

Rituximab-induced lung disease

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SUMMARY

Pulmonary toxicity is a rare complication of Rituximab therapy. Although Rituximab is relatively safe and can be administered in an outpatient setting, Rituximab-associated lung disease has been reported and may cause mortality despite early detection. Typically the pulmonary toxicity occurs at around the fourth cycle of Rituximab. High index of suspicion is crucial and other concurrent pathology such as infective causes should be excluded. Radiological imaging and histological confirmation should be obtained and early treatment with corticosteroid should be initiated. Patients should receive counselling regarding respiratory symptoms and possible pulmonary toxicity.

KEY WORDS:

Rituximab-induced lung disease, acute respiratory distress syndrome

INTRODUCTION

Rituximab is a chimeric anti-CD20 monoclonal antibody. It is the standard of care for CD20-positive Non-Hodgkin lymphoma as it has been proven to provide superior response and disease-free survival.¹ Rituximab is a relatively safe drug although precautions are needed during its administration. Common side effects are infusion-related reactions and infections. Rarely, pulmonary toxicity has been reported. Recent systematic review suggests Rituximab-induced lung disease could be further divided into hyperacute early, acute and subacute or chronic onset based on its temporal correlation with last Rituximab infusion.² Here we report a case of subacute Rituximab-induced lung disease with unfavourable outcome.

CASE REPORT

A 49-year-old gentleman was diagnosed with stage IVB plasmablastic lymphoma. He presented with jaundice, night sweats and bilateral cervical swelling for three weeks. Further examination and investigations revealed bilateral cervical lymphadenopathy, autoimmune haemolytic anaemia with left internal jugular and brachial vein thrombosis. The International Prognostic Index (IPI) score was two. The baseline staging CT scan revealed no significant abnormalities in the thorax (Figure 2A). He received two cycles of R-HyperCVAD (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Dexamethasone) and two cycles of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone) with intrathecal

chemoprophylaxis during every cycle (Methotrexate, Cytarabine, Hydrocortisone). Apart from one episode of neutropenic sepsis during the first cycle, he tolerated the chemotherapy well with good clinical response. Past medical history included hypertension and occult Hepatitis B infection on antiviral treatment. One week prior to the fourth cycle chemotherapy he developed type 1 respiratory failure and pulmonary embolism was excluded. He recovered well with antibiotics and received the fourth cycle R-CHOP with no immediate complications.

On day seven post fourth cycle R-CHOP, he developed neutropenic sepsis with neutropenia $0.7 \times 10^9/L$. He received meropenem and granulocyte colony stimulating factor (G-CSF) injection. Despite neutrophil recovery, he was still febrile. At this time he was on a slow tapering dose of prednisolone 30 mg daily for the AIHA. Microbiologic investigations were negative for bacterial infections. He was then started on empirical Amphotericin B. On day 14, he complained of difficulty in breathing especially on talking and exertion. There was no orthopnoea, paroxysmal nocturnal dyspnoea or pedal oedema. On examination, he was not septic looking. The respiratory rate was 30 breaths per minute and he was only able to speak in short sentences. The oxygen saturation was 78% on room air. His respiratory examination revealed normal vesicular sounds with mild reduction of breath sounds at bilateral lower zones. The rest of the physical examination was normal. Chest radiograph showed bilateral opacities (Figure 1). High resolution CT thorax showed a combination of bilateral crazy paving pattern and peribronchial thickening (Figure 2B). There were no lung nodules, consolidation or effusion. Due to raised inflammatory markers; C-reactive protein 33.75mg/dL (NR <0.5) and procalcitonin 2.44ng/ml (NR <0.05) with a backdrop of immunosuppressive state, empirical co-trimoxazole was started. Initial sputum cultures were negative. Serum aspergillus antigen and candida antigen were negative. Initial bronchoalveolar lavage (BAL) for infective causes particularly *Pneumocystis jiroveci* and tuberculosis was negative, and BAL cultures for bacteria and fungus were also negative. Therefore the most likely cause for the acute respiratory distress syndrome (ARDS) was Rituximab-induced lung disease. A transbronchial lung biopsy was deferred due to coagulopathy. His condition deteriorated with moderately severe hypoxaemia (P_{aO_2}/F_{iO_2} of 110 mmHg) despite non-invasive ventilation support and high dose methylprednisolone 250mg daily. He required mechanical ventilation and later succumbed in the intensive care unit.

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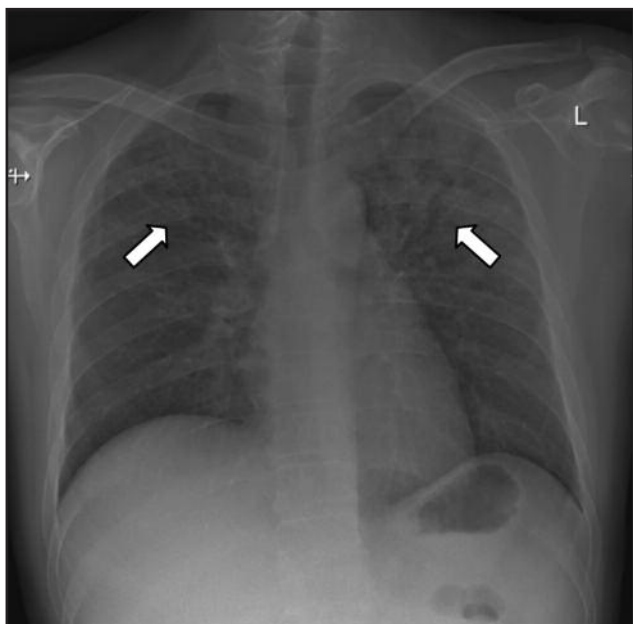


Fig. 1: Plain chest radiograph on Day 14 post fourth Rituximab infusion which showed bilateral pulmonary interstitial infiltrates, more prominent at the upper zones.

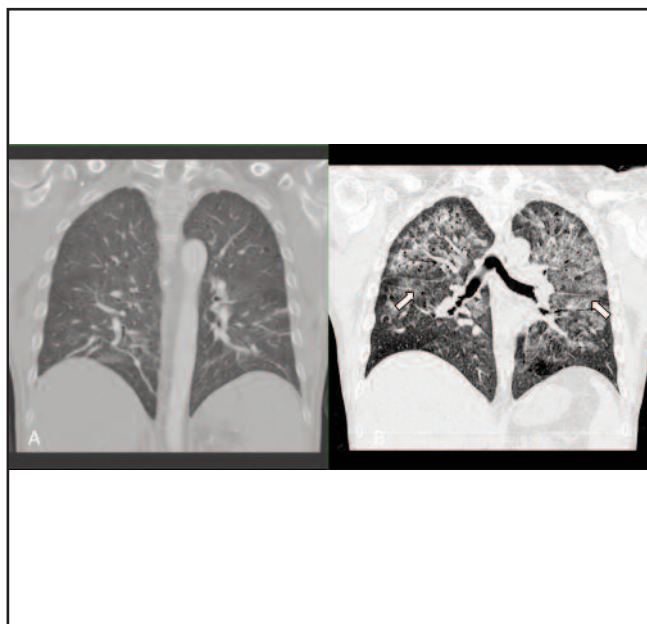


Fig. 2: (A) Coronal section of CT thorax pre Rituximab therapy which was normal. (B) CT thorax on Day 14 post fourth Rituximab infusion with ground glass opacity and crazy paving appearance which gave rise to suspicion of *Pneumocystis jiroveci* pneumonia and possibility of Rituximab-induced pneumonitis.

DISCUSSION

Rituximab was approved for treatment of CD20-positive Non-Hodgkin lymphoma. It is relatively safe and can be given in the outpatient setting. Severe pulmonary reaction was not known during clinical trials. Post marketing surveillance detected anaphylactic shock and acute respiratory distress syndrome, fatal in 0.04-0.07%.² Also, there are increasing reports of Rituximab-induced lung disease with prevalence of 0.01-0.03%.³ Despite early detection, it can be associated with poor prognosis and mortality.³

Based on systematic review, the temporal correlation of Rituximab-induced lung injury can be subdivided to hyperacute early (within day 1), acute and subacute (7-21 days) and chronic (>28 days) from the last administration of Rituximab.² Our patient fits into the subacute onset group, which is known to be the commonest form, usually occurring around the fourth cycle of Rituximab. The underlying process probably reflects hypersensitivity reaction to the immunogenic chimeric anti-CD20 antibody.² Common radiological findings in Rituximab-induced lung injury are diffuse pulmonary infiltrates, ground glass opacification, pulmonary fibrosis, alveolar haemorrhage and consolidative changes. Histologically, the predominant pattern was organising pneumonia, or nonspecific interstitial pneumonia, or usual interstitial pneumonia.²

Despite high suspicion of Rituximab-induced lung disease, empirical Amphotericin B and co-trimoxazole was initiated due to the underlying immunosuppressive state and exertional desaturation. Literature reviews recommend early treatment with steroids, although mortality may still occur.³ Our case illustrated that despite early treatment with corticosteroids, Rituximab-induced lung disease still proved to be fatal. Patients should receive counselling regarding possible pulmonary toxicity, and respiratory symptoms should be routinely sought after each Rituximab administration. Radiological imaging and histological confirmation is warranted to exclude other causes of ARDS.

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REFERENCES

1. SAW Fadilah. Fundamentals of the management of Non-Hodgkin Lymphoma. *Med J Malaysia* 2009; 64 (4): 333-40.
2. Liote H, Liote F, Seroussi B, Mayaud C, Cadranet J. Rituximab-induced lung disease: A systematic literature review. *Eur Respir J* 2010; 35: 681-7.
3. Hadjinicolaou AV, Nisar MK, Parfrey H, Chilvers ER, Ostor AJK. Non-infectious pulmonary toxicity of rituximab: a systematic review. *Rheumatology* 2012; 51: 653-62.