Rapidly progressive pulmonary fibrosis in a patient treated with danazol for idiopathic thrombocytopenic purpura

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The case of a patient that developed pulmonary fibrosis two months after initiation of danazol for treatment of idiopathic thrombocytopenic purpura is described. Bilateral pneumothoraces and pneumomediastinum complicated the rapidly fatal pulmonary fibrosis. An association between danazol therapy and the development of pulmonary fibrosis is suspected. There is only one other case report with this connection in the literature.

Key Words: *Danazol; Idiopathic thrombocytopenic purpura; Pulmonary fibrosis*

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease resulting from antibodies directed against antigens on platelet glycoproteins, leading to accelerated platelet clearance by phagocytic cells. The mainstay of treatment for patients with ITP is corticosteroids, although intravenous immunoglobulin and splenectomy is used in certain settings. Refractory ITP has been treated with immunosuppressive drugs, anti-Rhesus D and danazol. Danazol, an attenuated androgen, has been effective in increasing platelet counts in doses ranging from 50 mg/day to 800 mg/day (1,2). The mechanism of action is postulated to be danazol-induced reduction of Fc receptors on phagocytic cells (1,2).

In the literature, the short and long term safety of danazol has been described, and there are two reports of pulmonary complications (3-7). We present the case of a woman with ITP who developed pulmonary fibrosis and pneumothoraces while on danazol for refractory ITP.

CASE PRESENTATION

In June 1998, a 78-year-old woman was found to have a low platelet count on routine blood work. Other than mild osteoarthritis, she was previously well. She was admitted to a local hospital for further investigations. Though she denied any bleeding tendencies, petechiae were present on her trunk. Bone marrow aspiration and biopsy revealed normal megakaryocytes and decreased iron stores. The workup for secondary causes of thrombocytopenia was negative, and she was diagnosed with

Fibrose pulmonaire à évolution rapide chez un patient traité au danazol pour un purpura thrombocytopénique idiopathique

Voici un cas de fibrose pulmonaire qui est apparue deux mois après l'amorce d'un traitement au danazol pour un purpura thrombocytopénique idiopathique. Des pneumothorax bilatéraux et un pneumomédiastin sont venus compliquer la fibrose pulmonaire, qui a évolué rapidement vers la mort. On soupçonne l'existence d'un lien entre le traitement au danazol et l'apparition de la fibrose pulmonaire. Toutefois, la documentation ne fait état que d'un seul autre cas de même nature.

ITP. Prednisone was started at 100 mg/day, but the platelet count did not rise above $10 \times 10^9/L$. She was treated with intravenous immunoglobulin, and her platelet count rose to $60 \times 10^9/L$. She was discharged home on prednisone 100 mg/day.

On follow-up three weeks after discharge, the platelet count had decreased to $12 \times 10^9/L$. Treatment with danazol 200 mg three times daily by mouth was added to the prednisone. After six weeks of treatment with danazol, she presented to an emergency room with shortness of breath and pleuritic chest pain. There was no history of exposure to any organic or inorganic dust. On examination, she was hypoxic with an arterial oxygen saturation of 87% in room air. Her respiratory rate was 36 breaths/min, and she was in moderate respiratory distress. There was no clubbing or cyanosis. Auscultation of the chest revealed reduced breath sounds on the right side and coarse crackles bilaterally. The rest of the examination was normal. A chest x-ray showed bilateral pneumothoraces (right side greater than left) and bilateral diffuse interstitial infiltrates. The chest x-ray taken at the time of presentation with ITP had been normal. Bilateral intercostal drainage tubes were inserted. A high resolution computed tomography (HRCT) scan showed interstitial lung disease involving predominantly the lower lung zones (Figure 1). Her immunological workup, including rheumatoid factor, antinuclear antibodies and antineutrophilic cytoplasmic antibodies, was negative. Serology for hepatitis B and C was also negative. Results of C3, C4 and serum immunoelectrophoresis were normal. On bronchoscopy,

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Figure 1) High resolution computed tomography scan of the lungs showing bilateral peripheral thickening of the interstitium with patchy air space disease, worse on the left side than on the right. A small pneumothorax is seen on the left side anteriorly

the visualized airways appeared normal, and bronchoalveolar lavage was negative for bacteria, fungus, mycobacteria and malignancy. Differential cell count could not be obtained because the sample was inadequate. Her platelet count was normal throughout her hospital stay. She was transferred to a tertiary care centre for an open-lung biopsy. A biopsy of the left lower lobe and lingula revealed an acute interstitial pneumonia (6) of proliferative to fibrotic nature. Predominantly, there were mixed lymphocyte/plasma cell infiltrates, interstitial and air space fibrosis, and alveolar lining cell regenerative atypia. Fibrosis was more severe in the lingula and appeared to be rapidly progressive, resulting in distortion of air spaces and cystic remodelling of lung parenchyma (Figure 2). There were no granulomatous or eosinophilic component and no findings specific for etiology, including examination for microorganisms and viral cytopathic effects. Cultures of biopsy tissue for bacteria, mycobacteria, fungi and *Legionella* species were negative. After the lung biopsy, she was discharged home on treatment with prednisone 100 mg/day, danazol 200 mg three times daily and oxygen.

Two weeks after discharge, she was readmitted with worsening shortness of breath and intermittent chest pain. At this stage, her oxygen requirement increased and she was desaturating to 70% on 10 L/min of oxygen. A repeat HRCT revealed pulmonary fibrosis as well as a pneumomediastinum, left pneumothorax and bilateral pleural effusions. She was treated with a left intercostal drainage tube. The pleural fluid revealed a nonmalignant transudative effusion. Abnormalities in her blood work were significant for liver dysfunction (aspartate aminotransferase 331 U/L, alanine aminotransferase 337 U/L, alkaline phosphatase 575 U/L, bilirubin 24 µmol/L, albumin 27 g/L and international normalized ratio 1.05). An ultrasound of the liver and biliary system did not reveal any

Figure 2) Lung biopsy showing a remodelling of air spaces due to rapidly progressive interstitial fibrosis and alveolar collapse. The air spaces are distorted and lined by regenerating epithelial cells. (Hematoxylin and eosin stain, original magnification ×160)

abnormality. Tests for serum antimitochondrial antibody was negative. Treatment with danazol was discontinued, and cyclophosphamide 50 mg/day was added to the prednisone 100 mg/day. The prednisone was tapered to 50 mg/day over two weeks. Her serum transaminase level decreased to 112 U/L, but the alkaline phosphatase level continued to rise to 2200 U/L. She spent the next two months with the geriatric rehabilitation service, but her respiratory status did not improve. She was discharged home with home care and died of respiratory failure one month later.

DISCUSSION

The present case suggests an association between therapy with danazol and rapidly progressive pulmonary fibrosis. The patient developed pulmonary symptoms, as well as chest x-ray and HRCT abnormalities after the introduction of danazol. There did not appear to be any other confounding factors. Elevation of liver enzymes also occurred while on danazol therapy. This is a commonly reported side effect (2,5). Given the extensive fibrosis and a rapidly deteriorating clinical course, we were unable to assess the effects of danazol withdrawal on the liver and lung.

There is one case reported in the literature of possible danazol-associated fatal pulmonary fibrosis (7). A 72-year-old man with chronic lymphocytic leukemia was treated with danazol to taper steroid therapy. He developed rapidly progressive pulmonary fibrosis and died within 15 days of diagnosis. The only other danazol-associated pulmonary complication published in the literature is hypersensitivity pneumonitis in one patient (8). There is no mention of any possible mechanism of action causing lung injury in the literature.

CONCLUSIONS

The present case suggests an association between danazol use and the development of pulmonary fibrosis. Although this cause-and-effect relationship was not proven, it is suggested that patients treated with danazol should be followed up carefully for pulmonary symptoms.

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