Serum sickness with refractory nephrotic syndrome following treatment with rituximab

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Abstract

Rituximab (RTX) is effective for treating childhood refractory nephrotic syndrome (NS), such as steroid-dependent (SD), frequently relapsing (FR), and steroid-resistant (SR) NS. While RTX has been proven to be effective in treating SDNS, FRNS, and SRNS, it may cause serum sickness, a rare illness characterized by fever, rash, and arthralgia, 10–14 days after primary antigen exposure or within a few days after secondary antigen exposure, by producing human anti-chimeric antibodies (HACAs). A 17-year-old girl with refractory SDNS treated with RTX and oral cyclosporine A was admitted with fever and arthralgia 10 days after the fifth RTX dose was administered. After RTX was started when she was 14-years-old, SDNS remission was then achieved, and prednisolone was discontinued. Although antibiotics and non-steroidal anti-inflammatory agents were administered, fever and arthralgia continued. After various inspections and clinical course, we considered her as RTX-induced serum sickness (RISS). The patient had an elevated HACA level and was diagnosed with RISS. Fever and arthralgia disappeared 5 days after onset. To the best of our knowledge, this is the first reported case of RISS with NS. Fever, rash, and arthralgia after RTX administration can be the initial symptoms.

Keywords Steroid-dependent nephrotic syndrome · Refractory nephrotic syndrome · Rituximab · Human anti-chimeric antibodies · Serum sickness

Introduction

Nephrotic syndrome (NS) affects the kidneys and can result in hypoproteinemia and generalized edema. Although first-line treatment uses oral prednisolone (PSL), patients with frequent relapses or resistance to PSL need immunosuppressants such as cyclosporine A (CyA), cyclophosphamide, and mizoribine (MZB) to reduce the number of relapses and prevent adverse effects of steroids such as impaired glucose tolerance and reduced bone mineral density. However, immunosuppressants can cause significant adverse effects including chronic nephrotoxicity of calcineurin inhibitors or gonadotoxicity and carcinogenicity of cyclophosphamide [1].

Rituximab (RTX) is a chimeric murine/human anti-CD20 monoclonal antibody binding to the B-cell surface antigen

CD20; reports have described that RTX is effective for preventing relapse in refractory NS patients [2, 3]. An investigator-initiated clinical trial of RTX therapy for refractory NS was performed, and in August 2014 RTX was licensed for treating refractory SDNS and FRNS in Japan [4]. RTX has been used to reduce or discontinue PSL in refractory NS patients, although its mechanism remains unclear.

Previous studies have reported adverse events such as cough, dyspnea, fever, and erythema, as well as late adverse events such as severe infection and agranulocytosis in refractory NS patients treated with RTX [1, 4, 5]. Furthermore, RTX may produce human anti-chimeric antibodies (HACAs) and induce serum sickness [6]. Serum sickness is a rare type III hypersensitivity reaction after injecting foreign antigens, causing fever, rash, and arthralgia. Although serum sickness is relatively common among autoimmune disease patients, there are no reports in NS patients. To the best of our knowledge, this is the first report of RTX-induced serum sickness (RISS) in a refractory NS patient.

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Case report

A 17-year-old girl with refractory SDNS who was treated with RTX and oral CyA presented with fever and arthralgia 10 days after the fifth RTX dose was administered. Her physical examination revealed serious arthralgia, warmth, and swelling in the right knee, wrists, elbows, and shoulders.

She was diagnosed with NS when she was 7-years-old and was treated with oral PSL. Laboratory test results at that time revealed that her leukocyte count was $8600/\text{mm}^3$, erythrocyte count was $500 \times 10^4/\text{mm}^3$, platelet count was $39.9 \times 10^4/\text{mm}^3$, and erythrocyte sedimentation rate (ESR) was 12 mm/h and that her serum total protein, albumin, and creatinine levels were 4.3 g/dl, 1.7 g/dl, and 0.50 mg/dl, respectively. Urinalysis revealed protein excretion of 9.0 g/day with no granular casts. Her C3 level was 147 mg/dl, C4 level was 20 mg/dl, CH50 level was 59.0 U/ml, and anti-nuclear antibody (ANA) titer was <40. She tested negative for anti-DNA antibodies. Although proteinuria disappeared 6 days after PSL administration and complete NS remission was achieved, she had an NS relapse induced by a common cold when PSL was tapered (PSL dosage: 1 mg/kg/day). Therefore, she was re-diagnosed as having SDNS, and CyA and methylprednisolone pulse (MP) therapy (20–30 mg/kg for 3 days) in addition to PSL were started. Renal biopsy performed when she was 7-years-old revealed that she had minimal change disease. After 3 years of CyA administration, CyA was replaced with MZB because of concerns about its nephrotoxicity. However, after starting MZB, she had frequent relapses due to minor infections or PSL tapering. Therefore, CyA was restarted. At that time, she was 14-years-old and had experienced nine NS relapses. Thus, PSL could not be stopped.

RTX was then administered, and PSL was discontinued. Remission was achieved and maintained. She had the tenth NS relapse 24 months after the first RTX dose was administered. She achieved remission by steroid therapy with MP, and the second RTX dose was administered. When the number of CD19-positive cells increased, RTX was administered to maintain remission. After the third dose, the duration of CD19-positive cell depletion became shorter than that after the previous RTX doses and the decrease in the number of CD19-positive cells was attenuated (Fig. 1).

To prevent an infusion reaction, intravenous hydrocortisone sodium succinate, anti-histamine, and oral acetaminophen were administered before RTX as routine practice. She had no infusion reaction or adverse effects. The fifth RTX dose was administered 7 months after the fourth dose. She left the hospital with no infusion reaction, and her general condition was good. However, she presented with acute onset of fever ($38\text{--}39^\circ\text{C}$) and left knee joint pain 10 days after the last RTX dose was administered. Her arthralgia spread to the right knee, mandible, shoulders, elbows, wrists, and right foot. She was hospitalized because she could not move.

Her laboratory findings were as follows: leukocyte count, $14800/\text{mm}^3$ with 73% neutrophils; erythrocyte count, $449 \times 10^4/\text{mm}^3$; platelet count, $33.3 \times 10^4/\text{mm}^3$; ESR, 10 mm/h; C-reactive protein level, 0.14 mg/dl; uric acid level, 6.0 mg/dl; CH50 level, 34.5 U/ml; ANA titer, <160; anti-DNA antibody titer, <0.5 IU/ml; rheumatoid factor, 7 IU/ml; serum IgG level, 1138 mg/dl; anti-streptolysin O level, 36 IU/ml; and anti-streptokinase titer, 160. There was no serological evidence of acute infection with parvovirus B19 or Epstein–Barr virus. Urinalysis revealed that she remained in remission. Her electrocardiogram and echocardiogram were normal, and magnetic resonance images revealed no abnormalities in the shoulders.

Fig. 1 Clinical course and changes in CD19-positive B-cell count after the administration of RTX. RTX rituximab, MP methylprednisolone pulse therapy, CyA cyclosporine A, NS nephrotic syndrome, PSL prednisolone

She received empiric intravenous antibiotics until her blood culture results were known. A non-steroidal anti-inflammatory agent was also given for inflammation and pain control. Blood cultures revealed no microorganisms. Her fever and arthralgia were considered to have been caused by RISS because of the time period between the administration of RTX and onset and because there was no evidence of collagen disease, sepsis, rheumatic fever, and/or parvovirus-induced arthritis. As the serum HACA level measured by enzyme-linked immunosorbent assay increased to 184 ng/ml 2 months after the fifth RTX dose was administered, she was diagnosed with RISS. Her symptoms gradually improved without steroid therapy 5 days after admission, and she was discharged 4 days later. RTX administration was discontinued at the patient's request; she remains in remission to date.

Discussion

RTX has been used for treating malignant lymphoma, chronic immune thrombocytopenic purpura, and other autoimmune diseases. In Japan, RTX has been approved for treating childhood-onset refractory NS and has been effective in preventing relapses.

Possible side effects mentioned in its package insert include fever, chills, sweating, tiredness, fatigue, nausea, headache, rash, arthralgia, and increased susceptibility to infections, and laboratory abnormalities include decreases in leukocyte, neutrophil, and platelet counts [7]. In refractory NS patients treated with RTX, previous studies have reported adverse events such as cough, dyspnea, fever, and erythema, as well as late adverse events such as severe infection and agranulocytosis. However, to the best of our knowledge, no RISS case has yet been reported in NS patients, whereas approximately 50 cases have been reported in patients with diseases other than NS [1, 4, 5].

The first RISS case was reported in 2001. The patient developed RISS 10 days after being administered RTX infusion for autoimmune polyneuropathy [8]. RISS has been primarily reported in patients with autoimmune diseases such as Sjögren's syndrome [9]. It is considered that RISS incidence may depend on the primary illness and immunosuppressant [9]. Since most NS patients receive RTX with immunosuppressants, this may result in low RISS incidence.

The mechanism of RISS onset remains unclear, but it is considered that B-cells sensitized to RTX are lysed, resulting in the release of antibodies to RTX to the bloodstream and formation of immune complexes [10]. It is considered that immune complexes related to HACA cause tissue damage when deposited in target tissues, and trigger symptoms such as arthralgia, rash, and fever. Serum sickness is usually presented 7–14 days following antigen exposure. Similarly, it is reported that most RISS patients presented symptoms

7–14 days after RTX administration [9]. Although HACA development may be associated with serum sickness, this does not always occur in patients with elevated HACA levels. In a previous study, 6 of 11 patients who received RTX developed HACAs [9]. Other studies have reported that HACA development was associated with decreased treatment efficacy [11] and adverse events such as serum sickness [12]. One study reported that HACA-positive NS patients showed decreased effects of RTX treatment [13].

In our patient, HACAs may have developed after the third or fourth RTX dose was administered because of the decreased clinical efficacy of RTX. Presumably, she developed serum sickness because of B-cell lysis after the fifth dose of RTX had been administered. Although HACA development may provide important clues to diagnosing serum sickness, a diagnosis should be made based on symptoms, history, and laboratory findings as no specific markers exist. A similar symptom in RISS is delayed-type hypersensitivity reaction, which is a type IV hypersensitivity reaction occurring a few days after injecting foreign antigens, causing fever, rash, arthralgia, and muscular pain. Although it is difficult to clearly differentiate between RISS and delayed type hypersensitivity reaction, we diagnosed the patient with RISS due to her clinical course and detecting HACA.

According to reports on RISS, steroid therapy is mainly used. Although we were also considering using steroids for our patient, they were unnecessary because she improved spontaneously. In a previous study, four RISS patients were re-administered RTX with steroid therapy, and in one patient, serum sickness relapsed [9]. Thus, a thorough explanation is mandatory prior to re-administration. As our patient did not want to continue treatment with RTX, we plan to use steroids and immunosuppressants should there be another NS recurrence. When NS recurrence becomes refractory, the use of ofatumumab, such as human anti-CD20 monoclonal antibody, may be considered.

When decreased efficacy and treatment failure of RTX are suspected, HACA development should be considered. Furthermore, when arthralgia or fever develops after RTX administration, serum sickness should be considered along with side effects, as serum sickness presents non-specific symptoms.

In Japan, the number of RISS patients may increase because several RTX doses are administered to refractory NS patients. The RISS pathogenesis needs to be revealed and its risk factors clarified. Furthermore, as there is no report on the correlation between HACA levels and the severity of RISS, the accumulation of the data is required.

Compliance with ethical standards

Conflict of interest All the authors have declared that no conflict of interest exists.

Human and animal rights statement 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 all individual participants included in the study.

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