ADVERSE DRUG REACTION

Amiodarone toxicity presenting as pulmonary mass and peripheral neuropathy: the continuing diagnostic challenge

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A 64 year old man receiving long term amiodarone treatment presented with dyspnea, cough, and weight loss. Radiographs and computed tomography showed a lung mass with associated multiple pulmonary nodules. Biopsies of the pulmonary mass showed foamy histiocytes without malignant cells. However, findings on FDG-PET scan were consistent with a malignant tumour. These findings on computed tomography and PET scan and the unusually late resolution of the pulmonary lesions after withdrawal of amiodarone treatment posed a challenging diagnostic problem.

Amiodarone induced pulmonary toxicity (AIPT) typically presents as a non-specific interstitial pneumonia. Less commonly, AIPT can manifest as an organising pneumonia, resulting in a more patchy interstitial inflammation or nodular areas of consolidation.^{1–3} The differential diagnosis on computed tomography (CT) of such a mass or nodules centres on a neoplasm as illustrated in the following case report.

CASE REPORT

A 64 year old man was admitted to the medical ward for evaluation of low grade fever, cough, pleuritic chest pain, and weakness. The patient had lost 10 kg in weight. He was a lifelong non-smoker with no occupational exposures. His medical history included coronary artery disease, arterial hypertension, stable congestive heart failure, and ventricular tachycardia. A cardioverter defibrillator had been implanted seven years ago and amiodarone 400 mg daily was given (total cumulative dose of 950 g amiodarone). Attempts to decrease the dose of amiodarone were associated with frequent discharges of the cardioverter. Thus, the 400 mg dose that proved to be efficient was prescribed during the past seven years. Drugs at the time of the present admission included ramipril, amiodarone, carvedilol, isosorbide dinitrate, furosemide, digoxin, simvastatin, omeprazole, spironolactone, and warfarin.

Oral temperature was 37.8°C, heart rate 82 bpm, BP 132/80 mm Hg, and respiratory rate 22 breaths/min. Dry crackles were heard over the base of the left lung. An S3 gallop was heard on cardiac auscultation. There were no palpable lymph nodes and complete neurological examination was normal. Results of routine blood tests were unrewarding. The initial erythrocyte sedimentation rate was 82 mm 1st hour and C reactive protein 28 mg/dl (reference range 0–6 mg/dl). Tests for antinuclear antibodies, cANCA, pANCA, and antitopoisomerase were negative. Arterial blood gas measurements were PaO₂ 52 mm Hg, SaO₂ 85%, and PaCO₂ 36 mm Hg. The chest radiograph showed a 3×4 cm large opacity at the left lung base. On CT scan, a 3 cm large hazy mass was identified at the base of the left lung and, in addition, four nodules 0.8–1 cm

in size, in the left lower, right lower, and middle lobes. Attenuation of the mass and nodules was higher than that of adjacent muscles (fig 1A). Para-aortic and aorto-pulmonary lymph nodes were slightly enlarged. In considering the differential diagnosis of pulmonary nodules, the tuberculin skin test was anergic, c-ANCA was absent, and an iliac crest biopsy was unremarkable. CT guided fine needle aspiration of the lung mass showed foamy histiocytes, type II pneumocytes, and fragments of benign soft tissue without malignant cells, findings that are consistent with AIPT. On F-18 fluorodeoxyglucose (FDG) PET scanning, there was increased uptake of the tracer by the pulmonary mass and nodules. However, trucut biopsy specimens of the pulmonary mass were consistent with AIPT and did not enclose any malignant cells.

Later, the patient began to complain of bilateral leg weakness. Pronounced atrophy of the buttock and quadriceps muscles was noticed; the Achilles and patellar tendon reflexes were abolished. The clinical diagnosis of mixed sensory and motor neuropathy was confirmed by electromyography. Amiodarone toxicity was suspected, the drug was withdrawn, and prednisone treatment was started leading to improvement after two months: the temperature returned to normal, the cough and chest pain resolved. There also was slow recovery of the peripheral neuropathy, expressed by remission of paresthesias, recovery of tendon reflexes, and increased muscle strength in the legs. Repeated CT scans over a 12 month period showed a complete resolution of the parenchymal mass and mediastinal lymphadenopathy, but it took 24 months for disappearance of all pulmonary nodules (fig 1). At this time, the erythrocyte sedimentation rate was 42 mm 1st hour and C reactive protein 4.2 mg/dl. Pulmonary function tests showed mild restrictive pattern (FEV₁ 77%, FVC 76%, and FEV₁/FVC 87%). The PaO₂ while breathing room air was 64 mm Hg and SaO₂ 94%. Finally, the pulmonary mass and nodules as well as the peripheral neuropathy could be attributed to amiodarone toxicity. After an additional eight months of observation there was no recurrence of the pulmonary disorder. In applying the adverse drug reaction probability score⁴ to the patient here reported, the score of 7 was reached by two independent observers. This score implies that the strength of causal relation between amiodarone and the pulmonary and neurologic syndrome is “probable”.

COMMENT

The concurrent pulmonary and neurological complications in this patient illustrate multisystem toxicity of amiodarone. We could not find in the Medline database a report of pulmonary mass and peripheral neuropathy as symptoms of amiodarone toxicity.

The diagnosis of AIPT largely relies on imaging. The radiological manifestations of AIPT are variable. An uncommon

Abbreviations: CT, computed tomography; AIPT, amiodarone induced pulmonary toxicity

Figure 1 CT scans showing round lesions with irregular borders in the left upper lobe (A). The attenuation of the lesions is higher than that of adjacent muscles. The size and attenuation of the lesions diminished progressively eight months and 18 months later (B and C) and they were no longer visible 25 months after withdrawal of amiodarone treatment (D).

mon pattern of AIPT presents as nodular or mass-like opacities.^{1–3 5–8} These are usually high in attenuation because of the incorporation of iodine-rich amiodarone into type II pneumocytes.⁸ Such high attenuation of the pulmonary mass was noticed in our patient and was consistent with AIPT. However, the increased F-18 FDG uptake by the pulmonary mass and nodules suggested a malignant neoplasm. Repetitive biopsies of the pulmonary mass showed foamy histiocytes with absence of malignant cells. The presence of foamy macrophages in biopsy specimen confirms exposure to amiodarone but not necessarily proves that amiodarone was responsible in the causation of the clinical syndrome.⁶

Most patients with AIPT respond well to the withdrawal of amiodarone and to the addition of corticosteroid treatment, which is usually given for two to six months. It often takes several months for symptoms and radiological abnormalities to resolve because of the long half life of the amiodarone metabolites. The complete resolution of pulmonary mass or nodular lesions of AIPT can range from 2 to 12 months.^{1–3 5–8} In our patient the time to disappearance of different pulmonary nodules on sequential CT scans ranged from 8 to 24 months. Resolution of the clinical abnormalities with cessation of amiodarone treatment supported the working diagnosis that the pulmonary mass and nodules were expressions of AIPT.

Several features in this patient initially suggested a possible malignant neoplasm. These were severe weight loss, the

pulmonary mass and nodules, and increased uptake on FDG-PET scan. To our knowledge, high F-18 FDG uptake in AIPT lesions has not been previously reported. High uptake of F-18 FDG is similar to false positive PET scan occasionally reported in lipoid pneumonia as well as in other inflammatory or infectious lung disorders.⁹ The slower than usually perceived resolution of the pulmonary lesions after withdrawal of amiodarone treatment added to the diagnostic challenge.

The mechanisms involved in AIPT are incompletely understood. The hypothesis of a direct toxic reaction is supported by amiodarone pulmonary and neurotoxicity being usually dose related, the accumulation of cellular drug-phospholipid complexes that interferes with normal cellular metabolic pathways disrupting cellular and organelle membrane function, as well as generation of toxic oxygen species by amiodarone. The hypothesis of a hypersensitivity reaction to amiodarone is suggested by several patients who presented with features of a hypersensitivity pneumonitis with intra-alveolar buds, CD8 T-cell lymphocytosis, and IgG immunofluorescence in the lung.¹⁰

In conclusion, amiodarone toxicity is a diagnosis of exclusion and the clinician should be aware of the variability in its clinical and imaging appearances.

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Learning points

- The most serious adverse reaction of amiodarone is pulmonary toxicity (AIPT)
- AIPT may manifest as chronic interstitial pneumonitis, organising pneumonia, acute respiratory distress syndrome, pulmonary mass, or nodules
- On radiological imaging, pulmonary infiltrates induced by amiodarone are usually high in attenuation
- On biopsy, the presence of foamy macrophages confirms exposure to amiodarone but not necessarily proves that amiodarone is the responsible cause
- Most patients with AIPT respond well to the withdrawal of amiodarone and to the addition of corticosteroid treatment, which is usually given for two to six months

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