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Case report

Rituximab-induced serum sickness in multiple sclerosis patients

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ABSTRACT

Rituximab is a chimeric anti-CD20 monoclonal antibody that is an effective therapy for multiple sclerosis. Rituximab has been associated with the development of serum sickness (type III hypersensitivity) characterized by arthralgia, fever, and rash during the treatment of other conditions, such as rheumatoid arthritis. Here we describe serum sickness associated with rituximab in multiple sclerosis patients and discuss both the management of serum sickness itself and implications for utilizing alternative anti-CD20 monoclonal antibodies for disease management in this patient population.

1. Introduction

Rituximab, a chimeric anti-CD20 monoclonal antibody that depletes B cells, is approved and has been used for over 25 years to treat hematologic malignancies, rheumatoid arthritis, and other rheumatological disorders. It has also been shown to be an effective therapy for multiple sclerosis (MS) and is increasingly used off-label in clinical practice. This extensive clinical experience has allowed for a broader understanding of adverse events associated with rituximab. Reactions occurring during or immediately following rituximab infusion are common and are thought to be caused by cytokine release in response to the murine portion of the antibody or B-cell lysis. Characteristic symptoms include fever, chills, flushing, pruritis, tachycardia, and rash. Rituximab-induced serum sickness (RISS) is an uncommon consequence of infusion with presentation typically 7–14 days post-infusion (Karmacharya et al., 2015). Serum sickness (type III hypersensitivity) is thought to result from anti-drug antibodies (ADA) against rituximab that subsequently form immune complexes that deposit into tissues and cause activation of the complement cascade. Typical symptoms in patients who develop RISS include a triad of arthralgia (73%), fever (79%), and rash (70%), with all three occurring in about 50% of patients (Karmacharya et al., 2015). Laboratory findings such as elevated CRP and ESR, and reduced complement levels are variably present; RISS remains a clinical diagnosis. While RISS has been described in the setting of treatment of other diseases, we describe here five cases of this complication in MS patients.

2. Case report

A 69-year-old woman with MS was previously treated with glatiramer acetate, fingolimod, and dimethyl fumarate. She was switched to rituximab after having new lesions on MRI. The first 1000 mg rituximab infusion was well-tolerated. Two months later she was reinfused with 500 mg as her CD20 positive cells were incompletely depleted (130 cells/uL). This infusion was also well-tolerated. Seven days after the second infusion she presented with facial and bilateral hand swelling, diffuse arthralgias, an erythematous macular rash on her torso, and a low-grade fever. No infectious etiology was found. CRP and ESR were elevated. Complement levels were normal. Anti-drug antibody (ADA) level was > 5000 ng/ml. RISS was diagnosed. She improved clinically after one 40 mg dose of prednisone and completed a 5-day course. She was then off disease modifying therapy until being restarted on glatiramer acetate after two new lesions were found on a follow-up MRI.

Four additional MS patients with RISS were identified at our institutions, with details for all patients presented in Table 1.

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Table 1

Characteristics of Rituximab-induced Serum Sickness (RISS) in MS patients: Patient = patient age and gender; DMT = disease-modifying therapy; Infusion # = infusion of rituximab during which RISS occurred; Reaction Hx = prior reaction to rituximab infusion; Day of RISS = day after infusion patient presented with RISS; Y = yes, N = no; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; C3 / C4 = complement proteins C3 & C4, ↑ = elevated, nml = normal, n/a = test not performed; ADA = anti-rituximab antibodies detected; Post-RISS DMT = therapy patient was switched to following RISS; Recurrent SS = serum sickness occurrence with later infusion of an anti-CD20 monoclonal antibody.

Case	Patient	Prior DMT	Infusion #	Reaction Hx	Day of RISS	Fever	Rash	Arthralgia	CRP	ESR	C3 / C4	ADA	RISS Treatment	Outcome	Post-RISS DMT	Recurrent SS
1	69 F	glatiramer acetate, fingolimod, dimethyl fumarate	2	none	7	Y	Y	Y	↑	↑	nml	Y	oral prednisone 40 mg × 5 days	Symptom improvement after starting prednisone	glatiramer acetate	n/a
2	50 F	interferons, daclizumab, dimethyl fumurate, glatiramer acetate, fingolimod, natalizumab	2	pruritis & urticaria	11	N	Y	Y	n/a	n/a	n/a	Y	none	Gradual resolution over weeks	ocrelizumab	N
3	31 M	dimethyl fumurate	1	no prior infusion	14	Y	Y	Y	↑	↑	n/a	Y	none	Gradual resolution over weeks	fingolimod	n/a
4	27 F	none	1	no prior infusion	10	Y	Y	Y	n/a	n/a	nml	N	IV methylprednisolone 500 mg × × 3 days, then oral prednisone for 10 days	Sustained improvement only after 3 doses of IV methylprednisolone	ofatumumab	N
5	31 F	glatiramer acetate, fingolimod	1	no prior infusion	7	Y	Y	Y	nml	nml	nml	n/a	IV methylprednisolone	Symptom improvement after starting methylprednisolone	natalizumab	n/a

Note that all patients received pretreatment with acetaminophen, diphenhydramine, and methylprednisolone prior to rituximab infusion.

3. Discussion

Given the increasing use of rituximab and other anti-CD20 monoclonal antibodies in clinical MS practice, all neurologists should be aware of RISS (and its distinction from infusion reactions) as a complication. RISS remains a clinical diagnosis. 4/5 (80%) patients presented here had the associated triad of symptoms (fever, rash, and arthralgias), with one patient lacking a fever. It is notable that two patients developed RISS after a second infusion while the other three developed RISS after a single infusion. The significance of this, however, remains unclear, but it does suggest that RISS may occur early in the treatment process. There is variability in the lab presentation (Table 1); clinicians must be aware that RISS can be diagnosed without supportive laboratory findings. RISS was not diagnosed at time of treatment in two of these patients, which indicates a possible lack of awareness. It is important to identify RISS, and to treat it promptly with non-steroidal anti-inflammatories, antihistamines, and/or corticosteroids. In all the treated patients RISS resolved quickly. Other diagnoses that must be considered include viral exanthema, hypersensitivity vasculitis, reactive arthritis, and drug rash with eosinophilia and systemic symptoms (DRESS).

It is generally thought that generation of ADA is necessary for serum sickness associated with monoclonal antibodies. However, at least generally speaking, the presence of ADA alone is not sufficient for RISS; in the rheumatoid arthritis population, only a small minority of patients with ADA ever develop RISS (Edwards et al., 2004). Overall, the factors that contribute to immune-complex formation and downstream complement activation and immunogenicity remain unclear. How this relates to MS patients is unclear, but approximately 20% of MS patients treated with rituximab have ADA (Dunn et al., 2018). Further, while one of our two patients with prior exposure to rituximab before presenting with RISS had a history of infusion reaction, broader data on the use of rituximab in other diseases does not suggest a link between prior reaction and RISS (3/33 or 9% patients had prior reactions), despite possible overlapping immune mechanisms (Karmacharya et al., 2015). Note that in case 4 ADA were not detected despite clinical evidence of serum sickness; ADA may not always be detectable in cases of RISS due to consumption of the antibody by excess antigen (i.e., rituximab present in the serum). Other antibodies, including rheumatoid factor and anti-ribonucleoprotein which were detected in case 4, may also play a role.

Repeat infusions of rituximab after RISS may be inappropriate due to recurrent episodes of serum sickness. Due to the need for ongoing therapy in MS patients, the question of the safety of other anti-CD20 monoclonal antibodies for these patients remains. As a more fully humanized antibody, ocrelizumab should be less immunogenic than the chimeric rituximab, although the two antibodies bind to a nearly identical epitope within CD20 (Klein et al., 2013). Potentially, a patient who wishes to continue with anti-B-cell therapy may fare better with a fully human anti–CD20 therapy, ofatumumab, which is approved for chronic lymphocytic leukemia, and has been explored in Phase II trials for MS (Bar-Or et al., 2018). Notably, ofatumumab binds to an epitope on CD20 with no overlap with the epitope interacting with rituximab and ocrelizumab (Bar-Or et al., 2018). While not conclusive, it is notable that both patients who switched to an alternative anti-CD20 therapy, one with, and one without, significant overlap of CD20 epitopes, tolerated exposure without development of RISS. Finally, ADA is an all-encompassing term and functional properties of different ADAs remain to be characterized. ADAs to the chimeric portion of rituximab (anti-chimeric antibodies) may in theory cross-react against other chimeric monoclonal antibodies which has potential implications for alternate therapies.

It is our goal that reporting these cases of RISS raises awareness of this potentially serious complication and its treatment. Future studies are needed to identify patients who may be at increased risk of RISS and if other anti-CD20 monoclonal antibodies are also associated with

serum sickness.

Declaration of Competing Interest

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