Rituximab-induced serum sickness in the treatment of idiopathic membranous nephropathy

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Abstract

We report a case of rituximab-induced serum sickness in a 50-year-old female with idiopathic membranous nephropathy. Presentation was characterized by a widespread rash 1 week after rituximab administration followed by fever and profound haemodynamic instability, mimicking sepsis. Symptoms resolved over 48 h, although adjunct antibiotics, steroids and inotropes were used. This case is notable for being the first reaction with rituximab for a renal indication as well as the severity of presentation.

Key words: membranous nephropathy, nephrotic syndrome, rituximab, rituximab-induced serum sickness, serum sickness

Case report

A 50-year-old female with relapsing idiopathic membranous nephropathy (IMN) presented to our hospital in August 2016 with a maculopapular rash, having received the monoclonal anti-CD20 antibody rituximab 1 week prior.

The only background history is IMN first diagnosed in 2000 with complete remission attained with cyclophosphamide and prednisolone. Remission was maintained with methotrexate due to intolerance to cyclosporine. In July 2016, the patient presented with nephritic syndrome with intact renal function. Renal biopsy confirmed relapse and new nodular changes consistent with unrecognized, early diabetic nephropathy. Serum antiphospholipase-A2 receptor antibody was negative. Because of concerns about cumulative cyclophosphamide exposure, treatment with rituximab (two doses of 1000 mg a fortnight apart) was commenced. Trimethoprim-sulfamethoxazole was started for Pneumocystis jirovecii pneumonia prophylaxis and metformin for diabetes.

On admission to hospital she had a widespread maculopapular rash involving the face, torso and peripheries but was haemodynamically stable. The presumptive diagnosis was allergic urticaria and the patient was commenced on oral doses of prednisolone 30 mg, cetirizine 10 mg and promethazine 25 mg.

Twenty-four hours later she became hypotensive (systolic blood pressure 70 mmHg), febrile (38.1°C) and tachycardic (heart rate 110 bpm). She developed generalized myalgias, arthralgias and cervical lymphadenopathy. She did not respond to fluid resuscitation, prompting admission to the intensive care unit for inotropic support. Empirical antibiotics were commenced for potential sepsis and intravenous hydrocortisone for anaphylactic shock.

Investigations demonstrated leucocytosis (white cell count 24.9 × 10^9/L) with accompanying lymphocytosis (7.2 × 10^9/L); serum eosinophils and neutrophils were normal (0.0 × 10^9/L and 6.4 × 10^9/L, respectively). Blood film demonstrated a non-specific reactive leucocytosis. C-reactive protein was elevated (3581 nmol/L), C3 was low (0.63 g/L) and C4 was normal (0.20 g/L). Septic workup for infective aetiologies was negative. Biochemistry demonstrated lactic acidosis (lactate 15 mmol/L; pH 7.12) and acute kidney injury (serum creatinine 339 μmol/L). Urine microscopy showed 36 × 10^6 red cells without pyuria. Procalcitonin levels were not tested due to unavailability.
Symptoms resolved within 48 h, with inotropic support weaned within 24 h. Renal function normalized. Rituximab-induced serum sickness (RISS) was concluded as the most likely diagnosis due to the timeline of medication exposure and rapid clinical improvement. Antibiotics were ceased and hydrocortisone was changed to a 1 week weaning course of prednisolone. The patient was rechallenged with trimethoprim-sulfamethoxazole with no issues. Arrangements were made for outpatient skin allergen testing. The patient was discharged home and follow-up phone calls revealed no recurrence of symptoms over 3 months.

Discussion

Rituximab is a CD20 mouse monoclonal antibody designed to eliminate B cells by direct, complement and antibody-dependent cellular cytotoxicity. In Australia, it has been licensed for use in chronic lymphocytic leukaemia, non-Hodgkin’s lymphoma, rheumatoid arthritis and recently anti-neutrophil cytoplasmic antibody–associated vasculitis. It is not licensed for use in IMN but has been used off label for refractory disease. Dosage regimens have been either four weekly doses of 375 mg/m² or two doses of 1000 mg given a fortnight apart [1].

Rituximab reactions commonly occur with the first infusion, ranging from simple flushing and dyspnoea to anaphylaxis. Simple reactions are thought to be due to a cytokine release syndrome [2] potentially triggered by the murine element of the antibody, with studies looking into reducing reactions with pure human monoclonal CD20 antibodies (ofatumumab) [3].

RISS was first identified in 2001 and appears to be an immune complex–mediated type III hypersensitivity reaction that results in complement activation and mast cell degranulation. It typically occurs 1 week after exposure but can occur up to a month after. Incidence ranges between 1 and 20% [4]. The classical syndrome consists of a triad of fever, lymphadenopathy and polyarthralgia. Other symptoms can include rash, proteinuria and gastrointestinal symptoms. It is often

Table 1. Differential diagnosis of serum sickness

| Differential diagnosis | Onset | Clinical presentation | Notable investigations |
|-----------------------|-------|----------------------|-----------------------|
| Serum sickness        | Commonly 1–2 weeks, rarely 1 month Resolves within a few weeks of drug cessation | • Pruritic urticarial rash from the lower trunk spreading to the back, upper trunk and extremities • Sparing of mucous membranes • Rapid resolution of rash • High-grade temperatures • Lymphadenopathy • Myalgia, arthralgia | • Reduced C3 and C4 in severe episodes • Reduced neutrophils • Reactive plasmacytoid lymphocytes • Uncommon eosinophilia • Elevated CRP, ESR |
| Viral exanthema       | Variable depending on exposure | • Mucous membranes • Can cause urticarial rash • Low-grade temperatures • Arthralgia | • Reduced C3 and C4 • Positive serology, viral polymerase chain reaction |
| Hypersensitivity      | 7–10 days after exposure | • Palpable purpuric rash, maculopapular rash • Abdominal pain • Lymphadenopathy • Arthralgia • High-grade temperatures | • Reduced C3 and C4 • May have active urinary sediment and abnormal renal function • Skin biopsy: neutrophils around vessels |
| vasculitis and         |       |                      |                       |
| urticarial vasculitis  |       |                      |                       |
| DRESS                 | Delayed reaction 2–6 weeks after exposure | • Morbilliform rash confluent and desquamating • Uncommon urticarial rash • Diffuse lymphadenopathy • No arthralgia | • Eosinophilia • Elevated transaminases • Atypical lymphocytosis • HHV-6 positive (40–60%) |
| Reactive arthritis    | 1–4 weeks after infection | • Mucosa involved • Distinct skin lesions (circinate balanitis) • Low-grade temperatures • Joint effusions • Arthralgia | • Constitutional symptoms, headache and neck pain common • Elevated CRP and ESR |
| Bacterial endocarditis| Variable | • Typical peripheral stigmata (Osler’s nodes, Janeway lesions) • Febrile • Cardiac murmur • Potential history for initial source (dental work, skin cracks) | • Positive microbiology • Elevated CRP and ESR • Echocardiogram diagnostic |
| Generalized           | Rapid onset during course of therapy | • Typical urticarial rash • Angioedema, acute anaphylaxis | • Eosinophilia • Elevated serum tryptase |
| hypersensitivity       |       |                      |                       |
| and urticarial         |       |                      |                       |
| reactions              |       |                      |                       |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HHV-6, human herpesvirus 6.
accompanied by elevated inflammatory markers, low comple-
ments and lymphocytosis without eosinophilia.

It can be difficult to differentiate RISS from diagnoses such as bacterial infection or anaphylaxis. Table 1 offers a list of dif-
ferential diagnoses.

To date, there are only a few case reports of this reaction, confined to haematological and rheumatological populations [2, 4]. Only one report has documented RISS being associated with shock requiring inotropic support [5]. A systematic re-
view of 33 haematological and rheumatological patients with RISS found that the classic triad was only seen in 16 cases (48.5%) and symptoms resolved in 2.15 ± 1.34 days [2]. Corticosteroids were the most commonly used treatment. In total, 4 of the 33 patients were rechallenged with a further infusion. Two patients tolerated it well, one patient had a mild immediate reaction and one patient experienced RISS again [2].

Currently there are no reports of RISS in a renal population. Our case demonstrates that serum sickness can occur in this population and it is the second case report of such severity.

Conflict of interest statement
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