

Letter to the Editor (Case Report)

A case of rituximab-induced interstitial pneumonitis observed in systemic lupus erythematosus

SIR, Rituximab (anti-CD20 mAb) depletes B lymphocytes and is widely used for the treatment of B-cell malignant lymphoma [1, 2]. The incidence of life-threatening side effects is very low, but there are some case reports of rituximab-induced interstitial pneumonitis (IP) in patients with haematological disorders [3]. We report the first case of rituximab-induced IP observed in SLE.

A 24-year-old woman was diagnosed as SLE based on the presence of malar rash, oral ulcers, leucopenia ($1500/\mu\text{l}$), thrombocytopenia ($6.9 \times 10^4/\mu\text{l}$), hypocomplementaemia (C3, 61 mg/dl; C4, 9 mg/dl), positive test for ANA (1:640), anti-Sm antibody (158 U/ml) and anti-dsDNA antibody (10 U/ml) and CNS involvement. MRI of the brain showed areas with high intensity by T₂-weighted image and low intensity by T₁-weighted image in the white matter bilaterally. She was treated with 1000 mg rituximab with pre-treatment of 125 mg methylprednisolone, because of lack of response to intravenous methylprednisolone pulse and 1 mg/kg/day oral prednisolone. Before rituximab administration, chest radiograph and CT was normal (Fig. 1A–C). After finishing infusion of rituximab, she developed dry cough, but breath sounds were normal with an oxygen saturation of 99% and normal chest X-ray. Four days after the administration, chest X-ray revealed interstitial opacities in the lung base bilaterally (Fig. 1D). Chest CT revealed diffuse ground-glass attenuation in non-specific areas of both lungs without any structural distortion (Fig. 1E and F). Congestive heart failure was excluded by normal study of ultrasound cardiography and normal level of serum brain natriuretic peptide. The case was diagnosed as rituximab-induced IP based on the bronchoalveolar lavages fluid examination (increased total cell count, 1.26×10^8 ; increased lymphocytes, 68.9%; non-detection of eosinophils and neutrophils; low CD4/CD8 ratio, 0.19; negative PCR test for *Pneumocystis jiroveci* DNA and *Mycobacterium* DNA; and negative culture test for

bacteria, fungus and *Mycobacterium*), negative examination for serum anti-*Chlamydia* antibody, CMV-antigenaemia and *Legionella* urinary antigen and ground-glass appearance on chest CT. She had no allergic history, and was not taking any other medication. Treatment with 1 mg/kg/day of prednisolone was continued. Seven days after the diagnosis, dry cough subsided and chest X-ray and CT findings disappeared (Fig. 1G–I). Lupus-related symptoms, such as malar rash and oral ulcers disappeared, the numbers of leucocyte and platelet were increased to normal ranges, and titres of serum anti-Sm antibody and anti-dsDNA antibody were decreased. The dosage of prednisolone was tapered to 10 mg/day without any exacerbation.

Since several autoantibodies are presented in lupus patients and deposition of immune complex is shown in the affected organs, autoimmune B cells might be thought to have an important role for the pathogenesis of SLE. Rituximab has been used for the treatment of several autoimmune diseases, such as SLE [4, 5] and RA [6, 7]. So far, 16 cases with rituximab-induced IP have been reported and reviewed by Wagner *et al.* [3]. In all cases, rituximab was used for haematological disorders, including 12 patients with malignant lymphoma, 3 with chronic lymphocytic leukaemia and 1 with immune thrombocytopenic purpura. Analysis of the available information showed that the patients were 65.5 ± 3.1 years old (mean $\pm$ S.E.M.), the number of cycles of rituximab infusion was 4.1 ± 0.7 , all patients were treated with corticosteroids and 6 out of 16 patients died during the follow-up. Our patient was relatively young (27 years) and developed IP following the first dose of rituximab. Based on the PubMed database searches, this is the first report of an SLE patient who developed IP following initiation of rituximab therapy. Recently, rituximab-induced organizing pneumonia was reported in an RA patient [8]. Although it is rare, care should be taken with pulmonary complications when rituximab is prescribed not only for malignant lymphoma, but also for the other diseases, including SLE and RA.

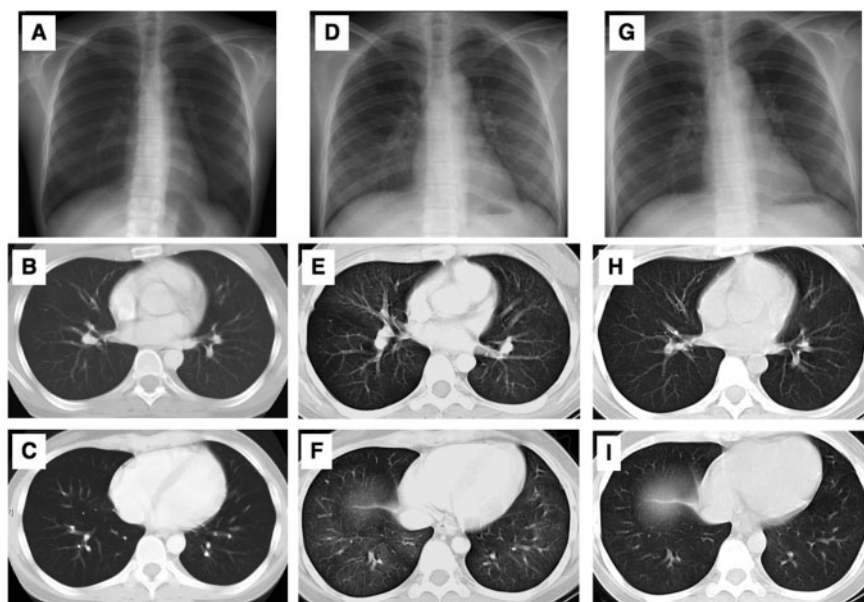


FIG. 1. Radiographic imaging. Before rituximab therapy, chest radiograph (A) and CT (B and C) showed normal findings. Four days after rituximab treatment, the chest X-ray showed interstitial opacities in the lung base bilaterally (D), and chest CT revealed diffuse ground-glass attenuation in non-specific areas of both lungs without any structural distortion (E and F). Seven days after the diagnosis of IP, the chest X-ray showed complete resolution (G) and disappearance of the chest CT findings (H and I).

For this patient, infusion of rituximab was performed according to the protocol of ongoing Phase II/III trial of SLE [9] and was well managed. Regarding the dosage of rituximab, twice infusion at 2 weeks interval of each 1000 mg rituximab was used in clinical trials of SLE [4, 5], ongoing trial [9] and also RA therapy [7] approved by the Food and Drug Administration in USA. In contrast, 4 weekly infusions of 375 mg/m² rituximab have been widely used in malignant lymphoma [2]. Therefore, an individual single dosage of rituximab is higher in SLE and RA, although total dosage is higher in lymphoma. This patient was treated with a single infusion of 1000 mg rituximab. Consequently, both individual and total dosage of rituximab may affect the development of IP. The etiology of rituximab-induced IP is unknown. It was reported that rituximab infusion was rapidly followed by activation of complements, B-lymphocyte cytolysis and TNF- α release [10]. These processes of infusion reaction to rituximab may provoke IP. Alternatively, this could be explained by allergic reaction to rituximab, which may not be dose related.

Rheumatology key message

- We describe the first case of interstitial pneumonitis induced by rituximab therapy in a patient with SLE.

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