Rituximab-Induced Hypersensitivity Pneumonitis

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Established Facts

- Rituximab has been associated with a variety of respiratory conditions and sporadically with hypersensitivity pneumonitis.

Novel Insights

- Hypersensitivity pneumonitis is associated with the use of rituximab and it responds to steroids.

Key Words

Rituximab · Hypersensitivity pneumonitis · Drug-induced lung disease

Abstract

Rituximab is a chimeric anti-CD20 monoclonal antibody used to treat CD20+ non-Hodgkin's lymphoma. Although pulmonary adverse reactions such as cough, rhinitis, bronchospasm, dyspnea and sinusitis are relatively common, other respiratory conditions like cryptogenic organizing pneumonia, interstitial pneumonitis and diffuse alveolar hemorrhage have rarely been reported. Only 2 possible cases of rituximab-associated hypersensitivity pneumonitis have been described to date. We present a case of hypersensitivity pneumonitis with classic radiographic and histopathologic findings in a patient treated with rituximab who responded to prednisone.

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Introduction

Rituximab is a genetically engineered chimeric (murine/human) anti-CD20 IgG1 monoclonal antibody that is used for the treatment of CD20+ non-Hodgkin's lymphoma.

Side effects of rituximab are commonly seen during the first infusion in up to 50% of patients and include fever, chills and rigors. These side effects are generally transient and directly related to the tumor burden, probably due to a greater degree of complement activation and pro-inflammatory cytokine release [1–6].

Respiratory adverse reactions have been reported in 38% of patients treated with rituximab in clinical trials, including cough, rhinitis, bronchospasm, dyspnea and sinusitis [4]. A few case reports have described more severe respiratory injuries associated with the use of rituximab, such as cryptogenic organizing pneumonia, interstitial

Fig. 1. Chest radiography shows bilateral infiltrates predominantly in the lower lobes.

Fig. 2. Chest computed tomography shows ground-glass opacities, small centrilobular nodules (long arrow) and areas of decreased attenuation or mosaic pattern (short arrows). These findings are characteristic radiographic features of subacute hypersensitivity pneumonitis.

pneumonitis and diffuse alveolar hemorrhage, some of which resulted in fatal outcomes [4]. According to the manufacturer of the medication, the calculated reporting rate of all possible cases of severe rituximab-induced lung injury is less than 0.03% [7].

Hypersensitivity pneumonitis is a diffuse parenchymal lung disease characterized by a non-IgE-mediated immunologic reaction to an inhaled allergen. Occasionally, hypersensitivity pneumonitis can be a manifestation of drug-induced lung disease wherein clinical, radiologic and histopathologic features are indistinguishable from those caused by inhaled organic antigens [8].

Rituximab has been sporadically linked to the development of hypersensitivity pneumonitis. Two reports [9, 10] in the medical literature have described the presence of histopathological findings suggestive of this condition. We present a case of hypersensitivity pneumonitis associated with rituximab treatment in a patient with chronic lymphocytic leukemia.

Case Report

A 59-year-old woman presented with symptomatic anemia with a direct antiglobulin test positive for IgG and complement. Evaluation of the warm autoimmune hemolytic anemia included a bone marrow examination that revealed chronic lymphocytic leukemia. Treatment with prednisone at 1 mg/kg resulted in an inadequate response, and weekly rituximab at 375 mg/m² was administered 4 times along with continuing steroid therapy. After rituximab was started, the hemoglobin level improved, and over a 6-week period, the prednisone was tapered from 90 to 20 mg daily. Ten days after decreasing the daily prednisone dose to 20 mg, the patient presented with a history of progressive dyspnea and dry cough for about a week. She had received the last dose of rituximab 3.5 weeks before this admission. Her initial vital signs were as follows: temperature 36.9°C, heart rate 88 beats/min, blood pressure 140/80 mm Hg, respiratory rate 20/min and oxygen saturation 91% on room air. Physical examination was unremarkable except for bilateral scattered inspiratory crackles. Laboratory examination revealed a white blood cell count of 5,900/mm³ (65.9% neutrophils, 24.3% lymphocytes and 1.4% eosinophils), hemoglobin 11.2 g/dl, platelet count 243,000/mm³, blood urea nitrogen 40 mg/dl, creatinine 1.2 mg/dl, calcium 10.4 mg/dl and glucose 92 mg/dl. An HIV ELISA test was negative. Tumor necrosis factor- α , determined by multi-analyte fluorescence detection, was undetectable. Chest radiography showed diffuse bilateral lung infiltrates (fig. 1). A computed tomography of the chest revealed diffuse bilateral ground-glass opacities, poorly defined centrilobular nodules and mosaic attenuation (fig. 2). The patient underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsies. Bronchoalveolar lavage fluid showed 40 red blood cells/mm³ and 15 white blood cells/mm³ (80% monocytes, 15% lymphocytes and 5% polymorphonuclear cells). The transbronchial biopsy revealed poorly formed granulomata, with

an increase in interstitial lymphocytes that were composed of predominantly CD3+/CD5+ lymphocytes, with a predominance of CD4+ over CD8+ T cells as seen by immunohistochemical stains (fig. 3). Special stains for acid-fast bacilli (Kinyoun acid-fast bacilli stain) and fungi/*Pneumocystis* (Gomori methenamine silver stain) were negative. A cytomegalovirus immunohistochemical stain was negative. Culture was negative for bacteria, fungi and mycobacteria. A meticulous review of the patient's environmental and occupational exposure showed no obvious external cause for hypersensitivity pneumonitis. The patient was treated with prednisone 1 mg/kg with an excellent clinical response including normalization of the oxygen saturation (97% on room air) within several days. The patient is currently being tapered off prednisone.

Discussion

Rituximab-induced interstitial lung disease is a rare but known complication. Its low incidence may be attributed to a failure to recognize the complication or resolution either spontaneously after discontinuing the medication or after a course of steroids [11].

In two comprehensive reviews [10, 11] of all reported cases of rituximab-induced interstitial lung disease, it is described that most patients were above 55 years old and had either a diagnosis of diffuse large B cell lymphoma or chronic lymphocytic leukemia. The majority of patients presented with progressive dyspnea, cough, fevers and hypoxemia after at least 4 cycles of rituximab. Chest radiographs and computed tomographies often showed diffuse bilateral interstitial infiltrates. Lung biopsies predominantly revealed alveolar damage and interstitial fibrosis. Although spontaneous resolution occurred with discontinuation of rituximab, more than half of the patients required high-dose corticosteroids. The duration of steroid therapy was usually 1–2 months [9–11].

Several confounding factors can affect the interpretation of these results. Firstly, only half of the reports described lung histopathology. Secondly, only a small number of patients were treated with rituximab as a single agent (other chemotherapeutic agents such as cyclophosphamide, doxorubicin, vincristine, bleomycin, videsine, mitoxantrone and etoposide were used in combination). Whether interstitial pneumonitis was a result of rituximab, other chemotherapeutic agents or a combination thereof is difficult to elucidate. Some authors have hypothesized that the pulmonary toxicity of chemotherapeutic agents can be enhanced by concomitant use of rituximab, through a synergistic cytokine activity or by production of deleterious reactive oxygen species [5, 12].

Fig. 3. Transbronchial biopsy (HE, ×400) showing an increase in interstitial lymphocytes with a poorly formed granuloma (long arrow) and intraluminal fibrous plug (short arrows).

Hypersensitivity pneumonitis represents an immunologic reaction that has not been explicitly associated with rituximab treatment; however, 2 case reports have described findings suggestive of this condition, as they point out the presence of loose non-necrotizing granulomas in a background of lymphocytic infiltrate [9, 10].

The first report [9] described a 65-year-old man with diffuse B cell lymphoma who received 5 cycles of rituximab and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). He presented with cough, dyspnea, macular rash, fever, hypoxemia and eosinophilia. The patient initially responded to prednisone 40 mg/day, but deteriorated after the 6th cycle of CHOP without rituximab. The ground-glass opacities progressed and the patient required mechanical ventilation and finally died of sepsis and multiorgan failure. Autopsy revealed intra-alveolar hemorrhage with diffuse alveolar damage along with loosely formed granulomas in a background of lymphocytic infiltrate.

The second report [10] described an 88-year-old man with Waldenström's macroglobulinemia who had received fludarabine and cyclophosphamide more than 3 years prior to presentation and had recently been given rituximab (8 doses). Eight weeks after the last dose of rituximab he experienced progressive dyspnea, cough and hemoptysis associated with hypoxemia, eosinophilia and bilateral alveolar/interstitial infiltrates on a chest computed tomography. Bronchoalveolar lavage fluid was suggestive of diffuse alveolar hemorrhage and was lymphocytic.

phocyte predominant. Transbronchial biopsy showed interstitial pneumonitis with scattered, loosely formed granulomas suggestive of a hypersensitivity-like reaction. The patient improved dramatically within 4 days of starting prednisone 60 mg/day.

Although both patients had histopathology suggestive of hypersensitivity pneumonitis, they also had peripheral eosinophilia and elevated IgE, which are not usually seen in true hypersensitivity pneumonitis.

Our patient had distinctive clinical and radiological findings in the absence of external causes of hypersensitivity pneumonitis. Our patient did not have peripheral eosinophilia in the blood and she was not receiving treatment with other chemotherapeutic agents that may have obscured the presentation.

Although the bronchoalveolar lavage in hypersensitivity pneumonitis is often lymphocyte predominant with a decrease in the CD4+/CD8+ ratio, in our case the bronchoalveolar lavage showed mononuclear cell predominance, and biopsy showed an increase in the CD4+/CD8+ ratio. Bronchoalveolar lavage findings may support the likelihood of certain lung diseases; however, the information is not specific, and in order to obtain a definitive diagnosis, further investigations are required [13, 14]. In drug-associated pneumonitis, a predominantly lymphocytic fluid is the most common finding in the bronchoalveolar lavage, but there are cases with normal cell differential [15]. Although the bronchoalveolar lavage fluid in our patient showed mononuclear cell predominance, the transbronchial biopsies evidenced a predominance of lymphocytes. While the lymphocyte CD4+/CD8+ ratio is usually reduced in hypersensitivity

pneumonitis, a broad range of possible CD4+/CD8+ lymphocyte ratios has been reported [14, 16].

Of the 2 previous reports describing possible rituximab-associated hypersensitivity pneumonitis [9, 10], one patient evidenced an increased CD4+/CD8+ ratio in the lung tissue [9] as in our case and the other showed a predominantly lymphocytic bronchoalveolar lavage fluid (CD4+/CD8+ ratio was not reported) [10].

The transbronchial biopsy in our patient was compatible with subacute hypersensitivity pneumonitis as it had all the necessary histological features for the diagnosis, i.e. bronchiolocentric interstitial pneumonitis with interstitial lymphocytic infiltrates, cellular bronchiolitis and poorly formed (loose) non-necrotizing granulomas [17].

It is unclear why our patient developed hypersensitivity pneumonitis while on low-dose prednisone. It is possible that low-dose prednisone (20 mg/day) was inadequate to suppress the development of pneumonitis. This theory might be supported by a case report of a patient on rituximab for refractory immune thrombocytopenic purpura who developed interstitial pneumonitis while on high-dose prednisolone therapy (60 mg/day) [18].

Conclusion

In patients receiving rituximab, hypersensitivity pneumonitis, though rare, should be considered in the appropriate clinical and radiographic setting. Rituximab should be discontinued; complete and rapid resolution is possible with systemic steroids.

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