

Diffuse Alveolar Hemorrhage: A Fatal Complication of Rituximab

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Abstract: Pulmonary toxicity is a rare but severe adverse effect of Rituximab, associated with significant morbidity and mortality. Despite increased reporting, few case reports associated with alveolar hemorrhage due to Rituximab have been published. The authors present the case of a 61 year old Caucasian male with a diagnosis of small lymphocytic lymphoma who recently completed chemotherapy with Rituximab and Bendamustine. The patient presented to the emergency room with a one week history of nonproductive cough associated with shortness of breath and low grade fevers. Differential diagnosis at the time of presentation included health care associated pneumonia, Rituximab-induced pulmonary toxicity, and *Pneumocystis jiroveci* infection given his history of lymphoma and treatment with Rituximab. The patient was initiated on intravenous (IV) broad-spectrum antibiotics, oral atovaquone, and IV methylprednisolone. A CT scan showed bilateral diffuse pulmonary opacities and a video-assisted thorascopic surgery guided lung biopsy revealed early diffuse alveolar hemorrhage with no evidence for infection. However, the remaining work-up consisting of blood cultures, blood tests, and bronchopulmonary lavage did not produce any suggestive findings. Despite initiating the above aggressive therapies, the patient continued to rapidly deteriorate. An autopsy revealed diffuse alveolar hemorrhage of the lungs, thought to be secondary to Rituximab toxicity. The authors recommend emphasizing the importance of early identification of worsening pulmonary symptoms in patients receiving Rituximab, with diagnostic consideration given to Rituximab-related toxicity.

Keywords: Rituximab, Rituximab-induced toxicity, Pulmonary toxicity, Alveolar hemorrhage.

INTRODUCTION

Rituximab is a chimeric monoclonal antibody frequently utilized in the treatment of hematologic malignancies. Pulmonary toxicity is a rare but severe adverse effect of the medication, associated with significant morbidity and mortality. Rituximab-induced interstitial lung disease is becoming increasingly reported, with recent estimated incidences ranging from 3.7-10%. [1] Further, Hadjinicolaou *et al* reported a mortality rate of 18% (18/99 cases) due to rituximab-induced pulmonary toxicity in a systematic review. [1] Despite increased reporting, few case reports associated with alveolar hemorrhage due to Rituximab have been published, adding to the uniqueness of this report. [2, 3]

CASE REPORT

The authors present the case of a 61 year old Caucasian male with a diagnosis of small lymphocytic lymphoma who recently completed his sixth cycle of chemotherapy with Rituximab and Bendamustine. Six weeks after completion of the last cycle of the chemotherapy, the patient presented to the emergency room with a one week history of nonproductive cough

associated with shortness of breath and low grade fevers. On presentation, he had a temperature of 36.7 °C, blood pressure of 133/50 mmHg, heart rate of 60 beats per minute and a respiratory rate of 30 breaths per minute with oxygen saturation of 92% on room air. Chest examination was significant for diffuse bilateral expiratory wheezing and scattered rhonchi. Laboratory findings revealed a white count of 8500 cells/ μ L with an absolute lymphocyte count of 420. Chest x-ray showed bibasilar lung infiltrates and a chest computed tomography (CT) revealed bilateral nodular ground glass opacities in the upper lobes. Arterial blood gas (ABG) was unremarkable. The differential diagnosis at the time included health care associated pneumonia (HCAP), Rituximab-induced pulmonary toxicity, and *Pneumocystis jiroveci* infection (PCP) given his history of lymphoma, treatment with Rituximab, and low absolute lymphocyte count.

The patient was initially started on empiric broad spectrum antibiotic coverage with intravenous vancomycin, ceftazidime, and levofloxacin for HCAP along with oral atovaquone 750 mg (history of allergies to sulfa drugs) twice daily and intravenous methylprednisolone 60 mg every eight hours to cover for pneumocystis infection. A bronchoscopy with bronchopulmonary lavage (BAL) was done on day two of hospitalization that was negative for pneumocystis, fungi, virus, mycobacterial strains, and malignant cells.

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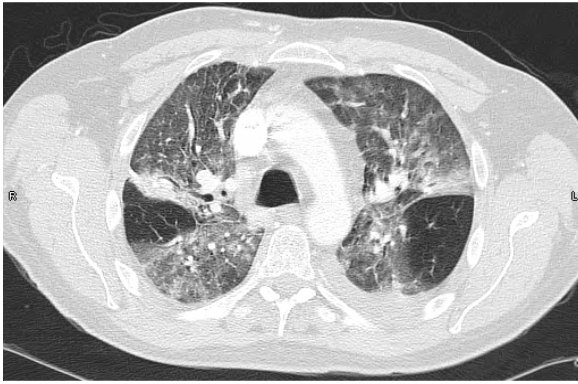


Figure 1: Chest CT Showing Bilateral Diffuse Ground Glass Infiltrate.

Blood cultures and tests for HIV, CMV, aspergillus, cryptococcal antigen, and urinary antigens for histoplasma were reported to be negative. The patient deteriorated clinically over the next few days with increased oxygen requirements that prompted a repeat chest CT which showed bilateral diffuse pulmonary opacities (mosaic ground glass pattern) interspersed

with areas of air cysts, suspicious for *Pneumocystis jirovecii* pneumonia. A repeat BAL was performed that was again negative for PCP. A video-assisted thorascopic surgery (VATS) guided lung biopsy was done that revealed early diffuse alveolar hemorrhage with no evidence for infection. Work-up for vasculitis, including ANA, ANCA, and anti-DNA antibodies, was negative with normal complement levels. The dosage of intravenous methylprednisolone was increased to 90 mg every eight hours with marked clinical improvement. However, as steroids were tapered down over the next few days, he became very tachypneic with a significant drop in his oxygen saturation. An ABG done at the time showed a pH of 7.60, pCO₂ of 35, paO₂ of 49, and HCO₃ of 34.4 on eight liters of oxygen. He was then transferred to the intensive care unit where he was intubated. A repeat chest CT excluded pulmonary emboli and showed further progression of his bilateral lung infiltrates (Figure 1). Unfortunately, his clinical status rapidly deteriorated and the patient passed away. An autopsy revealed

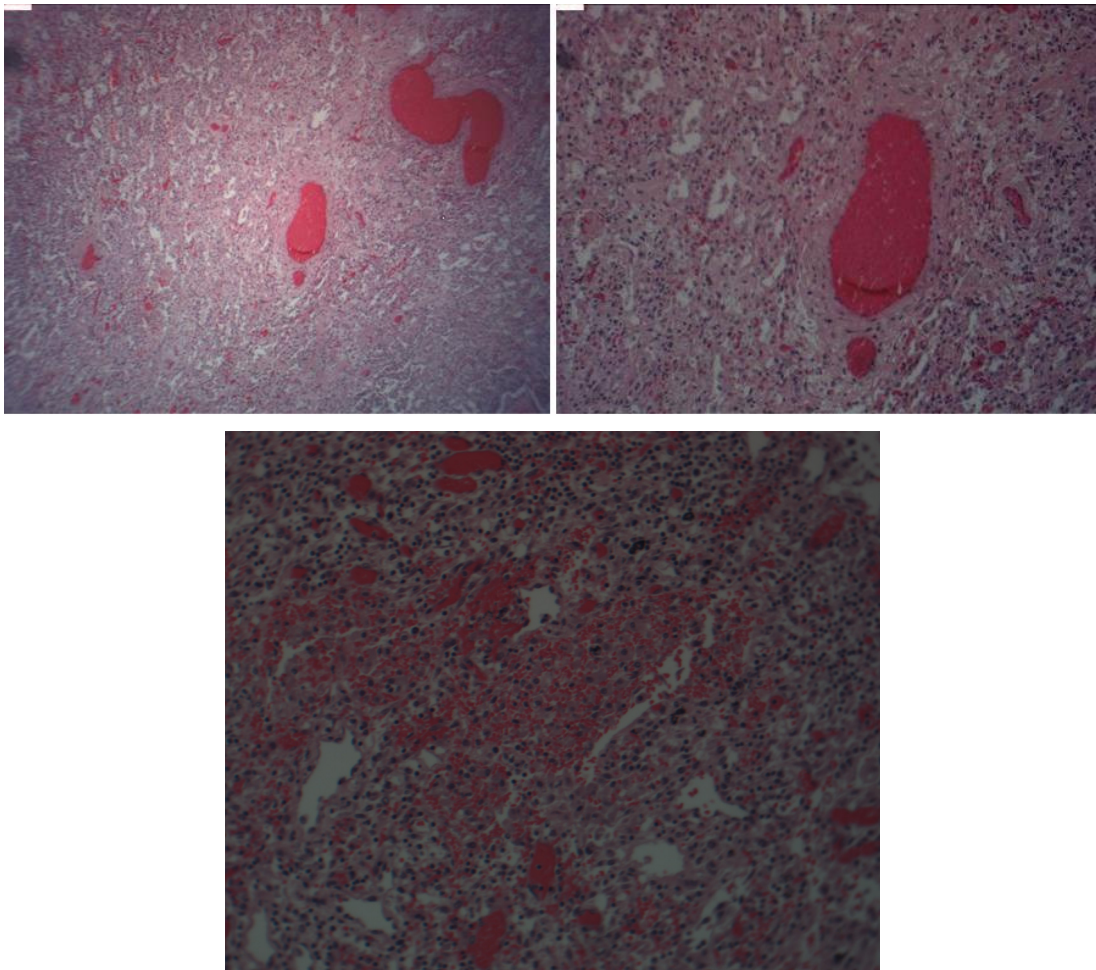


Figure 2: H & E Pictures of the Lung from Autopsy Showing Diffuse Alveolar Hemorrhage.

diffuse alveolar hemorrhage of the lungs (Figure 2), felt to be secondary to Rituximab toxicity.

CONCLUSION

Rituximab-induced pulmonary toxicities are usually severe and potentially fatal. The temporal timeline of this case is consistent with other reports of interstitial pneumonitis and associated alveolar hemorrhage [1-5]. Management of pneumonitis in this patient was consistent with that described in the current literature [1, 5, 6] and despite aggressive measures, the patient succumbed to Rituximab-related complications. The authors recommend emphasizing the importance of early identification of worsening pulmonary symptoms in patients receiving Rituximab, with diagnostic consideration given to Rituximab-related toxicity.

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