Rituximab-Induced Interstitial Lung Disease in Pemphigus Patients: Two Case Reports and Review of the Literature

Niporn Jariyakulwong MD, Julphat Intarasupht MD.
Department of dermatology, Phramongkutklao college of medicine, Thailand.

ABSTRACT:
Rituximab is a CD20-directed cytolytic antibody approved as a novel effective first-line treatment for severe pemphigus vulgaris and pemphigus foliaceus. Rituximab is generally safe, but uncommon fatal adverse events such as drug-induced interstitial lung disease have been reported. We reported two patients who developed rituximab-induced interstitial lung disease despite receiving the recommended standard dosages and review of the literature.
Key words: Rituximab, Drug-induced interstitial lung disease, Pemphigus

Introduction

Pemphigus is a group of potentially life-threatening mucocutaneous blistering disorders characterized by the binding of circulating immunoglobulin G (IgG) autoantibodies to intercellular adhesion molecules, leading to acantholysis[1]. Major types of pemphigus include pemphigus vulgaris (PV), pemphigus foliaceus (PF), immunoglobulin A pemphigus, and paraneoplastic pemphigus.

Current standard guidelines[2] recommend corticosteroids and/or other immunosuppressive agents as the classical therapy for pemphigus with improved treatment outcomes

Rituximab (RTX) is a chimeric human-mouse IgG1-κ monoclonal antibody that specifically targets the B-cell surface antigen CD20, leading to B-cell depletion through the activation of the complement cascade and natural killer cells[3]. RTX has been used since 2001 in non-Hodgkin's B-cell lymphomas, resulting in significant improvements in lymphoma-associated autoimmune phenomena including paraneoplastic pemphigus[4], and recently approved as a novel effective first-line treatment for PV and PF. Combining RTX with glucocorticoids is recommended in uncontrolled or refractory pemphigus[2].

The most frequent adverse effects associated with RTX are infusion-related reactions, with 38% of patients reporting respiratory adverse reactions including symptoms such as cough, rhinitis, bronchospasm, dyspnea, and sinusitis. Fatal adverse events of interstitial lung disease (ILD) such as cryptogenic organizing pneumonia, interstitial pneumonitis, and diffuse alveolar hemorrhage are also reported 0.03% of cases[5].

In Thailand, the incidence of RTX-induced ILD has been documented in patients with non-Hodgkin lymphoma who received RTX. However, there are no reports in patients with pemphigus[6]. To raise awareness, two cases of pemphigus were reported where patients developed RTX-induced ILD even when drugs were administered at the recommended standard dosage according to guidelines.

Corresponding Author: Julphat Intarasupht MD., email: julphat@gmail.com

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Case Report

Case 1

A 73-year-old woman without any underlying diseases presented with oral mucosal erosion and scattered flaccid vesiculobullous lesions on her trunk and extremities. A skin biopsy was performed and the results, along with direct immunofluorescence staining and the enzyme-linked immunosorbent assay, were consistent with a diagnosis of PV. The other physical examination findings were unremarkable, except for the patient's low body weight of 35 kg, body mass index (BMI) of 15.5 kg/m^2 and body surface area (BSA) of 1.2 m^2.

The patient was initially received treatment with 40 mg/day (1 mg/kg/day) of prednisolone for 2 months, but this proved ineffective in controlling the disease. Subsequently, 2 cycles of 1000 mg RTX were administered with a 2-week interval, resulting in improvement of the lesions. Concurrently, a tapering regimen of prednisolone with azathioprine was initiated. However, after one month, the patient experienced bicytopenia due to azathioprine, leading to the discontinuation of azathioprine. The patient continued prednisolone at a dosage of 10 mg/day.

Seven months after receiving the first dose of RTX, with a cumulative dosage of 2000 mg, the patient presented with a one-week history of acute dyspnea and a dry cough, with no prior history of illness. No evidence of environmental or occupational exposure suggested the development of an occupational lung disease. The patient's prior chest X-ray was unremarkable, and there is no history of pulmonary symptoms before the current presentation. She was admitted and treated as a hospital patient. As her condition worsened, intubation was required due to respiratory failure.

The respiratory virus panel, including real-time reverse transcription polymerase chain reaction (RT-PCR) for COVID-19, was negative. Sputum tests for Acid-Fast Bacillus (AFB) , Gene-Xpert, and the immunofluorescent antibody (IFA) test for Pneumocystis jirovecii (PCP) were also negative. CXR revealed hyperaeration and diffuse ground-glass opacity both lungs (Figure 1). Chest computed tomography (CT) demonstrated multiple generalized consolidations in both lungs, with peripheral ground glass opacities (Figure 2).

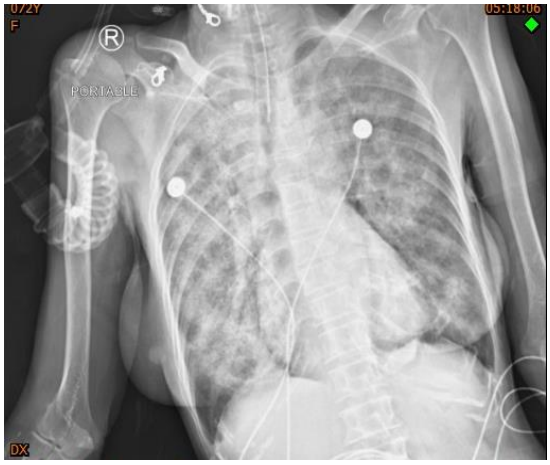

Figure 1 Diffuse ground-glass opacity both lungs, hyperaeration

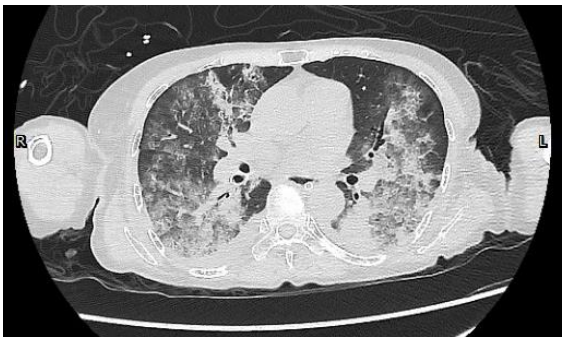

Figure 2 Multiple generalized consolidations both lungs with peripheral ground-glass opacities

The patient was administered empirical antibiotics to treat a suspected pneumonia and maintained systemic corticosteroids as a preventive against adrenal insufficiency. Following comprehensive investigations, a bronchoscopy and transbronchial biopsy were performed. Histopathological findings of bronchial tissue revealed acute pneumonia, with few intra-alveolar fibrin depositions without cell malignancy. Antibiotics were discontinued upon negative results in both blood and pulmonary tissue cultures. After excluding other potential causes, a pulmonologist diagnosed RTX-induced ILD one week after admission. The patient was then administered intravenous dexamethasone, followed by oral prednisolone at a dosage of 1 mg/kg. Her clinical symptoms ameliorated, with successful extubation within one weeks of starting the treatment.

Case 2

A 67-year-old man, who had underlying hypertension and dyslipidemia, presented to the hospital with multiple flaccid bullae on his trunk and extremities. A skin biopsy was performed, and the results, along with direct immunofluorescence staining, confirmed the diagnosis of PF. The other physical examination findings were unremarkable. The patient's body weight was 60 kg, with BMI of 20 kg/m² and BSA of 1.68 m².

He initially received treatment with prednisolone at 60 mg/day (1 mg/kg/day). Due to a history of azathioprine-induced transaminitis, mycophenolate mofetil (MMF) was introduced while tapering prednisolone. Despite a year of using 2g/day of MMF and 30mg/day of prednisolone, disease control was not achieved. Consequently, two cycles of 1000 mg of RTX with a 2-week interval were administered to treat the refractory PF. As a result of disease improvement, the patient continued with a regimen of 10mg/day of prednisolone and 2g/day of MMF.

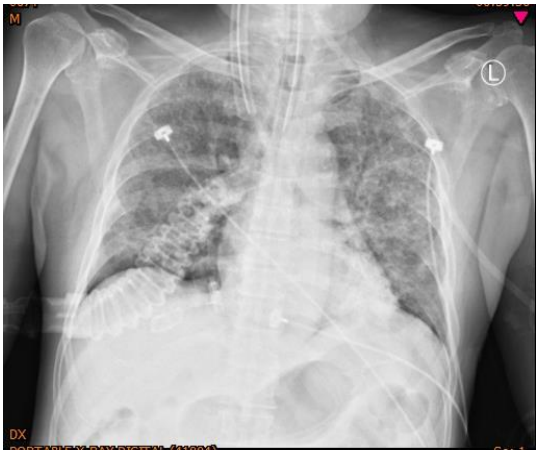

Figure 3 Diffuse ground-glass opacity both lungs, low lung volume

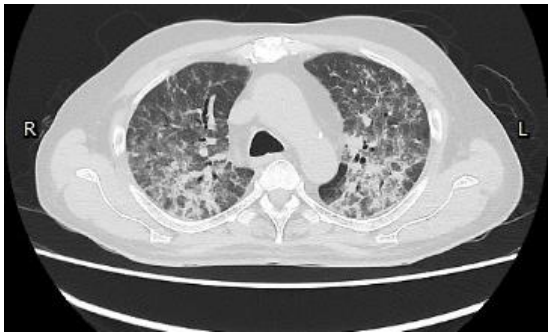

Figure 4 Multiple centrilobular nodules with ground-glass opacities both lungs with interlobular septal thickening

Two months after the first dose of RTX, with a cumulative dosage of 2000 mg, the patient complained of dyspnea on exertion, fever, and having a dry cough for 2 weeks, with no prior history of illness. No evidence of environmental or occupational exposure suggested the development of an occupational lung disease. The patient's prior CXR was unremarkable, and there is no history of pulmonary symptoms before the current presentation. In the emergency room, he experienced tachypnea with hypoxemia (90% on room air), requiring an intubation due to respiratory failure.

The respiratory virus panel, including RT-PCR for COVID-19, was negative. Sputum tests for AFB, Gene-Xpert, and IFA for PCP also yielded negative results. CXR revealed bilateral diffuse interstitial infiltration (Figure 3), while a chest CT showed multiple centrilobular nodules with bronchial wall thickening and ground glass opacities in both lungs (Figure 4). A pulmonary artery CT did not detect any signs of pulmonary embolism.

The patient was prescribed empirical antibiotics to treat a suspected pneumonia and maintained systemic corticosteroids as a preventive against adrenal insufficiency. Following thorough investigations, a bronchoscopy and bronchoalveolar lavage were performed, revealing no evidence of granuloma, fungal organisms, or malignancy. Special stains for AFB and PCP were negative. Cultures for fungi and mycobacteria also yielded negative results. After ruling out other potential causes, a pulmonologist diagnosed RTX-induced ILD two weeks after admission. The patient then received intravenous dexamethasone. While in admission, a nosocomial infection occurred, and the patient was treated with antibiotics tailored to the drug susceptibility of the organism. However, despite the treatment, the patient's clinical condition progressively deteriorated, and he passed away.

Discussion

RTX is a CD20-directed cytolytic antibody indicated for the treatment of non-Hodgkin lymphoma , chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and moderate to severe PV[5]. Overall, RTX is generally regarded as a safe treatment option. Common adverse events include infusion related-reactions, infections, and body aches[5].

RTX-induced ILD is rare, with an indicated incidence rate of only 0.03%[7,8]. The pathogenesis of RTX-induced ILD involves complement activation, indirect activation of cytotoxic T lymphocytes or release of cytokines such as TNF-α, IFN-α, IL-6, and IL-8 which can lead to vascular and alveolar damage[9]. The clinical manifestation of RTX-induced ILD may include progressing dyspnea, exertional dyspnea, persistent dry cough, fever or incidental findings on CXR or chest CT. These symptoms can emerge between 2 weeks and 10 months after the initial administration of RTX[9,10]. The CXR features of RTX-induced ILD include a decrease lung volume, accompanied by peripheral interstitial or ground-glass infiltrations. Similarly, the characteristic CT chest findings typically reveal ground-glass opacity, centrilobular nodules, or interlobular septal thickening. In the preceding study, the cumulative dose of RTX-induced ILD was 2000 mg to 4,500 mg[11]. However, the diagnosis of RTX-induced ILD needs to exclude infection, malignancy, and autoimmune diseases.

In multivariate analysis, the established risk factors of RTX-induced ILD include the elderly, low serum albumin level and smoking[8]. Treatment of RTX-induced ILD is respiratory support and systemic corticosteroids may play a role in patients with respiratory failure[9].

The standard guideline for pemphigus[2] does not provide information on body weight in relation to RTX treatment. Additionally, the previous study on RTX-induced ILD did not include details about the body weight of individual patients, making it difficult to verify the relevance of this factor.

Both patients had no history of smoking and exhibited normal albumin levels. The common risk factor identified in the literature reviews is elderly. However, the female patient had low body weight of 35 kg (BMI 15.5 kg/m^2), while the male patient's body weight is 60 kg, notably below the average for individuals of the same age group in the Caucasian population[12] (159 pounds: 72 kilograms), where the standard

guideline treatment for pemphigus[2] is typically administered.

Clinical trials on the use of RTX in pemphigus[13] have shown no significance in complete remission and relapse rates between high-dose protocol (2000 mg) and low-dose protocol (<1500 mg) treatments. However, it is noteworthy that high-dose RTX treatment may result in a longer duration of remission[10]. Therefore, considering a low dose of RTX for treating pemphigus in individuals with low body weight may be more appropriate and suitable for this specific patient population.

This study reported on the development of RTX-induced ILD in pemphigus patients with elderly and low body weight, despite receiving the standard dose of RTX.

Conflict of interest and funding

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