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Rituximab-induced serum sickness: A systematic review

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ABSTRACT

Objectives: To report a case of rituximab-induced serum sickness (RISS) and perform a systematic review and characterize RISS in autoimmune diseases and hematological malignancies.
Methods: A comprehensive search of MEDLINE, EMBASE, ACR, and EULAR databases was performed for relevant articles of patients with RISS from inception to September 2014. Statistical analysis of demographic and clinical features was performed using Microsoft EXCEL 2007 and SPSS version 20.0.
Results: In the 33 patients with RISS, the mean age of presentation was 39.1 $\pm$ 17.5 yr with a female preponderance (n = 23, 76.67%). The majority of cases were associated with an underlying rheumatologic condition (n = 17, 51.5%), most commonly Sjögren's syndrome (n = 8, 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 rituximab 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). Corticosteroids were the most commonly used treatment (n = 21), with all cases reporting a complete resolution of symptoms in 2.15 $\pm$ 1.34 d.
Conclusion: It is important to recognize RISS clinically, as it may mimic exacerbation of various rheumatologic conditions. Although RISS is typically self-limited, further infusions of rituximab should be avoided, as it may provoke more severe symptoms.

Background

Rituximab is a chimeric monoclonal IgG1 antibody that binds to the CD20 molecule expressed on B lymphocytes; it leads to rapid cell lysis and has been frequently used to treat various autoimmune diseases in which B cells are participants [1], and for hematological malignancies in which CD20-bearing cells are increased (e.g., B-cell lymphoma) [2–5]. While it is approved for the treatment of patients with rheumatoid arthritis (RA) [6] and ANCA-associated vasculitis [7–9], rituximab has also been used in an off-label manner for the treatment of many other autoimmune conditions including Sjögren's syndrome [10–12] and idiopathic thrombocytopenic purpura (ITP) [13–18].

The administration of rituximab is commonly associated with general infusion reactions, including fever, chills, and rigors, as well as allergic (Type IV) anaphylactoid spectrum reactions such as urticaria, angioedema, and hypotension [19–21]. Symptoms typically occur during infusions, are most frequent and severe in relationship to the first infusion of the drug, and are more frequently seen in patients with hematologic malignancies than autoimmune disease [19]. The concurrent administration of corticosteroids and antihistamines with rituximab decreases the occurrence of these infusion reactions, and the symptoms can sometimes be reduced with slower infusion rates. Because these reactions often occur with first dose, it has been hypothesized that these represent reactions that are due to complement activation and mast cell degranulation in the setting of rapid cell lysis, rather than preformed Immunoglobulin (Ig) E against the molecule [22]. Serum sickness (or Type III) hypersensitivity reactions have been described less commonly in patients with rheumatoid arthritis

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receiving rituximab [19]. In contrast to infusion reactions described above, serum sickness reactions are the result of immune activation against the infused agent, and take significantly longer (7–21 d) to mobilize. Symptoms include fever, rash, and polyarthralgia or arthritis, which are potential mimics of the very diseases they are used to treat. Serum sickness reactions typically represent host immune responses mediated through complement-fixing IgM and IgG antibodies directed toward an immunogenic portion of a drug [13]. In an individual who has presented with presumed serum sickness to a drug, re-exposure can result in recurrent and more severe manifestations [12].

The pathogenesis of serum sickness with rituximab remains unclear. Serum sickness has been described in individuals with concomitant hypergammaglobulinemia and rheumatoid factor positivity, leading some to speculate about the potential pathogenic IgM rheumatoid factor-rituximab complexes [19,22,23]. However, the presence of RF and hypergammaglobulinemia are general characteristics of RA, Sjögren's syndrome, and other autoimmune conditions in general. In this report, we describe a patient with RA, who developed serum sickness 7 d following the first rituximab infusion as well as systematically review and analyze the English literature on this subject.

Case

A 57-year-old female with longstanding seropositive [RF positive, anti-cyclic citrullinated peptide (CCP) antibody negative] RA presented to the emergency department with a 1-day history of low-grade fever, pruritic maculopapular rash all over her body, and diffuse joint pains. The patient noted that the rash covered her face, scalp, trunk, and both upper and lower extremities. It did not involve her mucous membranes or her palms and soles. She did not report dyspnea, chest pain, angioedema, abdominal pain, or loose stools. She received her first infusion of rituximab 1000 mg for the treatment of RA 7 d prior, during which she experienced mild rigors that were relieved with diphenhydramine. She received pretreatment with acetaminophen and antihistamines; however, she had not received corticosteroid premedication. Her baseline medications included methotrexate 25 mg by mouth once weekly and hydroxychloroquine 200 mg twice daily for her treatment of active, refractory RA. She had previously failed multiple tumor necrosis factor (TNF) inhibitors, and she reported no history of infusion or injection reactions related to TNF inhibitors. Her medical history included a diagnosis of active pulmonary TB, necessitating a 7-month course of anti-tubercular therapy, which was completed 2 mo prior to presentation.

Physical examination revealed a temperature of 38.4°C, heart rate 87 beats/min, and blood pressure 123/69 mmHg. There was maculopapular skin eruption located over her face, scalp, trunk, and both upper and lower extremities. There was no parotid gland enlargement or lymphadenopathy. Her musculoskeletal examination revealed active synovitis in the metacarpophalangeal and proximal interphalangeal joints bilaterally. She has bilateral knee and left elbow replacements and bilateral ankle and wrist fusions. The remainder of her physical examination was unremarkable.

Laboratory parameters revealed a white blood cell count of 9710/mm^3, hemoglobin 8.9 g/dL (baseline = 9.0 g/dL) and platelet count 25,000 mm^3 (baseline = 30,000 mm^3). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 54 mm/h and 9.6 mg/L, respectively. Blood chemistries and liver function tests were within the normal range. Complements were low with C3 level of 57 mg/dL (79–152 mg/dL), C4 level 8 mg/dL (12–42 mg/dL) and CH_{50} 40 U/mL (31–60 mg/dL). Total IgM level was slightly decreased at 43 mg/dL (46–30 mg/dL) with normal levels of IgG of 1470 mg/dL (751–1560 mg/dL) and IgA 647 mg/dL (82–453 mg/dL). Urinalysis showed no proteinuria or hematuria. Blood culture and urine cultures were negative.

Diagnosis of rituximab-induced serum sickness (RISS) was made on the basis of her classic clinical trial of fever, rash, and arthralgia 7 d following a rituximab infusion. Her symptoms resolved spontaneously over the next 2 d and she did not require corticosteroids at the time of discharge. She was advised to avoid further therapy with rituximab.

Literature review

Search strategy and data collection

A systematic electronic search of MEDLINE, EMBASE, ACR, and EULAR for case reports, case series, and clinical trials reporting serum sickness associated with rituximab published from inception to September 2014, was performed using 2 broad search themes which were combined using Boolean operator "AND." For the search theme "Rituximab," the following search words were used: "rituximab," "CD20 antibody," "Mabthera," "Rituxan," "anti-CD20," and "anti-CD20" and for the theme "serum sickness," the terms used were: "Serum Sickness," "hypersensitivity," " type 3," and "type III." To minimize data duplication as a result of multiple reporting, we compared papers from the same author. Search was limited to English-language articles. Two authors (P.K. and D.R.P.) screened and retrieved reports and excluded irrelevant articles. Relevant data were extracted by 2 authors (P.K. and D.R.P.) and checked by another (S.G.). Additional investigator (R.P.) participated in the review process when uncertainty about eligibility criteria arose. Categorical variables are expressed as percentage and continuous variables as mean ± SD. Continuous variables were compared using *t* test and categorical variables using chi-squared tests. Independent *t* tests were used to compare differences in time to onset and time to resolution of RISS between 1000 mg vs. 375 mg/m^2, first vs. second treatment cycle, first vs. second dose of rituximab in the first cycle, and autoimmune vs. hematologic malignancies as an indication for rituximab.

Statistical analysis was carried out using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY). We used a 2-sided $P < 0.05$ to assess for statistical significance.

Results

Demographics and clinical presentation

We identified 33 cases of RISS from 25 articles (Fig.). The demographic variables, clinical presentations, laboratory data, associated conditions, response to treatment, and long-term outcomes were abstracted (Table). Significant female preponderance was seen (male vs. female, 23.3% vs. 76.7%, $P = 0.004$). Mean age of presentation was 39.1 ± 17.5 yr. The majority of the serum sickness cases were associated with an autoimmune condition ($n = 28$, 84.85%) [10–12,19,21–30], with immune thrombocytopenic purpura ($n = 10$) [13–18,20] most frequently reported followed by Sjögren's syndrome ($n = 7$) [10–12,27,29,30]. Other autoimmune conditions were cryoglobulinemia ($n = 3$) [23,24], polyclonal hypergammaglobulinemia ($n = 2$) [22], RA ($n = 1$) [19], mixed connective tissue disease (MCTD) ($n = 1$) [26], and autoimmune polyneuropathy ($n = 1$) [25]. In a case, it was given for acute cellular and humoral rejection following renal transplantation [28]. RISS was associated with a hematologic malignancy in 5 of the 33 cases (15.15%), which were all lymphomas [2–5]. Also 2 cases of Sjögren's syndrome had salivary mucosa-associated