Serum Sickness Reaction to Rituximab with Positive Immediate Intradermal Skin Test: A Case Report

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CASE REPORT

Serum Sickness Reaction to Rituximab with Positive Immediate Intradermal Skin Test: A Case Report

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Abstract:

Background: Rituximab is a chimeric murine/human monoclonal antibody against CD20. It can be used off-label in autoimmune diseases. Its administration can lead to several types of reactions; immediate infusional reactions and also delayed reactions like Serum Sickness Reaction (SSR).

Case Presentation: This is a case study of a 48 years old woman diagnosed with rheumatoid arthritis/systemic lupus erythematosus who developed refractory immune thrombocytopenic purpura and received treatment with rituximab. After treatment, she developed erythematous-violet lesions accompanied with fever of 38ºC, dyspnea, joints arthralgia and edema. In the emergency department, hypotension, fever, dyspnea, and shivering were observed, for which, intramuscular epinephrine, intravenous corticosteroids, antibiotics and salbutamol nebulization were administered. In our allergy unit, we performed an intradermal test (IDT) with rituximab (1mg/ml), which was positive at immediate (20min) and late (48h) reading. Based on the clinical manifestations and test carried out, she was diagnosed with rituximab SSR. We also studied the molecular mass of the IgE-reactive proteins present in rituximab product by SDS-PAGE Immunoblotting method according to Laemmli, in reducing and non-reducing conditions, with high sensitivity and using three different polyvinylidene difluoride (PVDF) membrane blocking substances (skimmed cow's milk, fish collagen and egg white). We did not detect IgE-binding to rituximab product.

Conclusion: The pathogenesis of SSR is not well known. The patients after reinfusion can develop immediate reactions suggesting involvement of IgE hypersensitivity. Nevertheless, there are patients who tolerated reinfusion. Further studies and assays are needed for a better understanding of these reactions and to lead to a safer re-administration if needed.

Keywords: Hypersensitivity reaction, Rituximab, Antibody, Immune-complex, Autoimmune disease, Serum sickness reaction, CD20.

1. INTRODUCTION

Rituximab is a chimeric murine/human monoclonal antibody against CD20, located on B cells that induce its apoptosis, diminishing the antibody production [1]. It is used for the treatment of B-cell non-Hodgkin lymphoma and Rheumatoid Arthritis (RA). It is used off-label in other autoimmune diseases such as Systemic Lupus Erythematosus (SLE) or Immune Thrombocytopenic Purpura (ITP) [2, 3]. Its administration can lead to several types of reactions; immediate infusional reactions, mostly characterized by fever, chills, nau-
2. CASE PRESENTATION

We present the case of a 48 years old woman diagnosed with RA/SLE with positive rheumatoid factor, who developed refractory ITP. She was successfully treated six years before with four doses of rituximab. She restarted weekly treatment with rituximab and 24H after the second dose, developed coalescing erythematous, edematous, pruritic and papular cutaneous lesions on the trunk and both arms and legs. She was diagnosed and treated for urticaria. Twenty-four hours later, the rash worsened and turned into erythematous-violet lesions with fever of 38°C, dyspnea, metacarpophalangeal joints with arthralgias and edema. She attended the Emergency Department with hypotension, fever, dyspnea, shivering, therefore, 0.3 mg of intramuscular epinephrine, 100 mg of intravenous hydrocortisone, 1 g of meropenem and nebulization of 10 mg of salbutamol were administered. A blood test was performed, finding decreased levels of C3: 72 mg/dL (91.0 - 189.0) and C4: 8.7 mg/dL (18.0 - 55.0), and increased levels of acute reactants: fibrinogen 778 mg/dL (150 – 450), and C reactive protein 7.9 mg/dL (0.0 - 0.5). An ELISA was made to detect circulating immuno-complexes, resulting in being inconclusive. Blood and urine cultures remained sterile. She was hospitalized and discharged after improvement 6 days later. She was referred to our Allergy Unit. We performed Intradermal Test (IDT) with rituximab (1 mg/ml), which was positive at immediate (20 minutes) and late (48 hours) reading. Attending to the clinical manifestations and blood test results, she was diagnosed with rituximab SSR. We studied the molecular mass of the IgE-reactive proteins present in rituximab product by SDS-PAGE Immunoblotting method according to Laemmli, in several conditions: reducing (with 2-mercaptoethanol; standard conditions) and non-reducing conditions (without 2-mercaptoethanol), with high sensitivity (low dilution of patient serum and low dilution of mouse monoclonal anti-human IgE) using three different Polyvinylidene Difluoride (PVDF) membrane blocking substances (skimmed cow’s milk, fish collagen and egg white). We did not detect IgE-binding to rituximab product.

3. DISCUSSION

Type III hypersensitivity reactions as SSR may occur after the administration of heterologous proteins, developing antibodies against these foreign proteins. Bielory et al. [6], proved increased serum levels of IgG, IgM, IgA, and IgE, and Lawley et al. [7], found IgM, IgA and IgE in lesional skin biopsies supporting the role of immune complexes. Nevertheless, the pathogenesis of rituximab-induced SSR is not clear [3]. Jhonson et al. [2], studied 25 patients with hypersensitivity reactions to rituximab, presenting late and early onset adverse reactions, concluding that risk of reaction on re-administration could not be predicted by a positive Skin Test (ST), and both positive and negative ST patients developed hypersensitivity reactions during desensitization with similar frequency. Kumar et al. [4], presented a patient who developed SSR after being treated with rituximab. Her symptoms resolved promptly, so she carefully received a second dose, but within minutes, she developed lips and periorbital angioedema, chocking sensation and tachycardia, receiving treatment with adrenaline. The ratio of antigen/antibody is important, and the excess of antigen may join circulating anti-rituximab antibodies and form precipitating immune complexes that obstruct the detection of free anti-rituximab antibodies [1]. These immune complexes activate the complement and mast cells leading to histamine release. Once the culprit drug is discontinued, clinical manifestations are generally self-limited in mild cases. Some authors describe rituximab reinfusion without new reactions [2, 3], others described reactions suggesting type I hypersensitivity requiring epinephrine [2, 4]. This may occur if the patient still has circulating IgG or IgE antibodies from the previous exposure, resulting in clinical manifestation features of anaphylaxis and SSR both. Goto et al. [8], found an increase of Human Anti-Chimeric Antibody (HACA) (rituximab-specific IgG) in the serum of an 8 years-old patient that developed SSR after rituximab treatment. He also analyzed 22 reported cases of SSR, some of them were HACA positive, but none tried to find IgE against rituximab as we did. Todd et al. [9], failed to detect HACA to rituximab, concluding “the utility of testing for complement levels or HACA to diagnose serum sickness remains unclear”. Vendramin et al. [1], developed an assay to detect anti-rituximab antibodies and encourage considering testing rituximab antibodies “to weigh benefits and risks of continuing/reintroducing rituximab”.

CONCLUSION

We present a patient who was reinfused rituximab and developed SSR with complement consumption. She presented an immediate positive IDT, suggesting circulating IgE antibodies, remaining positive 48 hours. In conclusion pathogenesis of SSR is not well known and more studies are needed in this matter. The patients after reinfusion can develop immediate reactions suggesting the involvement of IgE hypersensitivity, but more studies and assays are needed to reach this conclusion.

LIST OF ABBREVIATIONS

RA = Rheumatoid Arthritis
SLE = Systemic Lupus Erythematosus
ITP = Immune Thrombocytopenic Purpura
SSR = Serum Sickness Reaction
IDT = Intradermal Test
PVDF = Polyvinylidene Difluoride
ST = Skin Test
HACA = Human Anti-Chimeric Antibody

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This case was regular clinical practice, and approved by the Ethics committee of Hospital General Universitario Gregorio Marañón, Madrid, Spain.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the
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Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION
The patient included in the study has received sufficient information and has given informed consent in writing to participate in the study.

STANDARDS FOR REPORTING
CARE guidelines have been followed in this case report.

FUNDING
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CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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