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CASE REPORT

Rituximab-induced Acute Eosinophilic Pneumonia with Diffuse Alveolar Damage: A Case Report

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We describe a case of relapsed mantle cell lymphoma receiving four doses of rituximab (375 mg/m^2/week) as part of salvage chemotherapy. Acute respiratory distress with hypoxemic respiratory failure requiring ventilatory support was developed 6 weeks after the last dose of rituximab. The findings of microbiological studies did not identify any infectious agents. Bronchoalveolar larvage fluid showed eosinophilia which fulfilled the diagnostic criteria of acute eosinophilic pneumonia. The result of the open lung biopsy showed acute diffuse alveolar damage with interstitial edema, type II pneumocyte hyperplasia and hyaline membrane. Our patient exhibited a new pattern of rituximab-induced lung injury with an excellent and complete response to steroid therapy.

1. Introduction

Rituximab, a chimeric monoclonal antibody targeting CD20, is widely used in the treatment of B-cell neoplasms.[1–5] But some unexpected adverse effects with lethal potential may occur in patients treated with rituximab,[6–9] which probably impede its further use. Recently, much attention has been paid to acute respiratory reactions, including interstitial pneumonitis,[9–14] bronchiolitis obliterans with organizing pneumonia (BOOP),[15,16] diffuse alveolar hemorrhage[8–10] and pulmonary fibrosis.[7] To make the diagnosis of rituximab-induced pulmonary toxicity is difficult because there have been no precise criteria for a definite diagnosis and exclusion of other etiologies is necessary. Here, we report a case which developed acute eosinophilic pneumonia with diffuse alveolar damage after rituximab therapy.

2. Case report

A 69-year-old male nonsmoker patient was diagnosed to have mantle cell lymphoma, stage IVA in May 2005. After diagnosis, he received one cycle of CHOP (cyclophosphamide, doxorubicin, oncovin and prednisolone) and seven-cycle of CEOP (doxorubicin was substituted by epirubicin) with a complete response. However, lymphoma relapsed in January 2006 and he gave an informed consent to receive salvage chemotherapy, including cyclophosphamide, etoposide, oncovin, prednisolone, fludarabine and dexamethasone, followed by rituximab (375 mg/m^2) given weekly for four doses from August 22 to September 12, 2006. He achieved a subsequent second complete response. He developed fever and progressive shortness of breath on October 22, 2006. He was brought to our emergency department on October 23, 2006 with the body temperature being 38.2°C and an oxygen saturation 92%. The hemoglobin was 10.1 g/dL, platelet 139 × 10^9/L and white blood cell count 4.5 × 10^9/L with a differential of 83% neutrophils, 5.5% lymphocytes, 4.9% monocytes and 6.6% eosinophils. The initial chest X-ray showed perihilar infiltration and elevation of right diaphragm. Community-acquired pneumonia was impressed for which moxifloxacin was administered along with clarithromycin. But he had further worsened dyspnea with a rapid progression to diffuse hazy opacities of both lungs in the follow-up chest X-ray 2 days later (Figure 1). Cotrimoxazole (containing sulfamethoxazole 1200 mg and trimethoprim 240 mg every 6 hours) was initiated on October 25 for possible *Pneumocystis jiroveci* infection. The findings of the high-resolution computed tomography (CT)-scan on October 25, 2006 showed diffuse ground-glass and fine reticulonodular opacities (Figure 2). The arterial blood gas analysis in room air showed pH 7.264, PCO_2 34.7 mmHg, PO2 55.1 mmHg, HCO_3 15.4 meq/L and oxygen saturation 84.6%. Diagnostic bronchoscopy for bronchoalveolar larvage (BAL) performed on October 25, 2006 showed 26.2% eosinophils in the BAL fluid, which was consistent with eosinophilic pneumonia. Dyspnea became worse and then he

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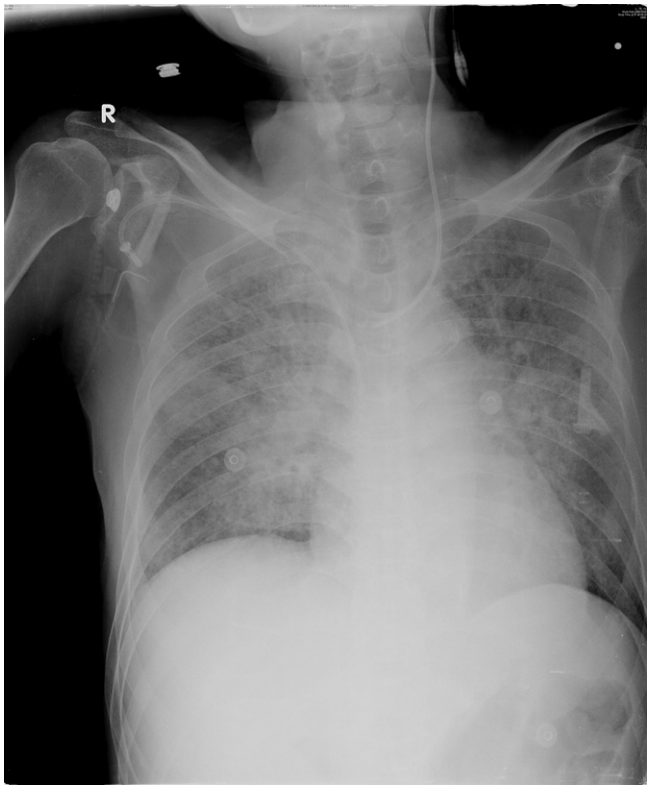

Figure 1 The chest X-ray showing diffuse reticuloalveolar pattern with ground glass appearance in both lungs.

required mechanical ventilatory support. He received transbronchial lung biopsy on October 27, 2006, showing interstitial fibrosis. Moxifloxacin and clarithromycin were substituted with teicoplanin (400 mg daily) and imipenem (500 mg every 6 hours) on October 29. Open lung biopsy with wedge resection of right middle lung was performed and showed acute diffuse alveolar damage (DAD) (Figure 3) without any identifiable pathogens including *P. jaroveci*, fungi or viruses. Immunohistochemical stain excluded the presence of residual lymphoma. All cultures and viral markers, including CMV IgM, EBV VCAM, HSV, HIV, Pavovirus B19, Coxakie virus B1-B6, Influenza A and B and parainfluenza 1–3, were negative except for the presence of a titer of 1:40 for CMV IgG. He was diagnosed with drug-induced interstitial pneumonitis and then received hydrocortisone 100 mg every 6 hours intravenously on November 3, discontinued teicoplanin, imipenem and cotrimoxazole. His respiratory pattern dramatically improved after steroid therapy and was successfully extubated 2 weeks later on November 16. His hydrocortisone was tapered gradually until it was completely withdrawn. The follow-up CT-scan on November 23 showed a complete resolution of pulmonary infiltrations. He tolerated room-air well in the following days and then he was discharged in a stable condition.

To establish a definite diagnosis of drug-induced lung injury is difficult. In 1976, Irey proposed a set of criteria to define drug reactions, consisting of two major principles to exclude other possible etiologies and temporal eligibility with an appropriate latent period.[17] Based on Irey's proposal, a clinical correlation with the two crucial points plays a more important role than pathological findings that are often nonspecific. In our case, we did not identify various microbiologic studies for most possible infectious agents. But we could not exclude infectious cause completely, especially viral infection. Exposure to any irritants was also ruled out by the history. However, pulmonary toxicity developed six weeks after rituximab along with no other newly-added drugs during this period, hence our patient fulfilled the two major criteria for the diagnosis of drug-induced lung injury.

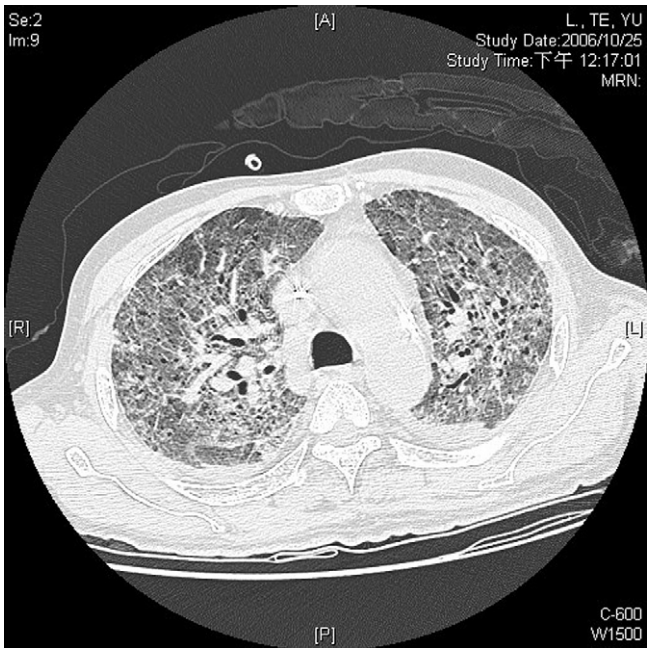

Figure 2 A single cut of the high-resolution computed tomography scan before steroid treatment showing diffuse ground glass and reticulonodular opacities, suggestive of interstitial pneumonitis.

3. Discussion

A review of literature on rituximab-induced pulmonary toxicity showed that in total six cases had a tissue-proved pathological diagnosis from lung biopsy (Table 1). Like our patient, they received three open lung biopsies[7,15,16] and diagnosis was made by transbronchial lung biopsy in other two cases. The pathological findings included DAD, BOOP and pulmonary fibrosis.[7–10,16] Many cases developed clinical symptoms of respiratory distress within

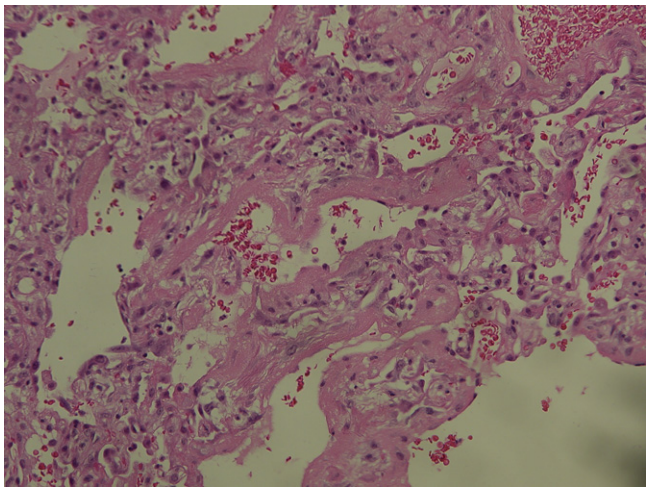

Figure 3 The wedge lung biopsy showing histologic features of diffuse alveolar damage characterized by interstitial edema, prominent type II pneumocyte hyperplasia and hyaline membranes lining the surfaces of alveoli (Hematoxylin & Eosin stain, 200x).