

Serum Sickness Following Rituximab Therapy in a Patient with Pemphigus Vulgaris: A Case Report

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Abstract

Serum sickness, a reaction presenting with a classic triad (fever, rash, myalgia/arthralgia) and considered as a rare adverse event following monoclonal antibodies and specifically following treatment with rituximab. This report describes a case of serum sickness in a newly treated young male patient with rituximab for pemphigus vulgaris.

Key Clinical Message

Clinicians should be vigilant for potential acute or delayed serum sickness as possible adverse reactions to weigh the benefits and risks of rituximab therapy in patients with pemphigus vulgaris.

Background

Monoclonal antibodies have been used for the modulation of immune responses in several disorders, including cancer, autoimmune, and infectious diseases.¹

Rituximab (RTX) is a chimeric monoclonal antibody that specifically binds to the B-cell surface antigen CD20 which mediate cytotoxicity in these cells.²⁻⁴ The mechanism of action of RTX including, regulating cell-cycle signaling, inducing apoptosis, improving cytotoxic drugs cells' sensitization, antibody-dependent cellular, and complement-mediated cytotoxicity.⁴

RTX is used in the management of previously untreated or treated adults with CD20+ chronic lymphocytic leukemia (CLL)⁵, granulomatosis with polyangiitis⁶, microscopic polyangiitis⁷, non-Hodgkin lymphomas⁸, pemphigus vulgaris⁹, rheumatoid arthritis¹⁰, and other off-label uses such as acquired thrombotic thrombocytopenic purpura¹¹, Waldenström macroglobulinemia¹², refractory autoimmune hemolytic anemia¹³, etc.

As a monotherapy, RTX (1000 mg) is administered weekly for one month or every 3 to 4 weeks when used in combination with chemotherapy.¹⁴

Pemphigus is one of the autoimmune diseases which characterized by cutaneous blisters and erosions and mediated by autoantibodies. Pemphigus Vulgaris (PV) is the major progressive subtype of pemphigus and may lead to death if it is not treated.¹⁵

The adverse events of RTX might be early (e.g., fever, cough, and dyspnea), or late such as agranulocytosis or severe infection.¹⁶

Serum sickness is an uncommon hypersensitivity undesirable reaction due to antigens, characterized by fever, rash, and arthralgia.¹⁷ RTX is induce serum sickness by producing human anti-chimeric antibodies.¹⁸ Although serum sickness is commonly reported in patients with autoimmune disease, few reports were published for patients with PV.

Case Presentation

A 33-year-old male was admitted with a history of fever, malaise, arthralgia, and myalgia for one day. Two weeks ago, he was started on RTX (1000mg IV 2 times per week) for the treatment of severe pemphigus vulgaris in addition to his previous treatment with intravenous immunoglobulin (IVIG) (2 g/kg per cycle), azathioprine (2.5 mg/kg), and prednisolone (2 mg/kg per day) which were started earlier. The symptoms appeared 11 days after the second dose.

Subsequent physical examination revealed fever (a temperature of 38.5degC), hemodynamic instability with sinus tachycardia of 130 - 140 bpm, mild tachypnea, malaise, generalized body rash (cutaneous blisters), and generalized body pain. He reported severe pain while moving his elbows, shoulders, knees, wrists, ankles, spine, metacarpophalangeal joints, and temporomandibular joints. However, no effusions, swelling, and erythema were noted. He was immediately started on a wide-spectrum antibiotic at the beginning in view of suspected sepsis and was discontinued shortly after admission.

Subsequent laboratory investigations revealed leukocyte count 26.4 ($4 - 10 \times 10^3/\mu\text{L}$), neutrophils 84.3%, platelet count 267 ($150 - 400 \times 10^3/\mu\text{L}$), erythrocyte count 6.4 ($4.5 - 5.5 \times 10^6/\mu\text{L}$), C-reactive protein level 112 (0.0 - 5.0 mg/L), uric acid level 7.7 (3.4 - 7.0 mg/dL), creatinine 144 (62 - 106 $\mu\text{mol/L}$). Coagulation profile, electrolytes, C3 and C4 levels within normal ranges, Urinalysis was within normal range except a trace of blood, and blood cultures and viral panel were negative.

Based on the medication history, physical examination, and excluding other potential causes; the patient was initially diagnosed with acute serum sickness associated with RTX therapy. Instantly, he was treated with methylprednisolone of 1mg/kg/day divided to 2 doses, ample analgesia with paracetamol, morphine, and fentanyl patches. He was immediately started on a wide-spectrum antibiotic at the beginning in view of suspected sepsis and was discontinued shortly after admission. His signs and symptoms resolved within 2 days from initiation of the above-mentioned treatment, his follow-up laboratory test results were normal. Four days later, he was discharged home and referred to a dermatology and allergy clinic where the treating physician has discussed with the primary physician the treatment options and possible complications for resuming the patient on RTX.

Discussion

Rituximab is a novel therapeutic agent for severe and recalcitrant pemphigus vulgaris (PV).¹⁹ In patients with PV, human antichimeric antibodies (e.g., RTX) are known to cause treatment failure and adverse effects especially with intravenous administration²⁰.

Rituximab-induced serum sickness (RISS) has been reported earlier in various autoimmune disorders including rheumatoid arthritis, Sjogren's syndrome, and hematological malignancies²¹. Typically, it has been explained by the presence of the murine component in RTX and B-cell lysis by forming complexes with antibodies due to the delivery of intracellular antigens to the serum which then precipitates systematically in the synovial membranes of joints^{22, 23}.

A 2015 literature review identified 33 reported cases associated with RTX where most of the reported cases were related to an underlying rheumatologic condition (such as Sjogren's syndrome). The classic triad (fever, rash, and arthralgia) of serum sickness was reported less than half of cases. The mean time from exposure to symptom onset with the RTX first dose was almost double compared to the second dose.²⁴

A recent study has described the epidemiological and clinical characteristics of 37 cases of RISS reported in France. Serum sickness occurred mainly 12 days after the first injection (54%). The most frequent manifestations were rheumatologic symptoms (92%), fever (87%), and skin lesions (78%). The incidence was significantly higher when RTX was used for autoimmune diseases than for hematological malignancies.²⁵

The role of RTX in severe refractory PV has been studied in the past few years. Some of the documented adverse effects include severe infections such as pneumonia, progressive multifocal leukoencephalopathy, anaphylaxis, Stevens-Johnson syndrome.¹⁹

In our case, the treating physician did not recommend resuming RTX to prevent any further severe reaction. Mainly, the diagnosis of serum sickness depends on clinical features. Other causes such as malignancy and any infection that can trigger serum sickness should be ruled out. In this case, investigations such as blood investigations (e.g., CBC, complement C3, C4, blood culture. etc.), ultrasonography abdomen, and urine analysis helped in ruling out malignancy and infectious potential causes. In our patient, clinical presentation, medication history, and quick response to treatment helped in making the diagnosis of RISS. Overall, all the clinical features, laboratory findings, quick response to corticosteroids were suggestive of serum sickness due to RTX (which was started two weeks ago) after excluding other possible causes.

Conclusion

Rituximab is considered an important treatment option in patients with moderate to severe refractory pemphigus vulgaris. RTX has been shown to be effective and well-tolerated in several autoimmune conditions. However, there are still concerns about its long-term adverse effects. Clinicians should be vigilant for potential acute or delayed serum sickness as possible adverse reactions to weigh the risks and benefits of continuing/reintroducing RTX for patients with pemphigus vulgaris. Further studies reporting the adverse effects of RTX are required to establish its safety and tolerability.

Abbreviations

RTX: Rituximab

PV: Pemphigus Vulgaris

IVIG: Intravenous Immunoglobulin

RISS: Rituximab-induced serum sickness

Declarations

Ethics approval and consent to participate

The article describes a case report. Therefore, no additional permission from our Ethics Committee was required.

Consent for publication

The consent for publication was obtained.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MYK, SMA, AJN: Data Collection, Literature Search, Manuscript Preparation

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