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CASE REPORT

Rituximab induced pulmonary fibrosis in a patient with lupus nephritis

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We describe a 26-year-old woman who was diagnosed eleven years ago with systemic lupus erythematosus and who had suffered multiple relapses. She presented with class IV lupus nephritis with thrombotic microangiopathy, for which she received three doses of rituximab along with plasmapheresis, with no response, and soon became dialysis dependent. One month after the last dose of rituximab, she presented with dyspnoea and hypoxia. A transbronchial lung biopsy revealed pulmonary fibrosis. A diagnosis of rituximab induced pulmonary fibrosis was made after excluding other causes and she was treated with intravenous methyl prednisolone with which there was marked improvement in symptoms and hypoxemia. This is the first report of rituximab induced pulmonary fibrosis in a patient with lupus nephritis. *Lupus* (2012) **21**, 1131–1134.

Key word: Lupus nephritis, pulmonary fibrosis, rituximab, systemic lupus erythematosus

Background

Rituximab is a B cell depleting antibody, which is now an established form of treatment for non-Hodgkin's lymphoma and rheumatological diseases.^{1,2} Rituximab induced interstitial lung disease (RTX-ILD) is a rare complication with unclear pathogenesis.³ According to the manufacturer, the reported rate of severe rituximab induced lung injury is less than 0.03%.¹ RTX-ILD is not related to the number of cycles or cumulative dose of the drug. A wide range of lung pathologies ranging from interstitial pneumonitis to pulmonary fibrosis can be seen with rituximab. RTX-ILD has mostly been reported in patients with lymphoma receiving rituximab as a part of chemotherapy; however, three cases have also been reported in patients with systemic lupus erythematosus (SLE).³ Of these three cases, two had interstitial pneumonitis and one developed pneumonia with no organism identified.^{3,4} Pulmonary fibrosis is a rare type of RTX-ILD and has not been reported so far in

patients with SLE. We report a young lady with SLE who developed pulmonary fibrosis after rituximab.

Case report

A 26-year-old female was diagnosed with SLE eleven years earlier when she had menstrual bleeding and polyarthralgia. On evaluation, she had thrombocytopenia and hypocomplementemia, and was ANA and dsDNA positive. She was treated with pulse methylprednisolone followed by oral steroids and on achieving remission was maintained on 10 mg oral prednisolone. Two years later, she developed irritability and altered behaviour and was diagnosed with central nervous system lupus. She received monthly pulses of intravenous cyclophosphamide for 6 months followed by 3 quarterly doses along with oral prednisolone. The patient developed a pericardial effusion along with increase in dsDNA titres and hypocomplementemia one year after the last pulse of cyclophosphamide, and was again treated with monthly cyclophosphamide pulses for 6 months and oral steroids. She subsequently remained well for the next 5 years, after which she developed oedema. Evaluation revealed proteinuria

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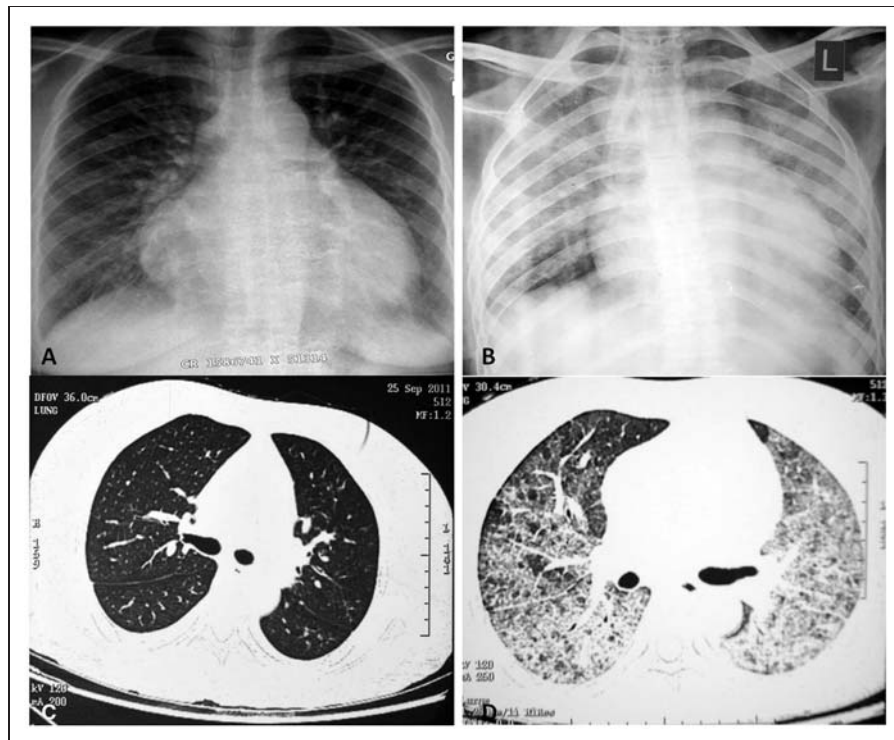


Figure 1 Before rituximab therapy, chest radiograph (A) and CT (C) showed normal findings. One month after rituximab therapy X-ray (B) and chest CT (D) revealed diffuse interstitial infiltrates in bilateral lung fields. 211x172mm (150 × 150 DPI).

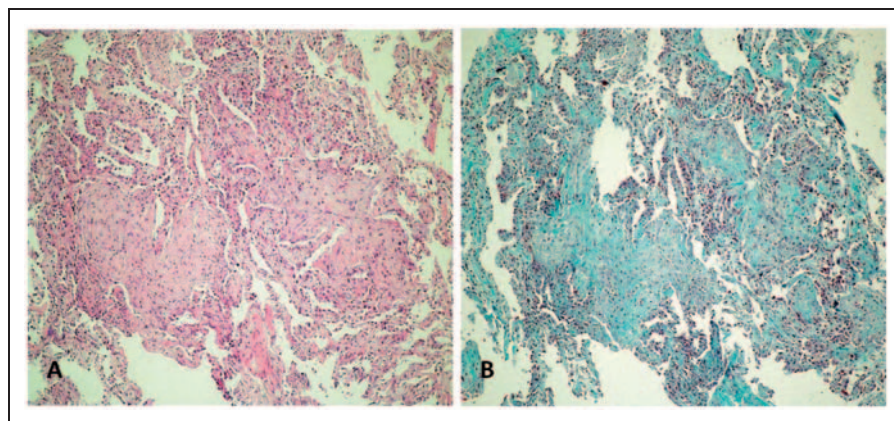


Figure 2 Transbronchial lung biopsy shows pulmonary interstitial fibrosis on H&E (A) and masson trichrome staining (B). 210x92mm (150 x 150 DPI).

of 3.8 g/day with normal renal function. Kidney biopsy revealed class-IV lupus nephritis and she was treated with mycophenolate mofetil (MMF) and steroids. She achieved remission with this treatment at 6 months and was maintained on MMF and low dose steroids. Two years later, she developed

gastrointestinal intolerance requiring stoppage of MMF. One year after stopping MMF, she presented with fever and pedal oedema. Investigations revealed nephrotic range proteinuria, a serum creatinine of 3 mg/dl, pericardial effusion and an increase in dsDNA titres. A repeat kidney biopsy

was performed which showed lupus nephritis class-IV (G-A/C) along with thrombotic microangiopathy (TMA). She was treated with three weekly doses of rituximab, 375 mg/m² each (1.5 g total) and 5 sessions of plasmapheresis. However, she had progressive deterioration in renal function requiring haemodialysis. One month after the last rituximab dose, she presented with cough and breathlessness; on examination she had tachypnoea, and respiratory distress with normal chest findings. Investigation revealed haemoglobin of 7.8 g/dl, normal leukocyte and platelet count, normal complement levels, negative dsDNA and type 1 respiratory failure on arterial gas analysis. A chest radiograph and contrast-enhanced computed tomography showed diffuse interstitial infiltrates in both lung fields (Figure 1). Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) was carried out. BAL fluid cultures as well as blood cultures were negative for bacteria, fungi and mycobacteria and staining for *Pneumocystis jiroveci* was negative. Polymerase chain reaction was negative for cytomegalovirus. The TBLB was suggestive of interstitial fibrosis (Figure 2). Meanwhile, she received empirical antibiotics as well as amphotericin with no response. A possibility of RTX-ILD was therefore considered and she was given three pulses of intravenous methyl prednisolone and the oral steroid dose was increased to 1 mg/kg. Within the next 48 hours, she showed marked clinical improvement and her oxygen saturation as well as her general condition gradually improved to normal, however, there was no radiological improvement on repeat chest radiograph and computed tomography. At one month, she was doing fine with no respiratory difficulties.

Discussion

Respiratory symptoms can be seen in up to 38% of patients on rituximab and include rhinitis, sinusitis, cough, bronchospasm and dyspnoea. Respiratory tract infections can be seen in about 10% of patients receiving rituximab.¹ Hadjinicolaou et al. have reviewed all non-infectious pulmonary complications of rituximab.³ Most of these patients were receiving rituximab for a haematological malignancy. Despite the increasing use of rituximab in SLE, RTX-ILD has so far been reported in only three patients with SLE including one with lupus nephritis.²⁻⁴ Two of these cases had interstitial pneumonitis, while one developed pneumonia with no definitive

organism. Amongst all pulmonary complications, interstitial pneumonitis with interstitial fibrosis seems to be the rarest and has been reported in only one case.³ Based on the Pubmed and EMBASE database searches, this is the first report of a patient with SLE developing interstitial fibrosis following rituximab therapy.

In the review by Hadjinicolaou et al., the average cumulative dose of rituximab before onset of symptoms was 1500 mg/m², while the mean time of onset of symptoms after the last infusion was 30 days (1–158 days). Clinical presentation was mainly with dyspnoea (70.7%), fever (40.2%), and cough (32.6%). Hypoxemia was almost universal. Physical examination of the chest was usually unremarkable in the majority of patients with some showing diffuse fine crackles. The lung pathology was variable and included bronchiolitis, organizing pneumonia, interstitial pneumonia, hypersensitive interstitial pneumonitis, idiopathic pulmonary fibrosis, lymphocytic interstitial pneumonitis and desquamative interstitial pneumonia. Therapy included discontinuation of rituximab and administration of glucocorticoids. Response to glucocorticoids was usually seen within days, but the mortality was about 20%.³

Another unusual feature in our case was the long gap of nine years between the onset of SLE and renal involvement. Usually lupus nephritis occurs within the first few years of the onset of disease and rarely after 5 years.^{5,6} The disease course in our patient was complicated by many relapses requiring multiple therapies in the past and necessitating the use of rituximab for the present relapse.

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Conflict of interest

None declared.

References

- 1 Genentech. Rituxan: highlights of prescribing information (revised), 2008. <http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf> (accessed 2 September 2011).
- 2 Panopoulos ST, Sfikakis PP. Biological treatments and connective tissue disease associated interstitial lung disease. *Curr Opin Pulm Med* 2011; 17: 362–367.
- 3 Hadjinicolaou AV, Nisar MK, Bhagat S, Parfrey H, Chilvers ER, Ostör AJ. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases: a systematic review. *Rheumatology (Oxford)* 2011; 50: 2297–2305.
- 4 Kishi J, Nanki T, Watanabe K, Takamura A, Miyasaka N. A case of rituximab-induced interstitial pneumonitis observed in SLE. *Rheumatology (Oxford)* 2009; 48: 447–448.
- 5 Baldwin DS, Gluck MC, Lowenstein J, Gallo GR. Lupus nephritis. Clinical course as related to morphologic forms and their transition. *Am J Med* 1977; 62: 12–30.
- 6 Nossent JC, Bronsveld W, Swaak AJ. Systemic lupus erythematosus. III. Observations on clinical renal involvement and follow up of renal function: Dutch experience with 110 patients studied prospectively. *Ann Rheum Dis* 1989; 48: 810–816.