Rituximab-Induced Serum Sickness in a Patient with Pemphigus Vulgaris: A Case Report

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September 10, 2020

Abstract

Serum sickness, a reaction characterized by fever, rash, myalgia, and arthralgia, can occur in patients who receive chimeric monoclonal antibody therapy. Serum sickness is considered as a rare adverse event following rituximab therapy. We report a case of serum sickness in a newly treated 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 risks and benefits of continuing/reintroducing rituximab for 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 produces antibody-dependent cell- and complement-mediated cytotoxicity in these cells. [2-4] The mechanism of action of RTX including, regulating cell-cycle signaling, inducing apoptosis, improving cells' sensitization to cytotoxic drugs, complement-mediated cytotoxicity, and antibody-dependent cellular cytotoxicity [4]

RTX has been used in the treatment of previously untreated or previously treated CD20-positive chronic lymphocytic leukemia (CLL) in adults[5], granulomatosis with polyangiitis[6], microscopic polyangiitis [7], non-Hodgkin lymphomas [8], pemphigus vulgaris[9], rheumatoid arthritis [10], and other off-label uses such as acquired thrombotic thrombocytopenic purpura [11], Waldenström macroglobulinemia[12], refractory autoimmune hemolytic anemia[13], etc.

As a single agent, RTX (1000 mg) is usually administered weekly for 4 weeks. When used in combination with chemotherapy, it is often administered every 3 to 4 weeks. The pharmacokinetics of RTX is like that seen with human immunoglobulin G (IgG). [14]

Pemphigus is an autoimmune disease characterized by blisters and erosions of the skin and mucosal membranes. It is mediated by autoantibodies that target the transmembranous adhesion glycoproteins desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). Pemphigus Vulgaris (PV) is the major subtype of Pemphigus and is characterized as having a progressive course that leads to death if the disease is not treated.[15]

Several 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 patients treated with RTX.[16]

Serum sickness is a rare hypersensitivity reaction due to foreign antigens, causing fever, rash, and arthralgia. [17] RTX may produce human anti-chimeric antibodies (HACAs) and induce serum sickness. [18] Although serum sickness is relatively common among autoimmune disease patients, there are few reports in 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 x10ˆ3/uL), neutrophils 84.3%, platelet count 267 (150 – 400 x10ˆ3/uL), erythrocyte count 6.4 (4.5 – 5.5 x10ˆ6/uL), 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 umol/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 his history of recent administration of RTX and on his physical examination and laboratory findings, the patient was presumptively diagnosed as having acute serum sickness secondary to RTX and 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 symptoms resolved within 48 hours after 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 administration[20].

However, there are not yet randomized trials assessing which protocol is better in terms of efficacy and safety. On the other hand, high dose regimens should be preferred instead of low-dose regimens, due to longer disease response. [9]

Rituximab-induced serum sickness (RISS) has been reported earlier in various autoimmune disorders including rheumatoid arthritis, Sjogren's syndrome, and hematological malignancies [21]. 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 linked with an underlying rheumatologic condition (n = 17, 51.5%), most commonly Sjogren's syndrome (44.4%). The classic triad of serum sickness (fever, rash, and arthralgia) was reported in 16 (48.5%) cases. Time from drug exposure to symptom onset was significantly greater with the first doses of RTX compared

to the second dose (mean time 10.00 vs. 4.05 d, P = 0.002), and time to resolution was significantly greater for rheumatologic vs. hematological indications (mean time 2.50 vs. 1.00 d, P = 0.035).[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

CMV: Cytomegalovirus

COVID-19: Coronavirus disease

IBD: Inflammatory bowel disease

AIDS: Acquired immunodeficiency syndrome

ICU: Intensive care unit

IL-6: Interleukin 6

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.

Funding

This study was not funded.

Authors' contributions

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

All authors read and approved the final manuscript

Acknowledgments

We thank the patient for allowing us to share his case. Open Access funding provided by the Qatar National Library

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