Rituximab-induced serum sickness in a 6-year-old boy with steroid-dependent nephrotic syndrome

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Abstract

Rituximab (RTX) is a murine–human chimeric monoclonal antibody against CD20 that has been proven effective for preventing relapse in frequently-relapsing or steroid-dependent nephrotic syndrome (NS). Serum sickness, a type-3 hypersensitivity reaction resulting from injection of foreign proteins, has been reported in patients treated with RTX. Herein, we describe a case of RTX-induced serum sickness (RISS) in a 6-year-old boy with steroid-dependent NS. He presented to the hospital with fever and polyarthralgia at 10 days after his fourth dose of RTX. Although he was started on empiric intravenous antibiotics, there was no evidence of septic arthritis and his symptoms resolved over the course of 4 days. He was diagnosed with RISS based on the chronology of RTX administration and the acute-onset self-limiting course of the polyarthrititis. His serum human anti-chimeric antibody (HACA) level on day 53 exceeded the limit of quantification (5000 ng/mL). The pathogenesis of RISS and the role of HACAs remain unclear. It is important for clinicians to recognize RISS, because further infusions of RTX may cause more severe reactions in patients with a history of RISS.

Keywords Nephrotic syndrome · Rituximab · Rituximab-induced serum sickness · Human anti-chimeric antibody

Introduction

Childhood nephrotic syndrome (NS) is a renal disorder characterized by increased leakage of protein into the urine through the glomerular filter, resulting in the triad of proteinuria, hypoalbuminemia, and generalized edema. It is the most common glomerular disorder in children with an incidence of five cases per 100,000 children per year in Japan [1].

Although most patients respond well to steroid treatment, up to 50% of steroid-sensitive NS patients progress to frequently-relapsing or steroid-dependent NS. Furthermore, 10–20% of NS patients are steroid-resistant. Immunosuppressants such as cyclosporine, cyclophosphamide, tacrolimus, and mizoribine are the standard treatments for frequently-relapsing, steroid-dependent, or steroid-resistant NS. However, in addition to being ineffective in certain

patients, these immunosuppressants can have long-term adverse effects such as chronic nephrotoxicity [1].

Rituximab (RTX) is a murine–human chimeric monoclonal antibody against the B-lymphocyte antigen CD20. It is used for many hematological malignancies and autoimmune diseases, and has also been shown to enable discontinuation or reduction of steroids and other immunosuppressive agents in frequently-relapsing or steroid-dependent NS [2].

Besides the common side effects of RTX like infusion reactions, neutropenia, skin reactions, and infections, RTX-induced serum sickness (RISS) has also been reported. Serum sickness is a type-3 hypersensitivity reaction resulting from injection of foreign proteins and the classic triad is fever, rash, and arthralgia. A systematic review in 2015 described 33 published cases of RISS in autoimmune diseases and hematological malignancies. The most common clinical presentations were fever, arthralgia, and rash, with the classic triad reported in nearly half of the cases. The onset was usually within 14 days from the last RTX dose. Symptoms were self-limited in mild cases and corticosteroids were the most commonly used treatment with prompt and complete resolution [3]. The first case report of RISS in an NS patient was published in 2018 [4].

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Herein, we report a case of RISS in a 6-year old boy with steroid-dependent NS and review the literature on RISS.

Case report

A 6-year-old boy with a history of steroid-dependent NS presented with fever and polyarthralgia at 10 days after his fourth dose of RTX. The patient was diagnosed with steroid-resistant NS at 1 year of age and a renal biopsy at 2 months after diagnosis showed collapsing focal segmental glomerulosclerosis. He achieved remission after 11 months of treatment with cyclosporine and pulse methylprednisolone. Three weekly doses of RTX 375 mg/m² were given after remission, and remission was maintained with oral cyclosporine. He relapsed for the first time at 6 years of age and achieved remission with prednisolone 2.0 mg/kg/day and cyclosporine 3.2 mg/kg/day but became steroid-dependent. A single dose of RTX 375 mg/m² was subsequently given uneventfully.

However, at 10 days after the last RTX dose, he presented to the emergency department with a history of fever and severe arthralgia in the bilateral wrists, hips, knees, and ankles for a few hours. Physical and neurological examinations were unremarkable and no redness or swelling was seen in the joints. No rash was noted.

Routine laboratory tests (Table 1) were notable for leukocytosis of 19,600/μL with 81.2% neutrophils and elevated C-reactive protein of 0.60 mg/dL. Other blood counts, chemistry panels, coagulation tests, and urinalysis were normal. Tests for antinuclear antibodies, rheumatoid factor, and anti-MMP-3 antibodies were negative.

A radiograph of the hips and knees showed no evidence of fractures or femoral head osteonecrosis. An enhanced MRI scan demonstrated synovitis in both hips and inflammation in the surrounding soft tissue (Fig. 1). Arthrocentesis of the right hip yielded clear fluid with 20,100 WBC/μL and no crystals or fungi. Synovial cultures for bacteria and mycobacteria were negative.

The patient was started on empiric intravenous antibiotics (cefepime) and later placed on optimal antibiotics after one of two sets of blood cultures showed positivity for *Streptococcus salivarius* on day 3. The affected blood culture was considered a contamination, because *S. salivarius* is commonly found among normal oral flora and was identified in only one of two specimens obtained. A transthoracic echocardiogram on day 8 showed no evidence of vegetation. He did not show any symptoms associated with connective tissue diseases or viral infections. Fever and arthralgia were controlled with acetaminophen and resolved over the course of 4 days. Cyclosporine was continued at the dose of 3.2 mg/kg/day and prednisolone was tapered in accordance with the

Table 1 Laboratory tests on admission

Urinalysis		Serum chemistry	
Specific gravity	1.015	Total protein	6.7 g/dL
pH	7.0	Albumin	4.2 g/dL
Protein	Negative	Aspartate aminotransferase	21 U/L
Glucose	Negative	Alanine aminotransferase	29 U/L
Ketones	Negative	Lactate dehydrogenase	300 U/L
Occult blood	Negative	Gamma glutamyl transpeptidase	26 U/L
Nitrites	Negative	Alkaline phosphatase	260 U/L
Leukocytes	Negative	Creatine kinase	26 U/L
		Total Bilirubin	0.7 mg/dL
Complete blood count		Blood urea nitrogen	14.4 mg/dL
White blood cell count	19,600/μL	Creatinine	0.29 mg/dL
Neutrophils	81.2%	Sodium	137 mg/dL
Lymphocytes	15.1%	Potassium	4.1 mg/dL
Monocytes	3.4%	Chloride	99 mg/dL
Eosinophils	0.1%	Calcium	8.9 mg/dL
Basophils	0.2%	Inorganic phosphate	3.5 mg/dL
Red blood cell count	467 × 10 ⁴ /μL	C-reactive protein	0.60 mg/dL
Hemoglobin	15.2 g/dL		
Hematocrit	43.2%	Coagulation tests	
Mean corpuscular volume	92.5 fL	PT-INR	0.83
Platelet count	27.3 × 10 ⁴ /μL	APTT	23.7 seconds
		Fibrinogen	350 mg/dL
		D-dimer	0.5 μg/mL

Fig. 1 A gadolinium-enhanced fat-suppressed T1-weighted magnetic resonance image showing joint effusion in the bilateral hips (arrows), thickening and enhancement of the synovium, and enhancement of the surrounding soft tissue

initial treatment plan for NS (1.6 mg/kg/day on days 1–4 and 1.2 mg/kg/day on days 5–18). The patient was discharged on day 10.

After ruling out septic arthritis, the diagnosis of RISS was reached based on the chronology of RTX administration and the acute-onset self-limiting course of the polyarthritis. His serum anti-RTX antibody level on day 53 exceeded the limit of quantification (5000 ng/mL).

Discussion

RTX has been proven effective for preventing relapse in frequently-relapsing or steroid-dependent NS, and was approved for treatment of these syndromes in Japan in 2014. The first case of RISS in NS was reported in 2018 in a 17-year-old girl with steroid-dependent NS, who presented with fever and arthralgia at 10 days after her fifth dose of RTX [4]. To our knowledge, there are two other case reports of RISS in NS patients in Japan. RISS has been reported to mimic sepsis in severe cases [5]. Because patients receiving RTX are often immunocompromised by RTX itself or concurrent immunosuppressive therapies, empiric antibiotics may be necessary until bacterial infections can be ruled out.

The risk of developing RISS has been shown to depend on the underlying disease. In a 2015 review of 33 reported cases of RISS, the majority (84.85%) were associated with autoimmune conditions like immune thrombocytopenic purpura and Sjogren syndrome [3]. In another study involving 37 RISS cases in France, the incidence of RISS was more than 12 times higher in autoimmune conditions ($6.4/10^5$ doses) than in hematological malignancies ($0.5/10^5$ doses) [6]. A hypothesis for the higher incidence of RISS in autoimmune conditions is that B-cell lysis induced by RTX may deliver intracellular antigens into the serum and subsequently induce immune complex formation, especially in

patients with autoimmune conditions, which can also explain cases of RISS in the absence of previous RTX administration [6]. Another possibility is that concurrent chemotherapy for hematological malignancies may suppress humoral immunity and thus be preventive against RISS development [7]. Although there are insufficient data to assess the incidence of RISS in NS patients, it is possible that immunosuppressive agents widely used in NS treatment, such as cyclosporine, may reduce the risk of RISS [6].

In our patient, the serum anti-RTX antibody level exceeded the limit of quantification. Production of anti-RTX antibodies, or human anti-chimeric antibodies (HACAs) against the murine fragments of RTX, has been described in other RISS cases, including NS patients [3, 4]. However, the presence or absence of HACAs has not been consistent with the development of RISS. Among 11 cases of RISS with HACA measurements, only 6 were positive in the 2015 review [3]. Some authors have speculated that excessive amounts of RTX may have consumed all the HACAs in serum, making HACAs undetectable [7]. Furthermore, cases positive for HACAs did not necessarily develop RISS. In a phase I/II trial of RTX in systemic lupus erythematosus, 11 of 17 patients developed detectable HACAs at some time during the study period, but none showed clinical manifestations of RISS [8]. Similarly, 5 of 117 rheumatoid arthritis patients treated with RTX developed HACAs, but showed no clinical manifestations of RISS [9]. In previously reported RISS cases, HACAs were measured at various disease phases using different testing methods, because there are no commercially available assays for HACAs. Detailed data on the chronological changes in HACA levels in RISS patients and a unified method for HACA quantification are necessary to further clarify the role of HACAs in RISS pathogenesis.

Re-administration of RTX in RISS patients has been reported with varying outcomes. Some authors described safe re-administration of RTX without recurrence [3, 10], while others reported more severe reactions including anaphylaxis or recurrence of RISS following re-administration [11, 12]. In the 2019 analysis of 37 cases, there was one recurrence in 7 re-administration cases, but the recurrence rate was estimated to be higher, because this retrospective analysis of clinical data found a probable history of RISS in > 14% of RISS patients [6]. In our patient, we considered that further use of RTX was inappropriate given the risk of anaphylaxis or RISS recurrence. Some case reports have described that ofatumumab, a human monoclonal antibody against CD20, may be a therapeutic option for NS patients who have experienced allergic symptoms or severe infusion reactions with RTX administration [13, 14]. Therefore, ofatumumab may also be a possible alternative to RTX in patients with RISS.

In conclusion, it is important for clinical nephrologists to recognize RISS, because frequently-relapsing or

steroid-dependent NS patients may receive RTX multiple times and thus be at risk of anaphylaxis or recurrence of RISS. The role of HACAs in RISS pathogenesis remains unclear. The risks and benefits of continuing RTX should be carefully assessed in patients with a history of RISS, and ofatumumab may be an alternative option in such cases.

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Compliance with ethical standards

Conflict of interest All authors have declared no competing interests.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient.

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