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Case Report

Acute Respiratory Distress Syndrome after Rituximab Infusion

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Abstract

Rituximab, a humanized monoclonal antibody approved for malignant lymphoma, is being increasingly, effectively, and safely used for immune thrombocytopenic purpura (ITP) and other humoral autoimmune disorders. We report the case of a 43-year-old man with ITP refractory to steroids and intravenous immunoglobulin who developed acute respiratory distress syndrome (ARDS) after a single infusion of rituximab. Dyspnea, hypoxemia, and pleuritic chest pain occurred within 24 hours of rituximab administration, and there was no other apparent explanation. Progressive hypoxemia mandated endotracheal intubation 1 week after rituximab administration and led to death 4 weeks after admission. ARDS has been associated with the administration of other monoclonal antibodies, such as infliximab, gemtuzumab ozogamicin, and OKT3 and is believed to be directly mediated by release of proinflammatory cytokines. ARDS is rarely associated with rituximab infusion for lymphoproliferative disorders, but it should be considered by those administering rituximab, especially when a patient develops severe pulmonary symptoms soon after infusion.

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Key words: Rituximab; Immune thrombocytopenic purpura; Acute respiratory distress syndrome; Monoclonal antibody

1. Introduction

Rituximab is a humanized monoclonal antibody against the B-cell surface antigen CD-20 and has been approved in the United States for the treatment of non-Hodgkin's lymphoma [1]. Recently, rituximab has shown efficacy in the management of immune (idiopathic) thrombocytopenic purpura (ITP) refractory to corticosteroids and splenectomy. Two recent studies have shown an overall response rate of approximately 50% with half of the platelet responses sustained 6 months or longer [2,3]. Rituximab may act in ITP by inhibiting autoantibody production, but it may also inhibit macrophage Fc receptor function, inhibiting clearance of immunoglobulin G–coated platelets [4,5]. We report the case of a patient with newly diagnosed, initially refractory ITP who unexpectedly developed acute respiratory distress syndrome (ARDS) after a single infusion of rituximab, bringing to our attention the possibility of such a reaction.

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2. Case Report

A 43-year-old man presented to an emergency department with severe headache and was admitted because of severe thrombocytopenia (platelet count, 2×10^9/L). Hemoglobin concentration and leukocyte count were normal, and the blood smear results were consistent with the clinical diagnosis of ITP. The results of bone marrow aspiration and biopsy were normal with abundant megakaryocytes. The results of a human immunodeficiency virus test were negative. The findings at admission computed tomography (CT) of the brain were normal. The platelet count did not improve significantly with oral corticosteroids, and intravenous immunoglobulin 1 g/kg per day was administered on hospital days 1 to 3. Because of persistent severe thrombocytopenia, rituximab 375 mg/m^2 was given on hospital day 11, and low-grade fever and chills accompanied the infusion. The following day the patient complained of dyspnea and pleuritic chest pain. Oxygen saturation was 78% on room air. CT of the chest showed diffuse pulmonary ground-glass opacities (Figure 1A). There was no evidence of pulmonary embolus on either CT or ventilation-perfusion scans. The patient was afebrile with no other evidence to suggest infection. An echocardiogram revealed a cardiac ejection fraction of 60% to 64%. Hypoxemia did not improve with diuresis. By the

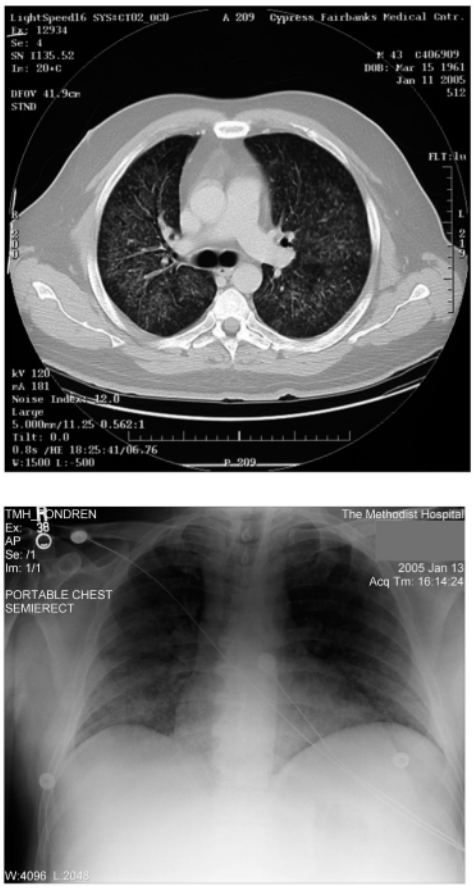

Figure 1. A, Computed tomographic scan of the chest obtained less than 24 hours after rituximab infusion. Diffuse bilateral ground-glass opacities are evident. B, Portable chest radiograph obtained on admission to the intensive care unit shows bilateral pulmonary opacities.

third day after rituximab infusion, the patient needed transfer to the medical intensive care unit (MICU). He needed 100% oxygen and noninvasive positive-pressure ventilation. Arterial blood gas evaluation revealed the following results: pH, 7.40; PCO_2, 43 mm Hg; and PO_2, 40 mm Hg. A chest radiograph on admission to the MICU revealed the bilateral presence of pulmonary infiltrates (Figure 1B). The platelet count remained 1×10^9/L. A diagnosis of ARDS was made, and administration of methylprednisolone 500 mg intravenously daily was begun. Bronchoscopy was performed, and the results were normal. There was no evidence of intraalveolar hemorrhage, and culture results were negative. One week after administration of rituximab, the patient needed intubation and mechanical ventilation with positive end-expiratory pressure. During this time administration of danazol (200 mg 3 times daily) was begun, and oral cyclophosphamide (500 mg/d) was administered later. The platelet count normalized at 200×10^9/L. Two weeks after intubation, the patient became febrile (39°C) and hypotensive. The platelet count decreased to 40×10^9/L. Blood and respiratory cultures had positive results for *Pseudomonas* organisms. Pneumothorax developed and necessitated chest tube placement. The patient died 3 weeks after receiving rituximab.

3. Discussion

This case demonstrates that treatment with a single infusion of rituximab can lead to ARDS. ARDS has been reported rarely in patients with lymphoproliferative disorders receiving rituximab but not in patients treated with rituximab for other disorders [6]. The first published report of ARDS related to rituximab treatment stated that the reaction occurred after the third infusion in a patient with follicular lymphoma [7]. In that case, an anaphylactic reaction developed with tachycardia, hypotension, and hypoxemia within 3 hours of the start of the infusion. A chest radiograph showed bilateral pulmonary infiltrates and pleural effusions. A similar syndrome during the first rituximab infusion has been described in patients with lymphoproliferative disorders and large numbers of circulating tumor cells. This syndrome is characterized by fever, rigors, bronchospasm, and hypoxemia in conjunction with a rapid decrease in the number of circulating tumor cells and other laboratory evidence of tumor lysis (hypocalcemia and an increase in lactate dehydrogenase level). In the original description, pulmonary symptoms were reversible with oxygen supplementation and bronchodilators [8]. Reports of interstitial pneumonitis related to rituximab therapy have been published. However, symptoms were later in onset and had a clinical picture distinct from that of ARDS. In addition, as in the 2 cases reported by Burton et al, symptoms were reversible with prednisolone [9-12]. Our case appears unique in that ARDS developed in a patient treated for an autoimmune disorder (ITP), an area in which there is increasing interest in and use of rituximab. Our patient met consensus criteria for ARDS (acute onset of bilateral pulmonary infiltrates; PaO_2/FIO_2, <200; and normal cardiac function), the syndrome emerging on the heels of the first rituximab infusion and having no other obvious cause [13]. This case also is unique because ARDS occurred in the absence of any clinical evidence of either anaphylaxis or tumor lysis.

ARDS has been reported as a rare side effect of other monoclonal antibodies, such as muromonab [14], basiliximab [15], gemtuzumab ozogamicin [16], infliximab [17], and trastuzumab [18,19]. Muromonab, a murine antibody directed against the T-cell antigen CD3, may produce ARDS related to the transient release of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interferon γ, interleukin 2, and interleukin 6, with subsequent neutrophil sequestration in the lungs [14]. Rapid activation of both classic and alternative complement pathways by the antibody may result in enhanced binding of neutrophils to the pulmonary vasculature. Generated complement activation products such as C5a and SC5b-9 can also induce production of proinflammatory cytokines by monocytes [20]. In a study of 14 kidney allograft recipients, an interesting finding was that a monoclonal antibody against TNF, CB006, prevented severe muromonab-associated toxicities such as hypotension, neurotoxicity, and ARDS [21,22].

Gemtuzumab ozogamicin, a monoclonal antibody linked to the cytotoxic antibiotic calicheamicin and directed against the CD33 antigen on myeloblasts, has been associated with the development of ARDS in 5 patients within 24 hours of treatment [16]. In approximately one half of reported cases,

the patients had leukocyte counts greater than 60,000/μL. Although pulmonary leukostasis can have a similar clinical presentation in patients with very high blast counts, the temporal association suggests a drug reaction. To reduce the risk of severe pulmonary toxicity, it has been recommended that leukocyte counts be less than 30,000/μL prior to initiation of treatment with gemtuzumab [16]. ARDS has been reported as a delayed hypersensitivity reaction in a patient with Crohn disease 10 days after the second infusion of infliximab, a chimeric monoclonal antibody directed against TNF-α [17]. Very high titers of human antichimeric antibodies (HACA) were found in this patient. These antibodies can develop in approximately 13% of patients treated with infliximab. HACA is associated with a greater risk of delayed hypersensitivity reactions and a lupus-like syndrome [23].

In conclusion, the exact mechanism by which rituximab and other monoclonal antibodies cause ARDS is unknown, but with first-time infusions it may be related to cytokine release and complement activation. With subsequent infusions of chimeric monoclonal antibodies, ARDS may be the result of a delayed hypersensitivity reaction, such as those related to HACA. Our experience with a fatal case of ARDS after the first infusion of rituximab in a patient with a humoral autoimmune disorder should alert clinicians to the possibility of this type of reaction.

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