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/m²/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 lavage 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.

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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 damage;17-19 drug-induced lung injury;20 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/m²) 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%.

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required mechanical ventilatory support. He received trans-bronchial 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. jiroveci, 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. 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.

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 biopsies7,15,16 and diagnosis was made by transbronchial lung biopsy in other two cases. The pathological findings included DAD, BOOP and pulmonary fibrosis. Many cases developed clinical symptoms of respiratory distress within

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

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.

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).
<table>
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<th>Reference</th>
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<th>Diagnosis</th>
<th>Dose/cycles/ time after rituximab</th>
<th>BAL</th>
<th>Biopsy method</th>
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<th>Treatment</th>
<th>Mechanical ventilation</th>
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<tr>
<td>Leon et al, 2004</td>
<td>56/M</td>
<td>Follicular lymphoma</td>
<td>375 mg/m², 12 cycles, 3 wk</td>
<td>Data NA</td>
<td>OLB and TBLB</td>
<td>TBLB: interstitial fibrosis OLB: extensive interstitial fibrosis with focal chronic inflammation and organization, extensive arterial thrombosis LB: loose nonnecrotic granulomas in a background of mild fibrosis and rare eosinophils Autopsy: extensive intra-alveolar pulmonary hemorrhage, with severe acute and focal organizing diffuse alveolar damage</td>
<td>High dose steroids (dose NA)</td>
<td>(+)</td>
<td>Expired</td>
</tr>
<tr>
<td>Alexandrescu et al, 2004</td>
<td>65/M</td>
<td>Diffuse large B cell lymphoma</td>
<td>NA, 4 cycles, 0*</td>
<td>Lymphocyte predominant CD4/CD8 = 2.5</td>
<td>LB and autopsy</td>
<td>LB: loose nonnecrotic granulomas in a background of mild fibrosis and rare eosinophils Autopsy: extensive intra-alveolar pulmonary hemorrhage, with severe acute and focal organizing diffuse alveolar damage</td>
<td>Prednisone 40 mg/d</td>
<td>(+)</td>
<td>Expired</td>
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<td>Herishanu et al, 2006</td>
<td>80/M</td>
<td>Follicular lymphoma, Gr III</td>
<td>NA, 2 cycles, 10 d</td>
<td>ND</td>
<td>LB</td>
<td>Interstitial inflammation and edema, type II pneumocyte hyperplasia and atypia and foamy vacuolated histiocytes in air spaces</td>
<td>Methylprednisolone-ne 1 mg/kg/d (equivalent to prednisone 1.25 mg/kg/d)</td>
<td>(+)</td>
<td>Expired</td>
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<tr>
<td>Mian et al, 2006</td>
<td>64/M</td>
<td>Diffuse large B cell lymphoma</td>
<td>NA, 7 cycles, 7 d</td>
<td>ND</td>
<td>OLB</td>
<td>diffuse alveolar damage, fibrosis, extensive organizing pneumonia bronchiolitis obliterans with organizing pneumonia scattered, loosely formed granuloma</td>
<td>High dose steroids (dose NA)</td>
<td>(+)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Biehn et al, 2006</td>
<td>61/M</td>
<td>NonHodgkin's lymphoma</td>
<td>375 mg/m², 4 cycles, 2 mo</td>
<td>ND</td>
<td>OLB</td>
<td>Prednisone 40 mg/d</td>
<td>Resolved</td>
<td>(-)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Heresi et al, 2007</td>
<td>88/M</td>
<td>Waldenstrom's macroglobulinemia</td>
<td>375 mg/m², 12 cycles, 8 wk</td>
<td>Lymphocyte predominant Eosinophilia CD4/CD8 = 3.12</td>
<td>TBLB</td>
<td>TBLB: interstitial fibrosis OLB: diffuse alveolar damage, acute and organizing, with interstitial edema, prominent type II pneumocyte hyperplasia and hyaline membranes lining the surfaces of alveoli</td>
<td>Prednisone 60 mg/d</td>
<td>(-)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Present case, 2008</td>
<td>68/M</td>
<td>Mantle cell lymphoma</td>
<td>375 mg/m², 4 cycles, 6 wk</td>
<td>TBLB and OLB</td>
<td>TBLB: interstitial fibrosis OLB: diffuse alveolar damage, acute and organizing, with interstitial edema, prominent type II pneumocyte hyperplasia and hyaline membranes lining the surfaces of alveoli</td>
<td>Hydrocortisone 400 mg/d (equivalent to prednisone 100 mg/d)</td>
<td>(+)</td>
<td>Resolved</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BAL = bronchoalveolar lavage; LB = lung biopsy of unknown method; M = male; NA = not available; ND = not done; OLB = open lung biopsy; TBLB = transbronchial lung biopsy.

* Rituximab-induced lung injury occurred during the treatment (not related to infusion).
Rituximab-induced acute eosinophilic pneumonia

3 weeks after the last dose of rituximab6–8,11–13,15 although delayed pulmonary toxicities have been reported with a longest latency of 2 months.10,16

Acute eosinophilic pneumonia induced by rituximab has not been reported previously and it is a unique pulmonary disorder defined by Allen et al as diffuse interstitial infiltrates in presentations of the chest X-ray, hypoxemic respiratory failure, greater than 25% eosinophils in BAL and absence of active infections.18 Clinical manifestations with a characteristic BAL finding are essential for a definite diagnosis of acute eosinophilic pneumonia which usually presents pathologically with acute and organizing DAD, interstitial edema, type II pneumocyte hyperplasia and hyaline membranes as described by Allen et al.19,20 Our patient fulfilled all the diagnostic criteria for acute eosinophilic pneumonia and also had the same microscopic features of lung pathology. It may be argued against no increase in eosinophils in the open lung biopsy sample. Because the administration of hydrocortisone was initiated immediately when the diagnosis of acute eosinophilic pneumonia had been made on October 26, 4 days had elapsed before open lung biopsy was performed on October 30. Our acute eosinophilic pneumonia responded well to steroid therapy. The time lag of 4 days in the current case might minimize or wipe out some findings of acute eosinophilic pneumonia in the biopsy section, may probably attribute to no increase in eosinophils in open lung biopsy. Heavy alveolar or interstitial infiltration by eosinophils is not a common finding in acute eosinophilic pneumonia although its presence may further support the diagnosis.20

Cyclophosphamide has been reported to be implicated in DAD and BOOP patterns of acute lung injury21 with two distinct types, early-onset occurring within 4 months after exposure to cyclophosphamide, and late-onset developing several years later.22,23 The latent period of 7 months, incompatible with either early-onset or late-onset lung injury induced by cyclophosphamide made the possibility of cyclophosphamide-induced lung injury unlikely in our patient. Fludarabine has also been known to result in pulmonary toxicity. Helman et al analyzed nine patients with fludarabine-induced pulmonary toxicity, and concluded that these patients are apt to develop clinical symptoms within 1 week after fludarabine treatment.24 For our patient, he received fludarabine treatment at a daily dose of 40 mg for 3 days in each course from March to July 2006 for total six courses and his clinical manifestations occurred in October 2006. A time lag of more than 3 months in the current case made fludarabine as a leading cause of pulmonary injury unlikely in our patient. Besides, diffuse and chronic interstitial inflammation and fibrosis are major patterns of lung injury caused by fludarabine. Diffuse alveolar damage, which is the major pathological finding of our patient, is not characteristic of fludarabine-induced lung injury. Thus, we suggest that rituximab is strongly related to drug-induced pulmonary toxicities in the current case.

Corticosteroid is universally adopted as first-line therapy for drug- (including rituximab) induced pulmonary toxicities and a dramatic and complete recovery can be expected in most patients.6–10 No consensus exists on standard dosage of steroid therapy but a dose of 20–40 mg/d of prednisone is widely applied.8,11,12 Our case with acute eosinophilic pneumonia and DAD demonstrated an excellent response to hydrocortisone therapy.

We have described a new pulmonary injury pattern of acute eosinophilic pneumonia with DAD, induced by rituximab with a dramatic response to steroid therapy. Our case can stress that delayed pulmonary toxicities may occur in patients treated with rituximab-containing chemotherapy. Prompt administration of steroids will lead to a complete recovery of pulmonary toxicities from acute eosinophilic pneumonitis.

References


