodarone-induced hyperpigmentation may be relat-



Figure 5. CT scan seven months after stopping the amiodarone, which shows a complete resolution of the parenchymal masses.

ed to the basic action of the drug on the lysosome and to extra phototoxic-induced lysosomal damage. Using electron microscopy and high-performance liquid chromatography, amiodarone deposits have been identified in the hyperpigmented skin sample from a patient treated with this antiarrhythmic agent, indicating that amiodarone hyperpigmentation is related to drug deposition on photoexposed skin¹⁰. The pigmentation is clinically characterized by progressive blue-gray discoloration of predominantly sun-exposed areas and slowly fades after discontinuation of therapy but sometimes – as in our case – may persist for months to years¹¹.

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