



Case report

Amiodarone and cyclophosphamide: potential for enhanced lung toxicity

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Summary:

Antineoplastic therapy can be associated with drug-induced lung toxicity. With the increasing use of amiodarone for cardiac dysrhythmias there is an increasing possibility of its combined use with chemotherapies for various malignancies. We report a patient on long-term amiodarone who developed biopsy-proven drug-induced lung toxicity after receiving high-dose cyclophosphamide, at a time-frame much shorter than would have been predicted with cyclophosphamide alone. The potential for enhanced lung toxicity secondary to combination of amiodarone and cyclophosphamide is discussed. *Bone Marrow Transplantation* (2001) 27, 1109–1111.

Keywords: amiodarone; cyclophosphamide; oxidative stress; drug-induced lung toxicity; interstitial pneumonitis

Treatment-related lung toxicity has been reported in 10–64% of patients who undergo antineoplastic chemotherapy for various malignancies.¹ In many cases it can be difficult to differentiate acute infectious processes from non-infectious conditions, such as drug toxicity. Several mechanisms for the development of drug-induced lung toxicity have been proposed. For example, antineoplastic drugs such as busulphan, cyclophosphamide, bleomycin and BCNU may promote an imbalance in lung oxidants/antioxidants, resulting in enhanced oxidative stress and lung injury.^{1,2} Mechanisms by which these drugs interact with other potentially pneumotoxic drugs like amiodarone are poorly understood and lung protective strategies are lacking.

Case report

A 59-year-old Caucasian male with dendritic cell sarcoma was admitted to hospital with a 2 day history of progressive shortness of breath. He denied any cough, hemoptysis, fever or phlegm. At the time of admission he was being

evaluated for a bone marrow transplant and had received a single dose of cyclophosphamide (4000 mg/m²) 18 days before, for progenitor cell mobilization. His past history was significant for dendritic cell sarcoma diagnosed a year ago. He had initially received six cycles of cyclophosphamide (1400 mg), vincristine (2 mg), VP-16 (100 mg) and prednisone (80 mg) on days 1–4, followed by four cycles of cisplatin (100 mg/m²) on day 1, high-dose ara-C (2000 mg/m²) on day 2, and dexamethasone (40 mg/day) on days 1–4. Eighteen months before admission he was diagnosed with sick sinus syndrome and a pacemaker was placed. During that hospitalization he also underwent cardioversion followed by initiation of amiodarone therapy for new onset atrial fibrillation.

An admission physical examination revealed a dyspneic man with a blood pressure of 160/80 mm Hg, pulse 90, temperature 37.1°C and a respiratory rate of 20. Palpable lymph nodes were present bilaterally in the anterior triangle of the neck, as was a mildly enlarged spleen. Chest examination was significant for end inspiratory crackles in the right infrascapular region with absent breath sounds on the left side posteriorly below the mid interscapular region. A complete blood count showed a hemoglobin of 10.0 g/dl, platelet count of 101 × 10⁹/l and white cell count of 12.3 × 10⁹/l with a differential of 81% neutrophils, 6% lymphocytes and 13% monocytes. An admission arterial blood gas on 100% oxygen demonstrated a pH of 7.32, PaCO₂ of 41 mm Hg and PaO₂ of 92 mm Hg. The chemistries, gastrointestinal panel, amylase and lipase levels were all within normal limits. Electrocardiogram was suggestive of anteroseptal infarct and left anterior fascicular block, which was unchanged compared to 1 year before. A chest radiograph and computed tomogram done that day revealed new diffuse ground glass opacities present in the right lung and a large, but unchanged, left pleural effusion with compressive collapse of the left lower lobe (Figure 1A). Echocardiogram demonstrated a left ventricular ejection fraction of over 55%.

A left side thoracentesis performed on hospital day 2 yielded 1400 cm³ of straw-colored fluid. The pleural fluid pH was 7.43, lactate dehydrogenase level 338 IU/l (serum LDH 571 IU/l), protein 2.3 g/dl (serum protein 5.5 g/dl), 738 red blood cells per ml and 140 nucleated cells of which 41% were lymphocytes, 33% monocytes, 15% mesothelial cells and 11% other. On the same day, the patient

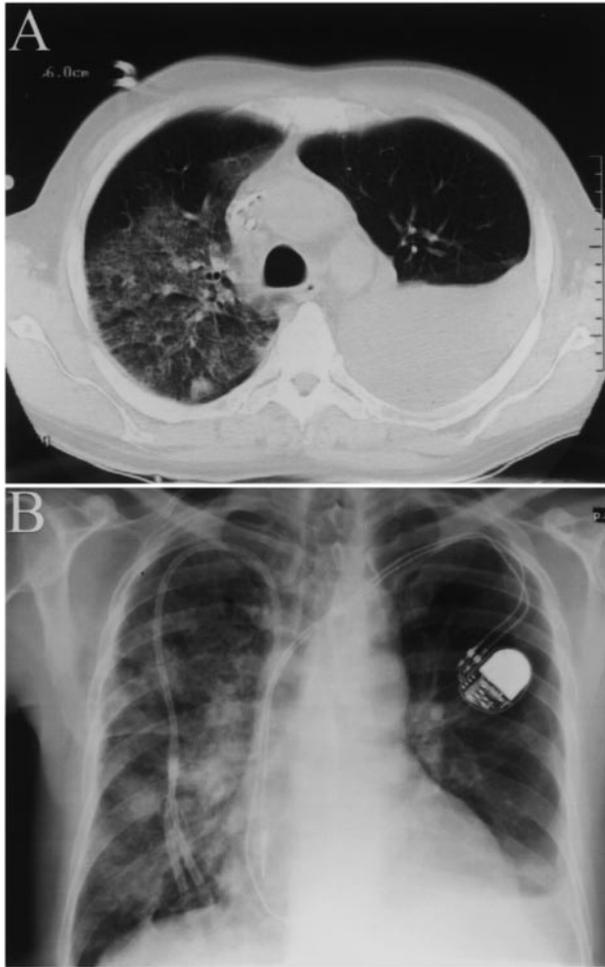


Figure 1 (A) CT scan of the chest showing a large left pleural effusion and ground glass opacities in the right lung indicative of drug-induced lung toxicity. (B) Chest radiograph post thoracentesis revealing normal left lung parenchyma with a minimal left pleural effusion and unchanged right lung parenchymal opacities.

underwent fiberoptic bronchoscopy with transbronchial lung biopsies from the right middle lobe. Pulmonary function test (PFT), performed on hospital day 3, revealed a severe restrictive defect (FVC of 2.08 l, 39% of predicted; TLC of 4.33 l, 55% of predicted) and a reduced, hemoglobin-corrected, single-breath diffusion for carbon monoxide (DLCO of 9.3 ml/min/mm Hg, 34% of predicted). Chest X-ray done on hospital day 3 showed persistent ground glass opacities in the right lung and a normal appearing left lung with a residual small pleural effusion (Figure 1B). On hospital day 5, the transbronchial lung biopsy pathology with special stains demonstrated chronic non-specific interstitial pneumonitis, associated intra-alveolar fibrin and foamy histiocytes, all suggestive of drug-induced lung toxicity (Figure 2). Amiodarone was discontinued and the patient initiated on oral prednisone at 60 mg/day. The patient's condition rapidly improved and was back to baseline activity not requiring supplemental oxygen by hospital day 10.

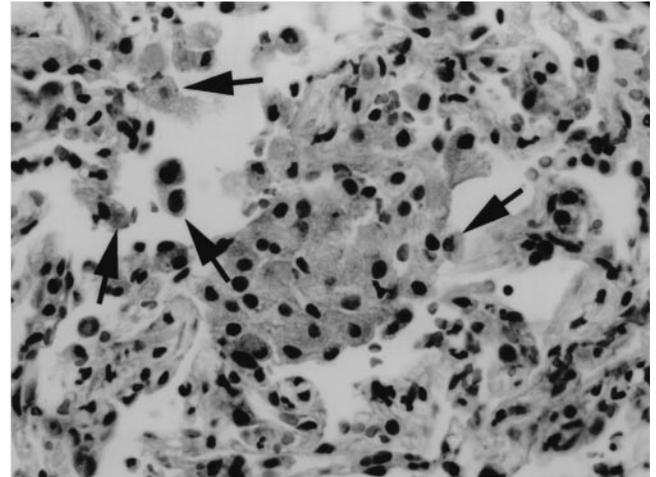


Figure 2 Histopathology of the right lung transbronchial biopsy showing mononuclear interstitial pneumonitis and intra-alveolar macrophages with granular and foamy cytoplasm (arrows), typical of amiodarone toxicity. Hematoxylin and eosin stained, original magnification 400 \times .

Discussion

Amiodarone is increasingly being used for managing cardiac dysrhythmias. In about 6% of patients, amiodarone-induced pneumotoxicity (AIPT) can be seen and is dose and duration dependent.³ Animal studies of amiodarone-induced lung toxicity have shown both membrane lipid peroxidation as well as increased generation of reactive oxygen species as the initial inciting event.⁴ Histopathology of the lung reveals lymphocytes and foamy histiocytes in 50% of patients on amiodarone. However, only one fifth of them develop a clinical picture consistent with AIPT.^{3,5} Clinically, the spectrum of AIPT ranges from hypersensitivity pneumonitis to nodular lung lesions to bronchiolitis obliterans to lung fibrosis.^{3,5} Thus, the diagnosis of AIPT is based on a combination of exclusion of other diagnoses as well as a consistent clinical and pathological picture.

An interesting feature of our case was the rapid onset of parenchymal lesions after high-dose cyclophosphamide. Clinically, cyclophosphamide may cause two types of lung toxicities. The early onset type is usually seen within 1–6 months of exposure. It is characterized by cough, dyspnea, fever, fatigue, reticular to reticulonodular lesions on chest radiograph and a restrictive pattern seen on pulmonary function tests. Histopathology shows lymphocytic infiltrates, chronic interstitial pneumonitis, fibrosis, diffuse alveolar damage, bronchiolitis obliterans organizing pneumonia and/or alveolar hemorrhage. Late onset disease has an insidious onset occurring in about 6 months and is characterized by lung fibrosis.⁶ In our patient, symptoms and signs of lung toxicity developed a little over 2 weeks following cyclophosphamide suggesting an accelerated pathogenic process.

Pneumotoxicity due to cyclophosphamide is enhanced in the presence of oxygen,^{3,5,7} whereas the addition of antioxidants can show lung protective effects.⁸ However, the non-specific elevation of some antioxidants, such as glutathione, in certain clinical situations may result in cyclophosphamide resistant tumor cells.⁹ Thus the combination of alkylat-

ing agents such as cyclophosphamide combined with amiodarone has the potential for enhancing oxidative stress and hence accelerated pneumotoxic effects.

Finally, the radiographic images following removal of the pleural fluid suggest that the left lung parenchyma was spared from toxic injury. This could imply that adequate ventilation and/or perfusion may be a prerequisite for cyclophosphamide/amiodarone accelerated lung injury to occur. Previous reports of patients on amiodarone undergoing thoracic procedures and who are unilaterally ventilated have shown acute pulmonary toxicity affecting only the ventilated lung, implicating oxygen and reactive oxygen species in this process.¹⁰

Our case suggests that the combination of amiodarone and high-dose cyclophosphamide may result in the development of accelerated lung toxicity. With the increasing use of amiodarone in general clinical practice, the possibility of its use in cancer patients receiving high-dose cyclophosphamide is increasing. Physicians caring for these patients should be alert to the possible enhanced lung toxicity using this combination of drugs. That this injury may be due, at least in part, to inflammation is supported by the patient's prompt response to prednisone.

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