

Desensitization Protocol for Rituximab-Induced Serum Sickness

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Abstract: Rituximab, a chimeric anti-CD20 monoclonal antibody, is used to treat rheumatologic and hematologic diseases. Serum sickness, a Type III delayed hypersensitivity reaction, has been reported with rituximab treatment. Traditionally, drug desensitization has been used to treat Type I IgE-mediated hypersensitivity reactions. We report the first case of successful drug desensitization to rituximab in a patient with medication-induced serum sickness. In our case, a 37-year-old woman with Sjogren's syndrome and papillary thyroid carcinoma developed serum sickness 72 hours following rituximab infusion for gastric mucosal associated lymphoma tissue (MALT). Her MALT progressed after stopping rituximab. She underwent a rapid 12-step intravenous rituximab desensitization without recurrence of serum sickness. Following the completion of 4 rituximab desensitizations, she had gastric MALT remission. She received 25 maintenance rituximab doses using this desensitization protocol quarterly without complications. This is the first report documenting rituximab desensitization for the treatment of delayed drug reactions like serum sickness.

Keywords: Desensitization, hypersensitivity, mucosa associated lymphoid tissue, rituximab, serum sickness.

INTRODUCTION

Serum sickness is a Type III delayed hypersensitivity reaction that is caused by immune complex deposition [1,2]. It typically develops 8-13 days following antigen exposure and can be associated with autoimmune diseases and a variety of medications, including rituximab [3,4]. The clinical presentation of serum sickness includes rash, fever, and polyarthralgias or polyarthritis. Treatment is usually supportive with medication avoidance.

Rituximab is a chimeric monoclonal antibody targeted against the CD20 antigen on the surface of B lymphocytes with a half-life of 18-32 days [5]. It is used to treat several rheumatologic diseases and hematologic malignancies including refractory gastric mucosa-associated lymphoid tissue (MALT). The majority of rituximab adverse events occur during the first infusion period, with fever and chills being the most common [6,7]. Acute infusion reactions to rituximab manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension were experienced by 27% of patients following their first infusion, whereas these reactions decreased to 9% in patients following the 2nd rituximab infusion [5]. Furthermore, delayed post-infusion syndromes have also been described with rituximab use such as serum sickness, Stevens-Johnson syndrome, and vasculitis [3,4,8-13].

Previously, rituximab desensitization has been used to treat patients with Type I immediate, IgE mediated hypersensitivity reactions to rituximab [14,15]. These drug desensitizations have shown efficacy in immediate, IgE mediated reactions, but to our knowledge this is the 1st

published desensitization protocol for delayed non-IgE mediated drug reaction to rituximab.

MATERIALS AND METHODS

A PubMed search using keywords: rituximab and serum sickness and drug desensitization from 1989 to present generated no cases. Additional PubMed search using keywords: rituximab desensitization and serum sickness from 1989 to present also generated no cases. This case report was approved by the Institutional Review Board (IRB) at our facility.

CASE REPORT

The patient is a 37-year-old female with Sjogren's syndrome and history of papillary thyroid carcinoma, who began experiencing right upper quadrant abdominal discomfort and underwent a workup to rule out gallstones, including a negative abdominal ultrasound. Following the occurrence of blood in the stool, she underwent a negative colonoscopy and esophagogastroduodenoscopy (EGD) which showed areas of abnormal mucosa which were biopsied and found to be gastric margin zone B cell lymphoma, mucosa-associated lymphoid tissue type (MALT). *H. pylori* was negative in the serum and on immunohistochemical stains. Three months later, an endoscopic ultrasound with stomach body and fundus biopsies showed extranodal marginal zone lymphoma and small lymphoid aggregates respectively, consistent with progression of gastric MALT and she elected rituximab treatment. Family history is significant for a mother with scleroderma but negative for any cancers. She is a former smoker with 10 pack year history.

After initial rituximab infusion, she experienced flu like symptoms and nasal congestion which resolved within 24 hours. One week later, immediately following the 2nd infusion, the patient experienced only nasal congestion.

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However, 72 hours later she developed fever, progressive and symmetric polyarthralgias of her small and large joints, and abrupt onset of a pruritic morbilliform rash on her ankles. Upon presentation to the emergency room, the rash had spread to her legs, abdomen, torso and arms. Laboratory studies showed a normal complete blood count, metabolic panel and Parvovirus B19 antibodies, negative Lyme antibodies, elevated total protein (9.6g/dL) and low C4 complement level (10mg/dL) consistent with serum sickness reaction to rituximab. She was admitted for an adverse drug reaction to rituximab, treated with 125 mg of IV methylprednisolone and 50mg IV diphenhydramine with some improvement of joint aches and rash by the following morning. Her rash resolved within 10 days, however her other symptoms gradually resolved by 1 month post-infusion with oral steroids and drug avoidance.

As her gastric MALT progressed in the absence of rituximab therapy, the remaining treatment options included radiation therapy or gastrectomy. The patient was hesitant to undergo radiation therapy due to the risk of secondary malignancy especially in light of her previous malignancies. She was reluctant to undergo gastrectomy due to fear of impaired quality of life. Therefore, the patient in conjunction with her oncologist decided to evaluate the possibility of additional rituximab treatment with referral to a university allergy-immunology clinic. We discussed with the patient at length that drug desensitization to rituximab for serum sickness had not been previously performed. The risks of the procedure, which included the recurrence of serum sickness and potential life-threatening complications were discussed with the patient who consented to be desensitized to rituximab.

She was admitted to the intensive care unit (ICU) and pre-treated with 650mg acetaminophen by mouth and 50mg diphenhydramine IV prior to the rapid 12-step IV rituximab desensitization (Table 1). She also received 60mg IV methylprednisolone, 20mg IV famotidine, and 180mg oral fexofenadine 1 hour before and 1 hour after desensitization. Vital signs were continuously monitored in the ICU with medications available at the bedside in the case of an allergic

reaction. She tolerated the desensitization without immediate hypersensitivity reaction or recurrence of serum sickness. Following the successful completion of 4 cycles of rituximab using this desensitization protocol, she had remission of gastric MALT based on negative endoscopy, biopsy and abdominal CT scan findings. She received 25 maintenance rituximab doses using this desensitization protocol quarterly without complications or recurrence of her disease.

DISCUSSION

Serum sickness is a non-IgE mediated Type III delayed hypersensitivity reaction. It can be associated with autoimmune diseases and a variety of medications, including monoclonal antibodies. Treatment is usually supportive with medication avoidance. Serum sickness reaction to rituximab is a rare complication of treatment of hematologic malignancies. Previous case report of serum sickness in a patient with marginal-zone B-cell lymphoma of MALT type identified three risk factors for serum sickness after rituximab infusion including administration of rituximab alone, the existence of Sjögren's syndrome, and polyclonal hypergammaglobulinemia [16].

Our patient with Sjögren's syndrome developed serum sickness following the 2nd rituximab infusion. In this case, the risks of repeating rituximab therapy included recurrence of serum sickness or a worsening hypersensitivity reaction. Unfortunately, in the absence of rituximab therapy, the patient had disease progression and the remaining treatment options for this patient's gastric MALT were radiation therapy and gastrectomy. Despite the risk of recurrence of serum sickness, rituximab therapy was chosen by the patient and her hematologist-oncologist as the most acceptable treatment given the complications associated with the other treatment options.

Medication desensitization has traditionally been used to treat IgE mediated allergic reactions. However, with the increasing use of monoclonal antibodies to treat a variety of diseases, clinicians should consider not only immediate drug reactions but also delayed reactions such as serum sickness.

Table 1. Rituximab Desensitization Protocol for Serum Sickness

Step	Administered Dose (mg)	Place in D5W (ml)	Cumulative Dose Infused (mg)	Infusion Time (min)	Rate (ml/hr)
1	0.01	50	0.01	15	200
2	0.025	50	0.035	15	200
3	0.05	50	0.085	15	200
4	0.1	50	0.185	15	200
5	0.25	50	0.435	15	200
6	0.5	50	0.935	15	200
7	1	50	1.935	15	200
8	2	50	3.935	15	200
9	5	50	8.935	15	200
10	10	50	18.935	15	200
11	20	50	38.935	15	200
12	561.065	280	600	224	75

Desensitization is contraindicated in patients who have experienced life-threatening severe exfoliative dermatitis syndromes and dermatoses with mucous membrane lesions [toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)] as well as in patients with a history of severe organ-specific involvement to the drug such as DRESS (drug reaction with eosinophilia and systemic symptoms) or acute generalized exanthematous pustulosis (AGEP) [17].

The proposed mechanism for desensitization in IgE mediated early hypersensitivity reactions is induction of a temporary tolerant state of mast cells and basophils to inciting drug allergens by incremental step-wise administration of the specific offending drug [18]. Three hypotheses have been suggested to explain the mechanism by which mast cells and basophils can be rendered temporarily unresponsive to drug antigen. These include internalization of the high affinity receptor for IgE (FcεRI) present on the surface of mast cells and basophils through cross-linking at a low antigen concentration, depletion of activating signal transduction components and sub-threshold depletion of mediators [19, 20]. However, it is unclear whether any of these proposed mechanisms play a role in desensitization procedures for delayed hypersensitivity reactions and further studies will be needed.

Importantly, this case demonstrates that rituximab desensitization can also be effective for delayed non-IgE mediated reactions, such as serum sickness. While treatment with steroids before and after desensitization is not commonly used in desensitization procedures for IgE mediated drug allergy, it may play a role in desensitization protocols for serum sickness hypersensitivity reactions. This case report has several limitations including the limited sample size and the retrospective nature of the analysis. However, this protocol was successfully repeated 25 times without adverse events and there have been no previous desensitization protocols for serum sickness reported. Further validation of this protocol would require a larger patient series with serum sickness hypersensitivity reactions to confirm the safety and efficacy of this protocol.

CONCLUSION

In conclusion, although rituximab desensitization has not been previously used for the treatment of non-IgE mediated drug reactions, our protocol represents the first successful desensitization procedure for serum sickness with monoclonal antibodies in a high risk patient. It remains to be determined whether these patients will require pre and post-desensitization treatment with steroids which will need to be evaluated in future prospective studies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT CONSENT

Declared none.

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