

Amiodarone pulmonary, neuromuscular and ophthalmological toxicity

Karen EA Burns MD FRCPC¹, Eugenia Piliotis MD²,

Bertha M Garcia MD FRCPC FCAP³, Kathleen A Ferguson MD FRCPC FCCP⁴

¹*Divisions of Respirology and Critical Care, Department of Medicine, University of Western Ontario;*

²*Internal Medicine, Department of Medicine, University of Western Ontario;*

³*Department of Pathology, University of Western Ontario; ⁴Division of Respirology,*

Department of Medicine, University of Western Ontario, London, Ontario

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Amiodarone is an iodinated benzofuran derivative class III antiarrhythmic that is highly effective in suppressing ventricular and supraventricular arrhythmias. It is also associated with an imposing side effect profile, which often limits its use. Numerous adverse effects have been documented including skin discolouration, photosensitivity, hepatitis, thyroid dysfunction, corneal deposits, pulmonary fibrosis, bone marrow suppression and drug interactions. These side effects are thought to be correlated with the total cumulative dose of amiodarone, but idiopathic reactions have been reported. The majority of adverse reactions resolve with discontinuation of the drug; however, rapid progression may occur, which may be fatal. The present report documents a patient who had a combination of serious amiodarone toxicities that, once recognized, were treated and eventually resulted in a good outcome.

Key Words: Amiodarone adverse effects; Drug-induced pulmonary disease; Drug toxicity; Phospholipidosis

Toxicité ophtalmologique, neuromusculaire et pulmonaire de l'amiodarone

L'amiodarone est un antiarythmique de classe III dérivé d'un benzofurane iodé qui est très efficace pour supprimer les arythmies ventriculaires et supraventriculaires. Cet agent possède également un imposant profil d'effets secondaires, qui en limite souvent l'utilisation. Ainsi, on a documenté de nombreux effets secondaires dont une décoloration de la peau, une photosensibilité, des troubles hépatiques, des dysfonctions thyroïdiennes, des dépôts cornéens, une fibrose pulmonaire, une insuffisance médullaire et des interactions médicamenteuses. On pense que ces effets secondaires sont en corrélation avec la dose cumulative totale d'amiodarone, cependant, des réactions idiopathiques ont aussi été rapportées. La majorité des réactions indésirables se résolvent avec l'interruption du traitement; toutefois, une progression rapide des symptômes peut survenir et qui peut être mortelle. Le présent article rapporte le cas d'un patient accusant une combinaison d'effets secondaires toxiques qui, une fois identifiés, ont été traités pour finalement aboutir à des résultats cliniques favorables.

Correspondence and reprints: Dr Kathleen Ferguson, University Campus, London Health Sciences Centre, 339 Windermere Road, London, Ontario N6A 5A5. Telephone 519-663-3606, fax 519-663-8806, e-mail kafergus@julian.uwo.ca

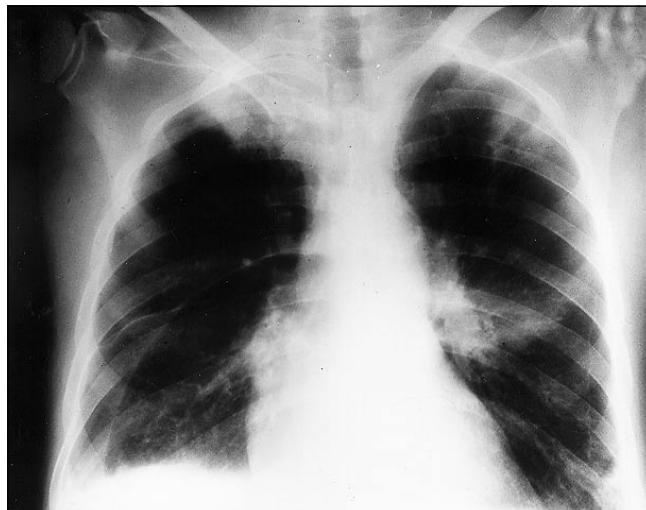


Figure 1) A chest radiograph showing apical pulmonary lesions and left hilar lymphadenopathy

A 62-year-old man with known hypertension, hypercholesterolemia, peripheral vascular disease, ischemic heart disease, ventricular arrhythmias and chronic obstructive pulmonary disease presented with a nine-month history of progressive dyspnea, lower extremity dysesthesias and weakness. Further inquiry revealed a history of a productive cough, fatigue and an 80 pack-year smoking history. He complained of decreased visual acuity, weakness and distal paresthesias. He had severe postprandial nausea and intractable vomiting, and had lost approximately 18 kg. There was no history of bowel or bladder dysfunction. He had a history of significant alcohol consumption. His medications consisted of isosorbide dinitrate 30 mg once daily, enteric coated ASA 325 mg once daily, pentoxifylline 400 mg bid, metoprolol succinate 50 mg bid, amiodarone 400 mg bid and diltiazem continuous delivery 120 mg once daily. At the time of admission he was experiencing low grade fevers, night sweats and dyspnea at rest, and was confined to a wheelchair because of weakness and ataxia. He was complaining of severe pain in his lower extremities, which was incompletely controlled with narcotics.

On examination, the patient had significant hip flexor weakness, proximal lower extremity atrophy and tenderness to palpation of the quadriceps muscle bilaterally. He showed flaccid weakness and hyporeflexia of both lower extremities associated with loss of vibration and pinprick sensation in a stocking distribution. He also had evidence of decreased dexterity, myoclonus, weakness and hypotonia in his dominant right upper extremity. His reflexes were preserved and Babinski responses were negative. He had decreased visual acuity in his left eye (20/50), with associated papillitis and diplopia at the extremes of gaze. An examination of the respiratory system was unremarkable. He was intubated after suffering an acute respiratory arrest shortly after arrival at the hospital. His acute respiratory deterioration was thought to be secondary to aspiration related to postprandial vomiting. Numerous investigations were conducted to arrive at a diagnosis.

Chest radiography (Figure 1) showed opacities in the apices bilaterally along with left hilar lymphadenopathy.

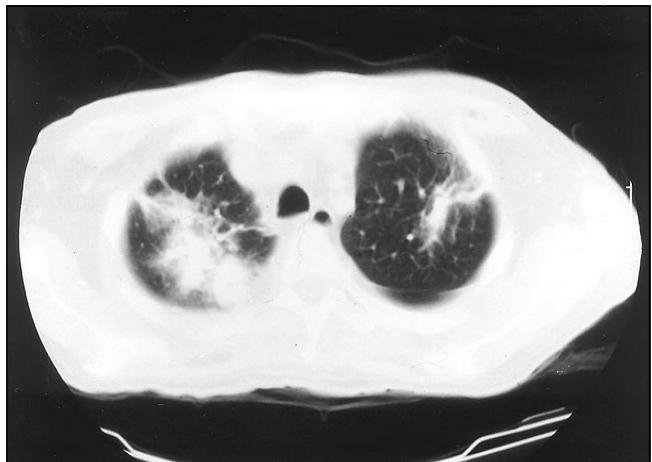


Figure 2) A computed tomographic scan showing masses in both apices

The patient was documented to have a normal chest x-ray six months before presentation. Multiple investigations had been completed at the time of transfer to the intensive care unit. The computed tomographic (CT) head scan, bone scan, carotid Doppler, magnetic resonance imaging of the spine, serum protein electrophoresis, tuberculosis skin test, urinalysis and vasculitic screen were normal. The lumbar puncture, V/Q scan and bronchoscopy were nondiagnostic. A CT scan of the chest confirmed multiple bilateral opacities, in particular, apical masses (Figure 2), small left hilar nodes and normal abdominal viscera, and revealed small bilateral pleural effusions. A CT-guided fine needle lung aspiration of one of the apical masses was nondiagnostic. Blood work revealed normocytic anemia with elevated acute phase reactants. An ultrasound of the abdomen showed gastric distention with no evidence of pyloric obstruction. The differential diagnoses included primary lung cancer with an associated paraneoplastic syndrome, systemic vasculitis and drug-induced lung disease.

Repeat bronchoscopy showed marked neutrophilia with negative microbiology and cytology specimens. Upper gastrointestinal endoscopy was normal. Electromyography revealed sensorimotor polyneuropathy, with predominant demyelinating features. Open lung, nerve and muscle biopsies were performed under general anesthesia to establish a definitive diagnosis. The open lung biopsy (Figures 3, 4) showed fibrosis of bronchioles and interstitium, foci of obliterative bronchiolitis, thickening of alveolar walls, numerous foamy macrophages and hyperplastic type II cells. A sural nerve biopsy confirmed a demyelinating neuropathy with severe secondary axonal degeneration (not shown). Electron microscopic review of the nerve biopsy revealed numerous lysosome-like inclusions within Schwann, fibroblastic and endothelial cells compatible with amiodarone neuropathy (not shown). A right vastus lateralis muscle biopsy (Figure 5) showed type II atrophy with vacuolization. The biopsy results supported the suspicion of amiodarone toxicity.

The patient had a lengthy stay in the intensive care unit complicated by nosocomial pneumonia, sepsis, unstable angina and *Clostridium difficile* diarrhea. The amiodarone

was discontinued after a total of 10 months of therapy, and intravenous methylprednisolone 100 mg every 6 h for five days was administered. After a gastrojejunal tube was inserted, oral prednisone was initiated at a dose of 50 mg once daily for four weeks followed by a tapering schedule of 5 mg every two weeks. Once the diagnosis was established and steroid therapy begun, the patient's clinical status improved significantly. His dysesthesias diminished, and he regained strength in his lower limbs. Dramatic radiographic resolution of the multifocal opacities occurred over three weeks. He was breathing independently within one week. He was discharged to his home hospital for intensive rehabilitation four weeks after the initiation of steroid therapy.

On follow-up, pulmonary function testing revealed a combined mild obstructive and restrictive pattern with a forced expiration volume in 1 s of 2.4 L (69% of predicted), forced vital capacity of 3.6 L (72% of predicted) and a diffusing capacity corrected for lung volume of 3.1 L/min/mmHg (59% of predicted). On neurological examination, he showed better than antigravity strength in all upper limb muscles, with a return of deep tendon reflexes to the biceps and brachioradialis on the right. The lower limbs showed severe muscle atrophy and weakness, with the right greater than the left. Muscle strength testing revealed Medical Research Council grades 2 to 4, with distal muscles weaker than proximal muscles. Vibration sense remained absent at the ankles, and light touch was absent up to the knees bilaterally. Deep tendon reflexes were absent in the lower extremities.

DISCUSSION

Amiodarone toxicity is often a diagnosis of exclusion, with improvement after drug withdrawal (1). The presenting features are nonspecific and may masquerade as an occult malignancy. Several studies in the literature describe the features of amiodarone toxicity; however, there is no reliable diagnostic tool to aid in early detection. We believe that our patient exhibited at least three pulmonary manifestations of amiodarone-induced pulmonary toxicity (AIPT), including mass lesions, interstitial fibrosis and obliterative bronchiolitis. He also showed rare neurological involvement, including neuromuscular toxicity, optic neuritis and probable autonomic gastroparesis.

Pulmonary toxicity: The clinical presentation of AIPT can be indolent and present a diagnostic challenge. Patients have cough, dyspnea, fever, weight loss, chest pain and rarely hemoptysis (2). These symptoms may occur from six days up to 60 months after the initiation of treatment, but most often occur in the first 12 months (3). AIPT occurs in 5% to 15% of patients on amiodarone and can be fatal in up to a third of those affected. Increasing age and pre-existing lung disease may predispose patients to AIPT, but no tests or clinical features can predict which patient will develop AIPT. The total cumulative dose, and higher daily maintenance doses, have been associated more consistently with an increased incidence of AIPT. However, pulmonary toxicity has been reported with short courses of low dose amiodarone (2). Noninvasive pulmonary investigations are not reliable pre-

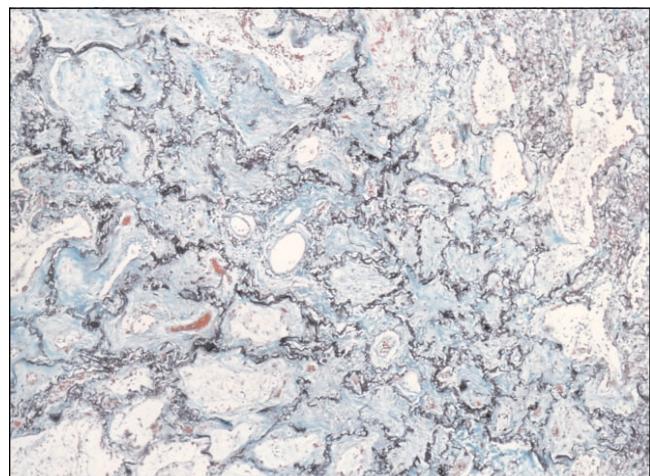


Figure 3) A lung biopsy (elastic trichrome stain) demonstrating extensive parenchymal fibrosis, foci of obliterative bronchiolitis, thickened alveolar walls and foamy macrophages. Original magnification $\times 40$

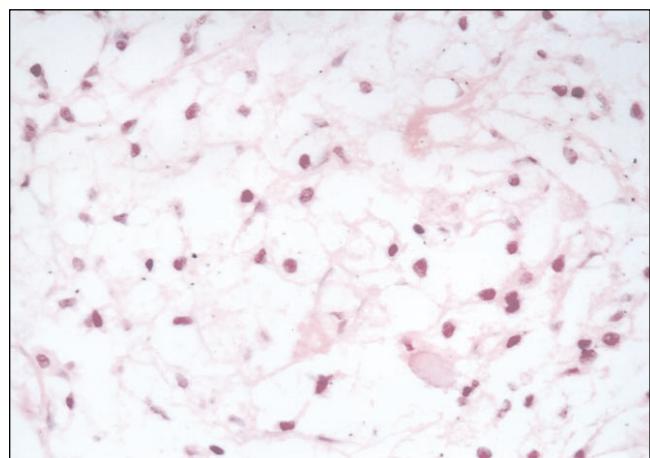


Figure 4) A lung biopsy specimen (Hematoxylin & Eosin stain) showing foamy macrophages in the alveoli consistent with amiodarone effect. Original magnification $\times 400$



Figure 5) A right vastus lateralis muscle biopsy (adenosine triphosphatase stain - pH 9.4) showing type 2 muscle fibre atrophy. Original magnification $\times 40$

ditors of the development of AIPT. However, a decrease in diffusing capacity by more than 20% should prompt closer investigation (4).

Manifestations of AIPT described include bronchiolitis obliterans with or without organizing pneumonia, chronic interstitial pneumonitis with or without fibrosis, solitary or multiple pulmonary masses or adult respiratory distress syndrome (1). CT scans may reveal high attenuation lesions in the lung parenchyma as well as in the liver and spleen, reflecting the accumulation of iodine in these tissues (5). The diffusing capacity may be decreased or the alveolar-arterial oxygen gradient may be increased (4). Bronchoalveolar lavage (BAL) features may include an increase in total phospholipid (phospholipid serine and phosphatidylinositol) content, but more often, BAL reveals a nondiagnostic increase in cellularity (6). Foam cells in a BAL are not diagnostic of AIPT because they are present in exposed individuals without toxicity, but their absence makes the diagnosis unlikely (1). Tissue examination reveals fibrosis, nonspecific interstitial pneumonitis, type II cell hyperplasia and foamy macrophages. However, biopsy cannot distinguish between exposure and toxicity (7).

The mechanism of AIPT is not clear. Amiodarone and its metabolites may cause direct toxic cellular damage through the inhibition of phospholipase A, resulting in cell membrane and organelle dysfunction. Cultured lymphocytes exposed to high concentrations of amiodarone show damage to mitochondrial membranes through the release of lactate dehydrogenase (8). Amiodarone may lead to the formation of toxic oxygen free radical species. Furthermore, amiodarone may induce its toxic effects indirectly through immune modulation or T cell-mediated hypersensitivity pneumonitis (9).

The treatment of AIPT is withdrawal of the drug with or without corticosteroid therapy. There are case reports of spontaneous remission of AIPT following early detection and discontinuation of the drug, but a prolonged course of corticosteroids is usually required. There are several reports of steroid-dependent and steroid-resistant cases where AIPT is fatal, and reports of symptomatic improvement while maintaining patients on lower doses of amiodarone if alternative treatments for lethal arrhythmia are not available (2).

Neuromuscular and ophthalmological toxicity: Evidence supporting the toxicity of amiodarone and its metabolites to the neuromuscular and ophthalmological systems is accumulating in the literature. Palakurthy and colleagues (10) reported a high prevalence of neurotoxicity (approximately 45%) in 102 patients treated with amiodarone. Forty-five patients treated with amiodarone for 9 ± 8 months developed tremor (44 patients), peripheral neuropathy (10 patients), ataxia (seven patients) and proximal myopathy (four patients). Neurophysiological studies showed varying degrees of demyelinating peripheral neuropathy. Neither age nor total cumulative dose was a risk factor for the development of neuromuscular toxicity (10). Others have studied nerve changes documenting both sensorimotor neuropathy and predominantly motor involvement characterized by demyelination with mild axonal loss (11). Other neurological

manifestations described include tremor, ataxia, peripheral neuropathy, dyskinesia, myoclonic jerks, extrapyramidal hypertonia and altered mental status. Tremor and ataxia with or without peripheral neuropathy were noted in approximately half the patients in one study. Neurological side effects improved or resolved within one month of discontinuing or decreasing amiodarone therapy (12). Advanced age, diabetes mellitus, renal failure and alcoholism appeared to be risk factors for the development of amiodarone neurotoxicity (13).

Rats given 50 mg/kg/day of amiodarone accumulated lipid in lysosomes. Interestingly, these inclusions were absent in regions with blood-nerve or blood-brain barriers. Of regions outside the vascular barrier, autonomic ganglia were most often affected, followed by the myenteric plexus (14). Costa-Jussa and coworkers (15) studied the effects of amiodarone in denervated skeletal muscle of mice. They noted the development of a myopathy characterized by phospholipid inclusions and vacuolization with sparing of type 1 fibres. Necrosis affected mainly type 2 fast twitch, high oxidative enzyme activity fibres.

The predominant features of myopathic involvement are proximal muscle weakness, increased enzyme levels and associated electromyographic and histological changes. A vacuolar myopathy is most frequently described (16,17). Type 2 atrophy has also been reported in addition to a rare necrotizing myopathy (18).

Ocular toxicity is extremely common, with asymptomatic corneal microdeposits noted in all 140 patients in one retrospective series (19). Coloured haloes surrounding light sources is a commonly reported symptom. On examination, opacities may be found on the cornea, retina, lens and optic nerves (13,20). Amiodarone has been associated with optic neuropathy (21), and impaired visual acuity secondary to papilledema and papillopathy.

CONCLUSIONS

This case presented a diagnostic challenge; it is unique in that the patient showed at least three of the four pulmonary manifestations of amiodarone toxicity. He also developed autonomic gastroparesis, a demyelinating sensorimotor polyneuropathy, proximal myopathy and ophthalmological involvement. An adequate lung biopsy to rule out other possible etiologies of pulmonary mass lesions in the presence of neuromuscular deterioration is essential. Phospholipid inclusions alone are not diagnostic; however, in the presence of parenchymal fibrosis and the appropriate clinical setting, this may be highly suggestive of AIPT. The use of corticosteroids resulted in dramatic resolution of our patient's radiographic abnormalities and significant improvement in muscle strength. We believe that our patient will ultimately regain strength in his lower extremities similar to the clinical course of patients with Guillain-Barré Syndrome.

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