CASE REPORT

A mild form of rituximab-associated lung injury in two adolescents treated for nephrotic syndrome

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SUMMARY

Rituximab is used as a steroid/calcineurin inhibitor-saving agent in patients with nephrotic syndrome. Safety is a crucial issue for justifying widespread use of the drug in this clinical setting. Rituximab-associated lung injury (RALI) is a severe and potentially life-threatening complication in oncohaematological and rheumatological patients, while it has only been anecdotally reported in association with idiopathic nephrotic syndrome (2 cases described, 1 with fatal outcome). We describe a benign form of RALI occurring in two adolescents treated with rituximab (single pulse of 375 mg/m²) for nephrotic syndrome. Before treatment, the patients were in good clinical condition while receiving a combination of steroids and calcineurin inhibitors (tacrolimus, case 1 and cyclosporine, case 2). The two patients developed full blown RALI (ie, ground-glass lesions on CT, negative bronchoscopy with bronchoalveolar lavage and deficit in diffusion lung CO transfer), 14 and 40 days after rituximab infusion, respectively. Recovery was rapid and complete after administering steroids in case 1 and with no therapy in case 2. We conclude that RALI may occur in stable non-immunocompromised patients with nephrotic syndrome and its frequency may be higher than expected. Clinical presentation may be mild and resolve after steroids, suggesting hypersensitivity as the main mechanism. Rapid recognition and prompt steroid therapy, if needed, are mandatory for resolution.

BACKGROUND

The chimeric anti-CD20 monoclonal antibody, rituximab (IgG1/κ human/murine), has been historically used to treat oncohaematological conditions such as non-Hodgkin's lymphoma, lymphocytic leukaemia, large B-cell non-Hodgkin's lymphoma and autoimmune diseases (thrombotic thrombocytopenic purpura, rheumatoid arthritis, etc).^{1–2} It binds to CD20 expressed by B cells and causes cell lysis via activation of the complement cascade and natural killer cells.³ Thus, rituximab infusion results in significant depletion of peripheral blood B lymphocytes that last 6–9 months after treatment. More recently, rituximab has been introduced in the therapeutic approach to nephrotic syndrome and, based on clinical trials, its use was limited to patients having proven sensitivity to steroids and cyclosporine.^{4–6} Resistance to both drugs is now considered a contraindication to rituximab use.⁷ Safety is a crucial point prior to considering more widespread use. Although this drug is generally well tolerated and has an acceptable toxicity profile, mild and severe complications have both been reported. Rituximab-associated lung injury (RALI) is included in the second group of

conditions since it is considered potentially life-threatening.⁸ This is a clinically and histologically polymorphic entity that may present as cryptogenic organising pneumonia (previously known as bronchiolitis obliterans organising pneumonia) and/or as interstitial and hypersensitivity pneumonia with or without fibrosis. Alveolar haemorrhage and acute respiratory distress can result in fatal outcomes. It is a diagnosis of exclusion based on clinical presentation and radiological CT features, and on exclusion of other possible causes, the first being of a primarily infective aetiology (bronchoscopy with bronchoalveolar lavage is required to rule out an infection). RALI has been described mainly in an oncohaematological and/or rheumatological context, while it is very rare in patients with renal disease.^{8–10} It has been reported in three cases with renal transplant, one received rituximab for post-transplant lymphoproliferative disease, whereas the other two patients were treated for post-transplant recurrence of focal segmental glomerulosclerosis.^{11–13} Only two patients treated with rituximab for primary nephrotic syndrome have been reported (table 1). One had a fatal outcome, the other recovered with immunoglobulin infusion.^{14–15}

We describe here the third and the fourth cases of RALI, occurring in two adolescents, in very good clinical condition, with nephrotic syndrome, who presented with full blown RALI after rituximab infusion; both patients had complete recovery, one with a simple steroid course (case 1), and the other with no therapy (case 2), suggesting variability in clinical presentation of an otherwise potentially life-threatening illness. The time course of rituximab sequelae and rapid response to therapy prompts some considerations on possible mechanisms.

CASES PRESENTATION**Case 1**

A 12-year-old girl presented with clinical onset of nephrotic syndrome because of steroid resistance; cyclosporine (4 mg/kg q12 h, orally) first and then tacrolimus (0.1 mg/kg q12 h, orally) were added to therapy and a renal biopsy was performed, showing a pattern compatible with focal segmental glomerulosclerosis. The association of steroids and tacrolimus-induced stable remission of proteinuria reappeared, however, when the steroids were tentatively suspended. For this reason, starting from 2 years after the clinical onset, three rituximab doses were given at intervals of 12 months (1 dose/year). No problems occurred after the first two rituximab infusions, with the exception of a mild cough, which resolved with an additional dose of antihistamine.

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Table 1 Clinical, radiological and histological features of nephrotic patients with RALI

	Chaumais <i>et al</i> ¹⁵	Bitzan <i>et al</i> ¹⁴	Case 1	Case 2
Diagnosis	MRNS	FSGS	FSGS	INS
Sex	F	M	F	M
Age at RALI (years)	9	14	16	15
Therapy for RALI	CsA	CsA, MMF	Tac	CsA
Years therapy	None	>12	4	3
RTX pulse	1	6	3	4
RTX doses (mg/m ²)	375	375	375	375
Presenting symptoms	Respiratory distress, hypoxia	Fever, cough, tachypnoea, hypoxia	Fatigue, weakness, palpitations, hypotension, fever	Fatigue, weakness, dyspnoea
Time from last RTX, days	3	19	14	40
CT lung findings	Bilateral opacities, pleural effusion	Bilateral 'ground glass'	Bilateral 'ground glass'	Bilateral 'ground glass'
Treatment	Antibiotics, ECMO, Ig anti-RSV	IVIg	Antibiotics, steroids	None
Histological findings	Extensive fibrosis	Not performed	Not performed	Not performed
Outcome	Dead	Fully recovered	Fully recovered	Fully recovered
Comments	Death caused by RSV infection and pulmonary haemorrhage	None	None	None

CsA, cyclosporine A; ECMO, extracorporeal membrane oxygenations; F, female; FSGS, focal segmental glomerulosclerosis; INS, idiopathic nephrotic syndrome; IVIG, intravenous immunoglobulins; M, male; MMF, mycophenolate mofetil; MRNS, multidrug resistant nephrotic syndrome; RALI, rituximab-associated lung injury; RSV, respiratory syncytial virus; RTX, rituximab; Tac, tacrolimus.

Two weeks later, after the third pulse (375 mg/m²), the patient began to report fatigue, weakness, palpitations, hypotension and fever; chest X-ray showed bilateral basal thickening, later confirmed as 'ground glass' pattern by CT scan. In the meantime, the girl developed oxygen-dependent respiratory failure. Bronchoscopy with bronchoalveolar lavage was negative for culture tests, including fungi; only a positive PCR for Epstein-Barr virus DNA was reported. Spirometry showed a mild-to-moderate restrictive syndrome with a severe deficit in diffusion lung CO transfer. Lung biopsy was not performed due to rapid clinical improvement.

Case 2

A 12-year-old boy presented with clinical onset of nephrotic syndrome because of steroid dependence; cyclosporine (4 mg/kg q12 h, orally) was added to therapy. Owing to frequent relapses and following the inability to wean from steroids in spite of the addition of cyclosporine, the boy was treated, with an initial rituximab dose (375 mg/m²) 2 years after the clinical onset of nephrotic syndrome. No problems occurred during infusion of rituximab with the exception of an itchy cough, which resolved after an additional dose of antihistamine. Following rituximab, cyclosporine and prednisone were discontinued and stable remission was maintained for 9 months. At that time, the nephrotic syndrome recurred and the boy received a second rituximab dose (375 mg/m²). Two weeks later, he began to report fatigue, weakness and dyspnoea during mild physical exercise; he was admitted to our department for suspicious of RALI, and a CT scan was performed, showing a 'ground glass' pattern. Bronchoscopy with bronchoalveolar lavage was negative for culture tests, including fungi. Spirometry showed a moderate restrictive syndrome with a deficit in diffusion lung CO transfer. Lung biopsy was not performed due to rapid clinical improvement.

TREATMENT

Case 1

At admission, due to suspicion of an atypical pulmonary pathogen infection in an immunocompromised patient, tacrolimus was temporarily suspended; after 2 days, in view of a probable

diagnosis of RALI, oral prednisolone 50 mg/day was started and maintained for three successive days, and then reduced to 25 mg/day. Further, empirical antibiotic therapy with piperacillin/tazobactam, cotrimoxazole and levofloxacin was added and O₂ therapy (5 L/min) was started due to acute respiratory failure. No additional drugs with known pulmonary toxicity had been administered. Owing to recurrence of proteinuria, tacrolimus was restarted. At discharge, the patient was maintained on low-dose steroids (25 mg/die), which were gradually tapered until suspension, and tacrolimus (3 mg/12 h) was started.

Case 2

No therapy was administered due to a strong suspicion that this was a mild episode of RALI. In the absence of any sign of acute respiratory failure, the patient was maintained under careful clinical observation both before and during hospitalisation.

OUTCOME AND FOLLOW-UP

Case 1

The patient presented a good clinical response with rapid resolution of respiratory failure and improvement of radiological findings. After 12 days of hospitalisation, the patient was discharged; she is now in good health, with complete CT resolution.

Case 2

This patient presented spontaneous resolution of clinical symptoms and improvement of spirometry values within 7 days from the onset of pulmonary symptoms. A radiological control was not performed due to satisfying improvement. After 9 days of hospitalisation, the patient was discharged; he is now in good health without the need of medication.

DISCUSSION

RALI is a very rare complication of rituximab therapy and almost exclusively reported in elderly patients with oncohaematological malignancies or degenerative conditions. Overall, it has been reported in 211 patients who received rituximab for cancer, lymphoma and/or other rheumatological diseases.^{8–10} In these settings, RALI is considered a serious, life-threatening

condition that may evolve to death in 10–20% of cases. The occurrence of RALI in children and the association with primary renal disease such as nephrotic syndrome is only anecdotal, probably because the use of rituximab for nephrotic syndrome has only recently been introduced in clinical practice and few patients have been treated so far.^{16 17} We report two new cases of RALI associated with nephrotic syndrome occurring in two adolescents who were receiving an association of steroids and calcineurin inhibitors (tacrolimus in the first patient, cyclosporine in the second). At variance with most of the cases of RALI found in the literature, which occurred in compromised patients, and also different from the first case of RALI described in a nephrotic little boy, the two patients described in this report were in very good condition at the time of infusion. Moreover, in spite of important pulmonary clinical symptoms at presentation, both had a rapid clinical and functional recovery with minimal (ie, steroids in the first case) or no therapy (as in the second patient). For all these reasons, our cases appear to have been a mild form of RALI that merits being considered a separate clinical entity. On the basis of the clinical outcome of these two patients, we believe that 'Mild RALI' requires minimal therapeutic intervention and that patients will attain complete recovery in about 10 days from the onset of respiratory symptoms. Modalities of onset and response to drugs also support different mechanisms of toxicity, and therapies should be evaluated on this basis. In fact, and according to current knowledge, mechanisms for pulmonary toxicity of rituximab may be different in relation to the rapidity of onset: (1) a very early onset (ie, a few hours from rituximab infusion) suggests cytokine release and/or tumour lysis syndrome, which clearly did not occur here; (2) an acute/subacute presentation of organising pneumonia, in general occurring 2 weeks from infusion, suggests hypersensitivity; (3) finally, the development of a late-onset pneumonia (several months after rituximab) is considered to be related to direct toxicity of the drug. On the basis of the history of our patients, their good clinical status at the time of rituximab infusion, the timing of onset of pulmonary lesions and the rapid response to steroids (in the first case), we believe that hypersensitivity is the most likely mechanism here. A second consideration is positivity for Epstein-Barr virus PCR in bronchoalveolar lavage of the first patient. This in some way contradicts the biology of Epstein-Barr virus, which is usually hosted in B cells, since CD20 cells at the time of bronchoscopy were undetectable in the blood. A possible explanation is that Epstein-Barr virus was hosted by other cells in this case or that B cells targeted by the virus are more resistant to rituximab.

What we can also learn from these two cases is that the occurrence of RALI is casual and cannot be predicted since our patients had been treated with rituximab one and two times, respectively, prior to the last dose, and had not presented any sequelae. Also, the state of immunodepression had minimal influence, since these patients were in double therapy with steroids and tacrolimus or cyclosporine, that is, minimal for patients with nephrotic syndrome. Finally, some aspects of Epstein-Barr virus may be related with those of pulmonary lesions. In respect to the outcome, 'Mild RALI' may improve spontaneously and steroids are, anyway, very effective in a few days.

In conclusion, RALI must be considered a potential complication of rituximab in patients with nephrotic syndrome. In adolescents, RALI may have minimal clinical impact, and spontaneous resolution cannot be excluded. Clinical conditions during therapy and timing of immunodepression seem unrelated and do not furnish any predictive element. A prompt diagnosis followed by steroids is crucial for a good outcome.

Patients' perspective

- Case 1: In the first days of May, I started feeling sick. I noticed that I was very tired all day long and I needed to sleep more than usual, but I thought I was just stressed. But when, during the following days, I started feeling worse and panted after a few steps, I understood that something was wrong. I told my parents, but at first they suggested I not worry about it because it was only a bit of stress. But when I couldn't stand up without panting, they brought me to the hospital. After a week of treatment in the hospital, I could walk without oxygen, and the week after I was home. I was completely healed. I really, really wanted to return home to my normal life, and I think this is one of the reasons I was healed in such a few days.
- Case 2: I started feeling bad over the weekend. I felt very tired doing simple things, like taking a little walk or a few steps. I thought it was nothing important and I just decided to rest a little bit. Days later I started feeling worse and realised that something was going wrong. After a more serious episode of 'dyspnoea' (so it's called), I told my mom, who immediately called the doctors who tend to nephrotic syndrome cases. They decided to admit me to their department. After some days, I started to feel better, and in 10 days I had completely recovered.

Learning points

- Rituximab-associated lung injury (RALI) is a potential, albeit rare, side effect of this therapy in patients treated for nephrotic syndrome.
- It may occur in patients already treated with rituximab and cannot be predicted on the basis of any clinical consideration. In particular, there is no correlation with other medications or with overall clinical conditions.
- Diagnosis is based on the presence of a 'ground glass' pattern at CT scan and on negative bronchoalveolar lavage tests.
- The two cases described here had very rapid improvement and pulmonary lesions resolved after 1 week leaving no residue. This can be defined as a 'mild' form of RALI.
- The clinical course suggests a mechanism linked to hypersensitivity.

Contributors GMG was involved in manuscript concept and writing. TB was responsible for manuscript concept and writing. MS and CG were involved in manuscript review.

Competing interests None declared.

Patient consent Obtained.

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