Case Report

Serum Sickness Following Treatment with Rituximab

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ABSTRACT. Serum sickness, an illness characterized by fever, rash, and arthralgias, can occur in patients who receive chimeric monoclonal antibody therapy. Rituximab, a B cell-depleting chimeric anti-CD20 monoclonal antibody, has been used with increasing frequency in the treatment of rheumatologic illnesses such as rheumatoid arthritis and systemic lupus erythematosus. Serum sickness has only rarely been reported following rituximab therapy. All prior reported cases have been in patients with autoimmune conditions. We describe a case of serum sickness in a patient treated with rituximab for mantle cell lymphoma. We also review the literature of rituximab-induced serum sickness. (First Release Jan 15 2007; J Rheumatol 2007;34:430–3)

Key Indexing Terms:
SERUM SICKNESS RITUXIMAB ARTHRITIS
CASE REPORT ADVERSE DRUG REACTION

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tissue damage on being deposited in target tissues, recruiting complement and activating mast cells and phagocytes. Serum sickness usually presents 10–14 days following primary antigen exposure or within a few days of secondary antigen exposure. Symptoms include fever, rash, and arthralgias. On occasion an overt arthritis can develop. Inflammatory markers are typically elevated, and serum complement concentrations may be depressed. The reaction is typically self-limited; corticosteroids provide rapid and complete relief of symptoms[1].

Historically, serum sickness has been described following administration of anti-toxin or anti-venom. More recently, serum sickness has been reported in patients receiving biologic immunotherapy with agents such as anti-thymocyte globulin (ATG), infliximab, and rituximab[2-4]. Rituximab, a partially humanized murine anti-CD20 monoclonal antibody, was developed to treat B cell lymphoma. It has also been shown to be beneficial in autoimmune conditions[5]. The US Food and Drug Administration recently approved rituximab, in combination with methotrexate, for the treatment of moderate to severe, active rheumatoid arthritis (RA) in patients with inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. During infusion, rituximab may cause rash, pruritus, dyspnea, and even hypotension. These symptoms are related to cytokine release from targeted cells, not circulating antigen-antibody complexes[6]. In contrast, serum sickness from rituximab has only rarely been reported. We describe a case of serum sickness that manifested as fever, rash, and polyarthritis occurring 13 days after a single dose of rituximab for B cell lymphoma. We also review the literature regarding rituximab-induced serum sickness. To our knowledge, this is the first documented case of serum sickness in a patient who received rituximab for a hematologic malignancy.

CASE REPORT

A 68-year-old man with stage 2A mantle cell lymphoma presented with the abrupt onset of severe polyarthralgias and joint swelling 13 days after receiving a single treatment of cyclophosphamide, vincristine, prednisone, and rituximab (375 mg/m^2) chemotherapy. Involved joints included the shoulders, elbows, wrists, metacarpal phalangeal (MCP) joints, hips and knees. He described a concurrent pruritic rash but felt otherwise well. He also had a history of hypertension, hypercholesterolemia, and a single prior episode of podagra that was never crystal-proven as gout. Medications on admission included hydrochlorothiazide, lisinopril, and rosuvastatin. He had no known environmental exposures. He denied neurological, ocular, cardiopulmonary, gastrointestinal, or genitourinary complaints. Examination revealed a nontoxic, normotensive male with a temperature of 100.8°F. He had erythema, warmth, and effusion of his elbows, wrists, MCP, and knees, with markedly reduced range of motion in these joints as well as both shoulders and hips. A blanching, erythematous, macular rash was present over his precordium and both ventral forearms. The remainder of his examination was normal.

Laboratory values were notable for a white blood cell count (WBC) 1.8 × 10^3 cells/mm^3 with 32% neutrophils and 36% band forms, hemoglobin 12.4 mg/dl, platelet count 3.2 × 10^5 cells/mm^3, albumin 3.7 g/dl, erythrocyte sedimentation rate 117 mm/h, C-reactive protein (CRP) 433 mg/l, uric acid 5.1 mg/dl, CH50 238 U/ml, C3 135 mg/l, C4 29 mg/l. In addition, antinuclear antibody (ANA), rheumatoid factor, and anti-cyclic citrullinated peptide antibodies were all within normal ranges. Serum anti-streptolysin O antibody was not elevated. He had no serologic evidence of acute infection with parvovirus B19, Epstein-Barr virus, or cytomegalovirus. Human anti-chimeric antibody (HACA) to rituximab was not detected by commercial laboratory assay (Prometheus® Therapeutics and Diagnostics, San Diego, CA, USA). Urinalysis was normal. Arthrocentesis of the right knee yielded 50 cc of synovial fluid with 9270 WBC/mm^3 (92% neutrophils), and arthrocentesis of the left knee yielded 20 cc of fluid with 4450 WBC/mm^3 (71% neutrophils).

Supported by National Institutes of Health Training Grant T32AR007530-21.

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Accepted for publication October 11, 2006.

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Neither sample demonstrated monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals when examined under polarized light microscopy by one author (DJT) and 2 other independent rheumatologists.

Our patient received empiric intravenous antibiotics for suspected polyarticular septic arthritis. Indomethacin was given for pain control, and corticosteroid therapy was initially deferred. Cultures of blood and synovial fluid yielded no organisms, and antibiotics were discontinued after 48 hours. He was discharged home on indomethacin monotherapy. Three days later, he returned to his oncologist with persistent polyarthritis. Arthrocentesis of the right knee yielded 100 cc of fluid with 1297 WBC/mm^3. There was no evidence of MSU or CPPD crystals, and fluid culture yielded no microorganisms. He received intraarticular methylprednisolone (80 mg) and concurrent oral prednisone (20 mg daily). His symptoms rapidly and completely resolved such that within 24 h he was able to shovel snow without difficulty. Prednisone was tapered over a 4-week period without recurrence of symptoms. He has remained completely symptom-free for over 4 months following completion of the course of corticosteroids.

DISCUSSION

This case has several features consistent with rituximab-induced serum sickness. First, clinical presentation was classic for serum sickness: fever, rash, and inflammatory polyarthritis about 2 weeks following chimeric antibody administration[1]. Second, his symptoms responded briskly and completely to corticosteroids but not to indomethacin. Third, and most important, there was little evidence to support infectious, microcrystalline, or other inflammatory causes for his illness. Thorough microbiologic investigations failed to reveal an offending microorganism. He had no MSU or CPPD crystals visible in synovial fluid, and there was no firmly established history of microcrystalline disease. Serologic investigations for RA, systemic lupus erythematosus (SLE), and post-streptococcal reactive arthritis were negative. His leukopenia and concurrent bandemia were likely explained by the exposure to chemotherapy with evolving bone marrow recovery. A serum sickness-like reaction has not been associated with any of the patient's other medications. Rarely, hydrochlorothiazide, statins, and angiotensin-converting enzyme inhibitors have been associated with drug-induced lupus, but the patient's negative ANA test essentially eliminates this possibility[7].

Interestingly, C3 and C4 levels were not elevated despite a markedly elevated CRP, another acute-phase protein. Also notable was absence of HACA during the acute phase of illness. Although HACA levels may be elevated in patients with monoclonal antibody-induced serum sickness, it is not diagnostic of the condition. HACA may have been undetectable because excessive amounts of antigen (i.e., rituximab) consumed completely any HACA present. In addition, serum sickness does not occur in the majority of rituximab-treated patients who develop elevated HACA[5].

Rituximab-induced serum sickness has been reported to occur in hepatitis C virus (HCV)-induced cryoglobulinemia[8], as well as a variety of autoimmune conditions including SLE, antiphospholipid antibody syndrome, immune thrombocytopenic purpura (ITP), autoimmune polyneuropathy, and Sjögren's syndrome (Table 1)[4,9-11]. Only one of these cases documented the presence of HACA[4], and complement levels were not universally depressed[10]. Three of 7 cases report serum sickness following primary exposure to rituximab. Six of 7 patients in these case reports were women, although it is likely that the apparent gender bias is attributable to the increased prevalence of these autoimmune conditions in women as opposed to an increased risk of rituximab-induced serum sickness. There is, for example, no such gender bias in patients who develop ATG-related serum sickness when treated for myelodysplastic syndrome[2].

To our knowledge, this is the first published report of serum sickness in an individual treated with rituximab for a hematologic malignancy. Serum sickness was not reported as an adverse event in the early large clinical trials of rituximab in B cell lymphoma, and HACA were detected in only 1% of these patients[12,13]. Serum sickness was also not reported as an adverse event in a large randomized trial investigating the clinical efficacy of rituximab in RA, although 5 out of 117 (4.3%) rituximab-treated patients developed HACA[5]. However, rituximab-induced serum sickness may occur more frequently in patients who receive rituximab for other autoimmune conditions.

Table 2 summarizes 3 clinical trials in which serum sickness was reported as an adverse event in patients receiving rituximab for pediatric chronic ITP or Sjögren's syndrome. Rates of serum sickness ranged from 6% to 20%[14-16]. To explain the disparate rates of serum sickness in RA compared to other autoimmune conditions, we postulate that rituximab-induced serum sickness may be underrecognized in patients with RA because of the clinical similarities between serum sickness and an exacerbation of RA.

Several factors may explain why rituximab causes serum sickness more frequently in patients treated for autoimmune conditions when compared to those treated for hematologic malignancies. It is conceivable that altered immune responses to foreign antigens may predispose patients with autoimmunity to develop rituximab-induced serum sickness. More likely, however, the humoral immune events that can lead to serum sickness are suppressed in cancer patients, who often receive concurrent cytotoxic chemotherapy with rituximab. Humoral immunity appears to be impaired in patients newly immunized with pneumococcal, *Hemophilus influenza* B, or hepatitis B vaccines during or immediately following chemotherapy for hematologic malignancies. Most of these patients fail to mount adequate *de novo* antibody responses[17]. A small subset of patients do generate antibodies, however, suggesting that cytotoxic chemotherapy does not completely abrogate adaptive humoral immunity in all patients[17]. The heterogeneity of immune impairment following cytotoxic chemotherapy may explain the development of serum sickness in our case.

The diagnosis of rituximab-induced serum sickness best explains this patient's clinical presentation, laboratory data, and treatment response. All prior reports of this entity occurred in patients with autoimmune conditions. Our case

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Table 1. Case reports of serum sickness following treatment with rituximab.

Age/sex	Condition	Rituximab Dosing, mg/m^2	No. of Treatments Prior to Serum Sickness	Symptoms	Days Since Last Rituximab Treatment	Reference
45 M	AIP	NA	1	Fever, rash, arthritis	10	4
60 F	HCV-related cryoglobulins	375, one dose	1	Fever, rash, arthralgias	7	8
28 F	SLE	375 wkly × 4	1 and 3	Rash, arthralgias	2	9
28 F	SLE, ITP, APS	375 wkly × 4	2, 3, and 4	Fever, rash, arthralgias	NA	9
43 F	SS, MALT lymphoma	375 wkly × 4	2 and 3	Fever, rash, arthralgias	NA	9
23 F	SLE, ITP	NA	2	Fever, rash, arthralgias	1–2	10
48 F	ITP	NA	2	Fever, rash, arthritis	6	11

NA: data not available; AIP: autoimmune polyneuropathy; APS: anti-phospholipid antibody syndrome; HCV: hepatitis C virus; ITP: immune thrombocytopenic purpura; MALT: mucosal associated lymphoid tissue; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome.

Table 2. Clinical trials reporting serum sickness following rituximab usage.

Condition	Rituximab Dosing, mg/m^2	Cases of Serum Sickness (%)	Age/Sex	No. of Treatments Prior to Serum Sickness	Days Since Last Rituximab Treatment	Reference
Pediatric chronic ITP	375 × 4	2/36 (6)	12 M	2	NA	14
			11 F	2	NA	
Adult SS	375 × 4	3/15 (20)	41 F	2	5–7	15
			39 F	2	5–7	
			27 F	2	5–7	
Pediatric chronic ITP	375 × 4	3/24 (13)	14 F	2	NA	16
			12 F	3	NA	
			12 F	1	NA	

NA: data not available; ITP: idiopathic thrombocytopenic purpura; SS: Sjögren's syndrome.

highlights that rituximab can cause serum sickness in patients treated for hematologic malignancies as well. Importantly, serum sickness remains a clinical diagnosis based on the triad of fevers, rash, and arthralgias occurring in the appropriate timeframe following antigen exposure. As in this case, infectious, neoplastic, and other inflammatory conditions must be excluded. The utility of testing for complement levels or HACA to diagnosis serum sickness remains unclear. With the increasing usage of rituximab in autoimmune conditions such as RA and SLE, clinicians should be alert for serum sickness as a possible adverse reaction to treatment.

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