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Case report

Organizing pneumonia after rituximab therapy: Two cases

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Abstract

Rituximab, a chimeric monoclonal antibody against CD20, very rarely causes lung toxicity. Clinical presentations include lung infiltrates, alveolar hemorrhage, and adult respiratory distress syndrome. Three cases of organizing pneumoinia (formerly called bronchiolitis obliterans with organizing pneumonia or BOOP) have been reported. In our experience, organizing pneumonia occurred in 2 of 25 patients treated with rituximab, for RA and Castleman's disease, respectively. Because organizing pneumonia may be asymptomatic, as illustrated by one of our cases, we recommend obtaining a chest radiograph routinely before rituximab re-treatment.

Keywords: Rheumatoid arthritis; Castleman's disease; Rituximab; Organizing pneumonia; BOOP

Rituximab is a chimeric monoclonal antibody against CD20 that was initially developed as a treatment for non-Hodgkin's lymphoma [1]. It is also among the therapeutic options for Castleman's disease [2]. Patients with rheumatoid arthritis (RA) who fail therapy with one or more TNFα antagonists may be given rituximab [3]. Lung toxicity seems exceedingly rare, with a rate of less than 0.03% among 540,000 treated patients [1]. Clinical presentations include lung infiltrates, alveolar hemorrhage, and adult respiratory distress syndrome [1,4]. Rituximab has been incriminated in three cases of organizing pneumonia (formerly called bronchiolitis obliterans with organizing pneumonia or BOOP) [5–7]. In our experience, organizing pneumonia occurred in 2 of 25 patients treated with rituximab, for RA and Castleman's disease, respectively.

1. Case report 1

This 64-year-old woman who had seropositive RA with joint erosions diagnosed 4 years earlier, in 2002, was taking 5–10 mg of prednisone per day in combination with methotrexate, then leflunomide, and finally methotrexate plus anakinra. TNFα antagonists were not used, as she had a history of lower-limb paralysis at 25 years of age consistent with a possible demyelinating disease. In October 2006, her disease remained active, as shown by the following variables: visual-analog-scale pain score, 69/100 mm; tender joint count, 8; swollen joint count, 14; erythrocyte sedimentation rate (ESR), 21 mm/h; and Disease Activity Score on 28 joints using the ESR (DAS28-VS), 5.7. Rituximab (MabThera®, Roche, Basel, Switzerland) was given as two doses of 1 g each at an interval of 15 days, after premedication with 100 mg of methylprednisone. Methotrexate (15 mg/week) and prednisone (10 mg/day) were continued. Marked improvements were noted after 12 weeks, when the DAS28 was 2.8. After 21 weeks, a dry cough with chest pain and asthenia developed. There was no fever. At the time, she was taking methotrexate (15 mg/week), prednisone (10 mg/day), and cefpodoxime prescribed by her primary care practitioner, to no effect on the symptoms. A chest radiograph showed three macronodular alveolar densities, which were further evaluated by computed tomography (CT) of the chest. The densities were located in the posterior segment of the right upper

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lobe, the lateral segment of the middle lobe, and the inferior segment of the lingula (Figs. 1 and 2). Lung function tests were normal. The bronchoalveolar lavage (BAL) fluid showed a high cell count (380,000/ml; normal < 200,000) with 17% lymphocytes (normal < 10%) and 35% neutrophils (normal < 3%). Microbiological studies identified *Haemophilus influenzae*, and amoxicillin–clavulanic acid was given for 14 days. Tests were negative for *Pneumocystis jirovecii*. The respiratory symptoms persisted, suggesting organizing pneumonia, and videothorascopic lung biopsy was performed. Specimens were obtained from the upper and middle lobes of the right lung. Histology showed inflammatory fibrous buds within the bronchiolar lumina, confirming the diagnosis of organizing pneumonia. Prednisolone in a dosage of 40 mg/day was started. The prednisolone dosage was tapered to 10 mg/day over 5 months, at which time the symptoms and right-lung densities had resolved.

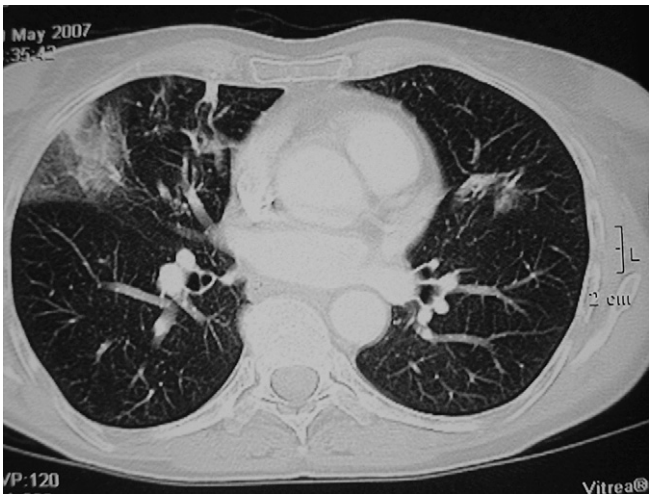

Fig. 2. Bilateral alveolar densities.

2. Case report 2

A 55-year-old woman with RA since 1970 had joint destruction despite limited disease activity. She had a history of valve replacement surgery in 2003 to treat aortic incompetence. In 2001, she was evaluated for urticarial vasculitis, high blood eosinophil counts, and marked bilateral lymph-node enlargement at multiple sites (groin, axilla, retroperitoneal space, and pelvis). Lymph-node biopsy findings consisted of atypical lymphoid hyperplasia, immunoblasts, and numerous polyclonal plasma cells. Methotrexate-related pseudolymphoma was diagnosed. The lymph nodes slowly decreased in size after methotrexate discontinuation. However, she experienced a recurrence 1 year later, with highly inflammatory lymphadenopathies in the right axilla, as well as lymphadenopathies at cervical and deep sites. Blood cell counts showed eosinophilia. A lymph-node biopsy showed atypical lymphoid hyperplasia with focal coagulation necrosis and proliferation of polytypical plasma cells. Again, the abnormalities resolved slowly without specific treatment. In July 2004, she experienced a third episode of multifocal lymph-node enlargement (axillas, mediastinum, groins, and pelvis) with lymphedema of the left lower limb. A biopsied node was found to contain a large population of monotypic plasma cells producing an IgA-kappa. A diagnosis of lymphoplasmacytic lymphoma was considered. Tests were negative for Epstein–Barr virus expression. The patient was finally given a diagnosis of monotypic Castleman's disease. No spontaneous improvement occurred, and rituximab (500 mg/week for 4 weeks) was started in June 2005, after premedication with 100 g of methylprednisolone. She was also taking prednisone (6 mg/day) and hydroxychloroquine. The manifestations improved rapidly. A chest CT scan obtained after 1 month showed marked shrinkage of the lymphadenopathies and normal lungs. After 4 months, all the nodes at superficial and deep sites were less than 1 cm in size; however, perivascular ill-defined alveolar densities measuring 1–2 cm were noted; there were seven densities in the right lung and three in the left lung. Ground-glass opacities were also visible (Fig. 3). The patient had no respiratory symptoms. Needle biopsy of a peripheral nodule under CT guidance failed to establish the diagnosis. Minithoracotomy on the right showed multiple indurated nodules in all three lobes. Histological examination of a nodule taken from the lower lobe showed inflammatory fibrosis with an abundance of fibroblasts. Connective tissue buds were visible in many alveoli and in the bronchioles, establishing the diagnosis of organizing pneumonia (Fig. 4). Prednisone was started in a daily dosage of 0.75 mg/kg for 15 days then tapered. The lung densities decreased in size. After 9 months, when the prednisone dosage was 7.5 mg/day, the densities recurred in both lungs. There was no evidence of Castleman's disease recurrence, and blood eosinophil counts were normal. Over the next 8 months, the lung densities alternately worsened and improved, although the prednisone dosage was left unchanged. There were no signs indicating a flare of RA or Castleman's disease.

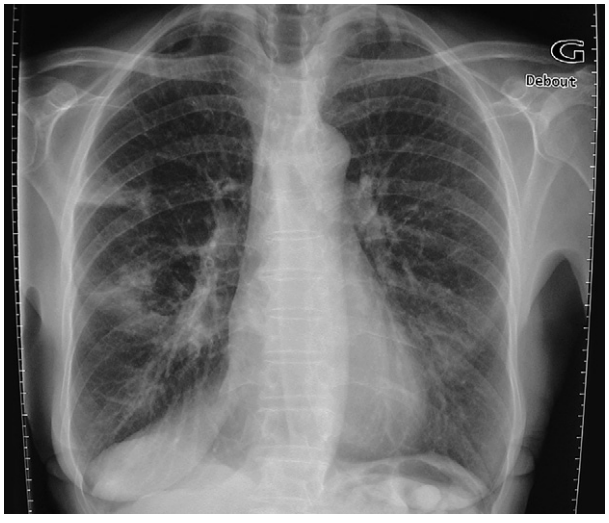

Fig. 1. Bilateral, poorly systematized, alveolar densities in the upper and middle lobes.