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BRIEF REPORT

Fatal pulmonary fibrosis after rituximab administration

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Abstract Idiopathic nephrotic syndrome is the most frequent glomerular disease during childhood. Although immunosuppressive agents are usually effective, some severe cases remain difficult to treat. We describe a female patient with secondary steroid-resistant nephrotic syndrome who no longer responded to conventional treatment. Owing to cyclosporine toxicity, rituximab was administered. Three days after treatment the patient's clinical condition dramatically worsened and she developed acute respiratory distress. Despite all means used to treat her, she died 5 weeks after rituximab infusion. A pulmonary biopsy showed extensive fibrosis, while the alveolar epithelium was no longer visible.

Keywords Nephrotic syndrome · Prednisone · Cyclosporine · Children · Virus

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Introduction

Idiopathic nephrotic syndrome is the most frequent glomerular disease in childhood. Most patients respond to steroid treatment, but in a small number, the condition is initially or secondarily resistant to steroid therapy. Although many immunosuppressive agents have proved to be effective [1], some severe cases remain difficult to treat. Recently, the efficacy of rituximab was reported in a few patients with nephrotic syndrome [2–5]. Here, we describe a patient with secondary steroid-resistant nephrotic syndrome and cyclosporin toxicity who was given rituximab and died from severe pulmonary fibrosis.

Case report

A 9-year-old girl weighing 25.6 kg was admitted for nephrotic syndrome with edema. Her serum albumin level was 12.6 g/l and she had 45 g/l of proteinuria. Remission was obtained after 10 days of prednisone treatment at a daily dose of 50 mg. A first relapse occurred 5 days later under the same prednisone dose. Steroid treatment was increased to 60 mg daily, and a stable remission (serum albumin 33 g/l, proteinuria 0.11 g/l) was observed after 13 days. The treatment remained unchanged for 4 weeks and the dosage was then reduced to 60 mg every other day. A second relapse occurred 4 weeks later and was treated with prednisone at a daily dosage of 60 mg. No remission was obtained after 4 weeks of therapy (serum albumin 4.1 g/l, proteinuria 68 g/l), and the patient was considered to have secondary steroid-resistant disease. Cyclosporin (Neoral®) was initiated orally (100 mg/day then 150 mg/day). Despite low cyclosporin plasma concen-

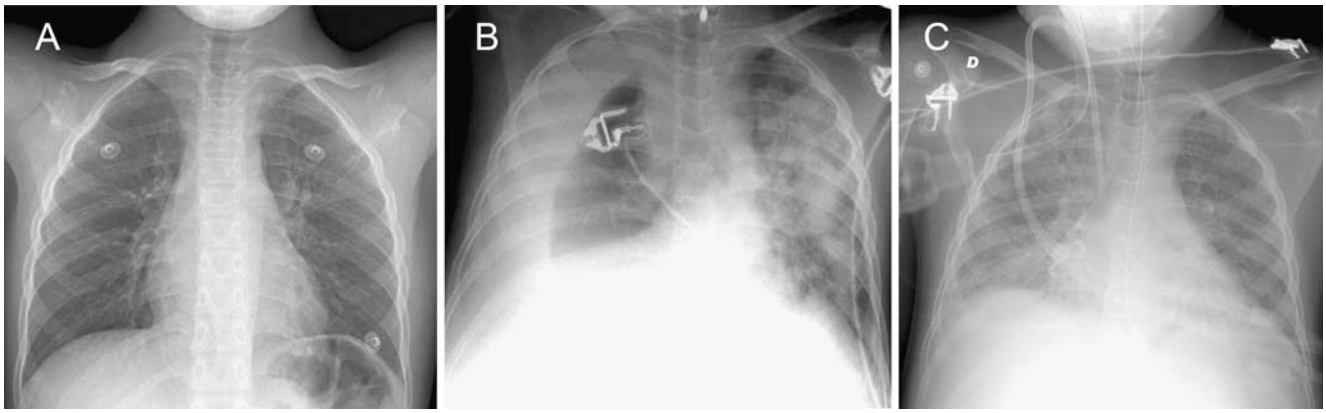

Fig. 1 **a** Normal chest radiograph at the onset of nephrotic syndrome. **b** Chest radiograph taken 4 days following rituximab administration, showing alveolar syndrome in the left lung and pleural effusion in the right one. **c** Chest radiograph taken 1 month following rituximab administration, showing bilateral interstitial syndrome

trations (71 µg/l), renal failure led to the withdrawal of cyclosporin. At that time, the patient experienced hypovolemia, which was treated with two infusions of human albumin. The patient developed hyponatremia, intractable edema with ascites and pleural effusions, despite a low sodium diet, water restriction and diuretic therapy. She also had paradoxical increases in blood pressure that required the administration of two antihypertensive drugs. Twice, she complained of thoracic pain associated with tachycardia and transient hypoxemia. A chest radiograph showed segmental atelectasia in the left lower lung. The diagnosis of pulmonary thromboembolism was discarded, because she was being treated efficiently with warfarin according to the international normalized ratio (INR: 3.28 to 5.65), and D-dimers remained in the normal range (0.5 mg/l).

Because the nephrotic syndrome remained very symptomatic and renal function improved following Neoral® withdrawal, cyclosporin (Sandimmun®, 35 mg/day) was started intravenously, associated with three intravenous bolus treatments with methylprednisolone (500 mg/1.73 m^2). However, this strategy was unsuccessful, as it did not improve the clinical and biological signs of the nephrotic syndrome (serum albumin 6.8 g/l, proteinuria 22.6 g/l). Consequently, it was decided to use the monoclonal anti-CD20 antibody rituximab, which was administered as an intravenous infusion of 375 mg/m^2 body surface area. The first administration was well tolerated, with no side effects. Three days later, she developed uncontrolled epistaxis due to warfarin overdosage and simultaneously developed acute respiratory distress (polypnea 41/min, saturation 91%). The patient was referred to the pediatric intensive care unit. Her clinical condition worsened dramatically, and she required mechanical ventilation, despite pleural puncture. Initial chest radiography showed pulmonary alveolar syndrome in her left lung in addition to contralateral pleural effusion (Fig. 1). She was apyretic, and three controls of tracheal secretion did not evidence any infectious agents, including syncytial respiratory virus. Empiric antibiotics therapy (aminopenicillin, vancomycin and quinolones) was initiated, as well as continuous hemofiltration, as she became anuric. Despite these treatments, the acute respiratory distress syndrome worsened, while the chest radiograph showed bilateral interstitial lesions (Fig. 1). A bronchopulmonary lavage found syncytial respiratory virus, which was treated with palivizumab (15 mg/kg) and ribavirin aerosols. Neither inhaled nitric oxide or almitrine treatment, nor the prone position, were effective. Extracorporeal membrane oxygenation was undertaken. A pulmonary biopsy showed extensive fibrosis, while the alveolar epithelium was no longer visible (Fig. 2). A search for BK virus using polymerase chain reaction (PCR) in the bronchoalveolar lavage and the pulmonary tissue was negative. Despite all the means used to maintain the patient's status, she died 2 weeks after the start of extracorporeal membrane oxygenation.

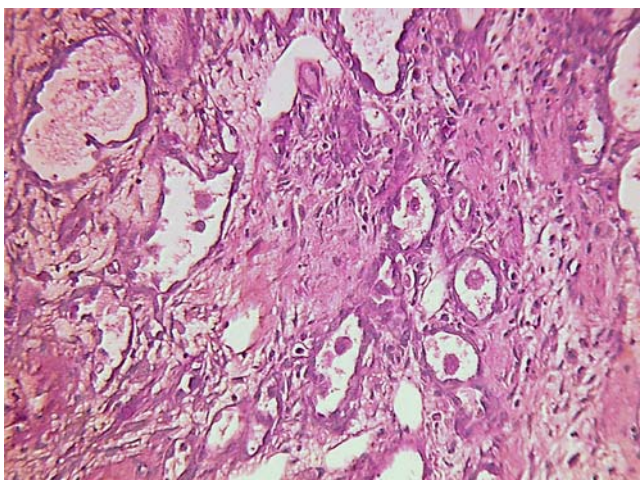

Fig. 2 Diffuse thickening of interalveolar walls due to fibrosis, edema and mononuclear cell infiltration associated with intra-alveolar pneumocytes hyperplasia (periodic acid–Schiff, × 400)

Discussion

We report here a major adverse effect associated with rituximab in a child with secondary steroid-resistant nephrotic syndrome. After the first infusion of rituximab, this child rapidly developed acute respiratory insufficiency with hypoxemia and died from diffuse pulmonary fibrosis.

Rituximab is a chimeric anti-CD20 monoclonal antibody approved as a therapy for B-cell malignancies. Although the use of this drug is quite recent, a few reports have shown that it has been effective in patients with steroid-resistant nephrotic syndrome [2, 4, 6].

In our patient an acute and severe respiratory distress syndrome occurred, and different diagnoses were discussed. Severe pulmonary infection may occur in immunocompromised patients, especially in those receiving long-lasting immunosuppressant therapy at high doses However, at the initial phase, lack of fever, negative findings for inflammatory parameters, and the search for microbial agents, were not contributive. In addition, there was no improvement when broad-spectrum antibiotics were given. The notion of a BK virus infection that might have led to severe pulmonary infection after rituximab administration was discarded. Nevertheless, the presence of syncytial respiratory virus in the bronchoalveolar lavage might have been determinant in the development of fatal pulmonary fibrosis, although such a complication has never been reported in children, with or without conventional immunosuppressive therapy. In addition, the specific antiviral therapy failed to prevent the fatal course.

Vascular overload may occur in patients with nephrotic syndrome who are developing acute renal failure, and it might have been a worsening factor, but intensive hemofiltration allowed a close control of sodium and water balance. Pulmonary hemorrhage, concomitant with the epistaxis and due to anticoagulant, might also be an explanation of the initial respiratory distress, but this has been rarely reported in the literature.

Pulmonary side effects associated with rituximab used in such indication include bronchospasm, severe hypoxia, and acute respiratory distress syndrome infiltrates during or shortly following drug infusion [7, 8]. Reversible or fatal interstitial pneumonitis, as well as rituximab-induced fatal pulmonary hemorrhage and fatal pulmonary fibrosis, occurring a few weeks after drug administration have been reported in rare cases [9–15]. In our patient there were concomitant risk factors: (1) pulmonary hemorrhage secondary to the association of rituximab and anticoagulant overdosage during the initial phase of acute respiratory distress syndrome; (2) a delayed rituximab toxic effect on the pulmonary parenchyma; (3) the deleterious effects of a bronchopulmonary infection with respiratory syncytial virus exacerbated by the unusual accumulation of immunosuppressive drugs and the nephrotic status, which were responsible for this fatal pulmonary complication.

In conclusion, the chronology and profile of clinical events in our patient support the idea that rituximab may have a major and central role in the fatal toxic complication.

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