The first case report of fatal acute pulmonary dysfunction in a systemic sclerosis patient treated with rituximab

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Systemic sclerosis (SSc) is a multisystem disorder that affects numerous organs. SSc-associated interstitial lung disease (SSc-ILD) is one of the main causes of death in SSc patients. Scleroderma renal crisis (SRC) is also well known as a life-threatening complication (1). Although rare, severe acute lung disease including diffuse alveolar haemorrhage (DAH) may develop as a complication of SRC; this is known as pulmonary renal syndrome (PRS) and has a poor prognosis (2). Here we report the case of an SSc patient with SRC who developed fatal respiratory dysfunction after rituximab (RTX) treatment. Lung complications were considered to be PRS and/or acute interstitial pneumonia (AIP). This is the first case report of a serious adverse event of RTX used against SSc-ILD.

A 70-year-old woman who was suffering from diffuse cutaneous SSc with positive anti-topoisomerase I antibodies had a history of treatment with immunosuppressants (Figure 1). When she was 69 years old she complained of elevated blood pressure. Laboratory examination showed red cell fragmentation, renal failure, a low platelet count, decreased haptoglobin, and positive renal tubular dysfunction markers. These data collectively indicated a diagnosis of SRC. On terminating the use of cyclosporin, angiotensin-converting enzyme (ACE) inhibitors improved her condition. As her pulmonary function was on the decline, RTX therapy was started when she was aged 70. One month after the initiation of RTX, she suddenly complained of haemoptysis. Chest computed tomography (CT) revealed bilateral ground glass opacity (supplementary Figures 1A and 2B). Pneumocystis pneumonia was not considered because beta-1-glucan was negative. A lack of increase in anti-neutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane antibodies indicated the absence of new-onset ANCA-associated vasculitis and Goodpasture’s disease. As lupus anticoagulant and anticardiolipin antibodies were not detected, catastrophic antiphospholipid syndrome was ruled out. CD20-positive cells were almost totally depleted, which was by confirmed by flow cytometric analysis (supplementary Figure 2). We began pulse methylprednisolone along with broad-spectrum antibiotics. Despite these efforts, the patient died of respiratory failure 20 h after her complaint of haemoptysis. Postmortem chest CT revealed diffuse bilateral infiltrations (supplementary Figure 1C). Hyaline membrane disease, which supported the existence of diffuse alveolar damage (DAD), was pathologically found in the bilateral lobe of the lung (supplementary Figure 1D). DAH was also detected but was not with capillaritis (supplementary Figure 1E). There was also no clear sign of infection in the lungs. Thrombotic microangiopathy (TMA) was found in the kidneys (supplementary Figure 1F). Afferent arterioles were clotted with platelet thrombus but there was no glomerulonephritis.

Our patient underwent a fulminant clinical course with hourly deteriorating respiratory function. The combination of dyspnoea, haemoptysis, and diffuse bilateral alveolar infiltrates shown on a chest X-ray were suggestive of AIP and/or DAH. Together with her renal failure, we presumed her condition to be PRS. Although the definition of PRS is not firmly established, DAH and concomitant TMA in the kidney are compatible with a diagnosis of PRS (3). Of the three entities into which PRS is categorized (4), our case was classified as PRS with TMA. Considering the existence of hyaline membrane disease, that is pathological findings of DAD, AIP also occurred. As the patient was under strong immunosuppressive therapy, we suspected that some viral or undetectable infection caused AIP (5). It is also possible that the RTX itself induced AIP (6).

A previous study indicated that there are no severe adverse effects of RTX therapy for SSc patients (7). However, our case indicates that RTX should be administered carefully. As SSc patients with severe ILD have lowered lung spare capacity, even non-severe pulmonary damage could be fatal. Past studies have excluded patients with low lung function. A review of the literature revealed that > 60% of vital capacity (%VC) and > 40% of diffusing capacity of the lung for carbon monoxide (%DLCO) can be regarded as standard (7). In our case, %VC and %DLCO were 64.5% and 30.0%, respectively. Overall, the criteria for the choice of SSc-ILD patients for RTX therapy might need to be more stringent.

RTX depletes B cells including regulatory B (Breg) cells, which are specific subsets that have the ability to produce immunosuppressive cytokines (8). Although remediual efficacy of RTX usually begins after several months (9), CD20-positive cells disappear within 2 weeks, which we have
confirmed in all of six patients tested (data not shown). Depletion of Breg cells might have caused autoimmunity leading to PRS and/or AIP in our case. A new drug that can deplete only pathogenic B cells is therefore required.

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Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary figure 1: The course of chest CT findings.
Supplementary figure 2: Flow cytometric analysis of the patient’s leukocytes.

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