A Case of Rituximab-Induced Acute Thrombocytopenia in a Patient with Splenic Marginal Zone Lymphoma and Chronic Hepatitis C Virus Infection

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Patient: Female, 46
Final Diagnosis: Rituximab induced acute thrombocytopenia
Symptoms: Abdominal discomfort
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Adverse events of drug therapy
Background: Rituximab is a chimeric monoclonal antibody to CD20 that is used to treat vasculitis, B-cell lymphoproliferative disorders, and B-cell non-Hodgkin lymphoma (NHL). A report is presented of a case of rituximab-induced acute thrombocytopenia (RIAT) in a woman with splenic marginal zone lymphoma (SMZL) and chronic hepatitis C virus (HCV) infection.

Case Report: A 46-year-old woman with SMZL complicated by chronic HCV infection presented with worsening B symptoms of fever, night sweats, and loss of weight. The patient had a history of recreational drug use. Intravenous treatment with rituximab (dose, 375 mg/m²) commenced with close monitoring in hospital. On the following day, the complete blood count (CBC) showed that her platelet count had dropped from her admission level of 167,000/μl to 7,000/μl, with no change in hemoglobin or white blood cell (WBC) levels. A diagnosis of RIAT was made. The patient was managed conservatively and monitored for the development of potential clinical complications.

Conclusions: RIAT is a rare complication of treatment with rituximab and may be poorly recognized. Further studies are needed to determine the incidence and causes of thrombocytopenia in patients treated with rituximab and the possible association with chronic viral infections, including HCV.

MeSH Keywords: Antibodies, Monoclonal, Murine-Derived • Drug-Related Side Effects and Adverse Reactions • Hepatitis C, Chronic • Lymphoma, B-Cell, Marginal Zone • Thrombocytopenia

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Rituximab is a chimeric monoclonal antibody to CD20 that has been widely used since its approval by the US Food and Drug Administration (FDA) in 1997 to treat vasculitis, B-cell lymphoproliferative disorders, and B-cell non-Hodgkin lymphoma (NHL) [1–3]. The use of rituximab has been reported to result in reactivation of hepatitis B virus (HBV) in a patient with carrier status, resulting in hepatic failure [4]. A previously reported multicenter study identified a significant risk of severe hepatotoxicity with rituximab infusion in patients with chronic hepatitis C virus (HCV) infection [5]. Rituximab-induced acute thrombocytopenia (RIAT) has been previously described as the occurrence of thrombocytopenia following rituximab infusion [6–8]. A report is presented of a case of RIAT in a woman with splenic marginal zone lymphoma (SMZL) and chronic HCV infection.

### Case Report

A 46-year-old woman with a diagnosis of splenic marginal zone lymphoma (SMZL) presented with a one-week history of drenching night sweats, abdominal pain, myalgia, fatigue, and flu-like symptoms. The patient had a history of recreational drug use. She reported significant unintentional weight loss over several months. She had been diagnosed with SMLZ four months previously and was diagnosed with chronic hepatitis C virus (HCV) infection. Initially, the plan was to treat the patient for chronic HCV infection, followed by an assessment of the status of her SMZL before considering rituximab and chemotherapy. Because of the known risk associated with the use of rituximab in patients with chronic HCV infection, the initiation of therapy with rituximab was a cause for concern. The gastroenterology service was consulted to provide the patient with an HCV treatment plan. However, the patient continued to use illicit drugs and was found to have positive urine drug screen results for methamphetamine and marijuana, which disqualified her for a chronic HCV treatment plan.

On physical examination, she was found to have hepatosplenomegaly without palpable lymphadenopathy. A complete blood count (CBC) showed a platelet count of 179,000/μl, hemoglobin of 7.9 g/L, and white blood cell (WBC) count of 4,200/μl, which were similar to previous values. A screen for human immunodeficiency virus (HIV) infection was negative, and her liver function tests were normal. Computed tomography (CT) imaging of the abdomen showed an enlarged spleen (craniocaudal diameter, 27 cm) and liver (craniocaudal diameter, 20 cm), and the liver was homogenous in appearance. Mesenteric and retroperitoneal lymphadenopathy was present. Given the severity of her symptoms, the imaging findings, and anticipated delays for HCV treatment, the decision was made to begin treatment with rituximab, without chemotherapy, and with inpatient monitoring. Treatment began with intravenous rituximab at a dose of 375 mg/m², with pre-treatment that included dexamethasone 10 mg and oral diphenhydramine 50 mg once daily. She was treated with oral naproxen 500 mg bd for generalized pain.

On the day following the start of rituximab infusion, a repeat CBC showed that the platelet count had dropped from her admission level of 167,000/μl to 7,000/μl, with no change in hemoglobin or WBC levels. Peripheral blood smears were also examined before and after transfusion with rituximab (Figures 1, 2). During the next 12 hours, the patient was transfused with 1 unit of platelets, which raised her platelet count to 24,000/μl. No site of bleeding was identified, and the patient was hemodynamically stable. No heparin had been given during the previous 30 days, which excluded a diagnosis of heparin-induced thrombocytopenia (HIT). An antinuclear antibody panel test was negative.

During the week following platelet transfusion, her platelet counts increased, returning to 139,000/μl at the end of one week. Acute severe thrombocytopenia was suspected to be drug-induced, and the drugs considered included naproxen, diphenhydramine, acetaminophen, and rituximab. The pharmacy records showed that the patient had been previously treated with diphenhydramine, acetaminophen, and naproxen, but this...
was the patient’s first exposure to rituximab. Laboratory tests using flow cytometry were performed to identify drug-associated anti-platelet antibodies. In the flow cytometry method, the patient’s serum was incubated with normal group O target platelets in the presence and absence of drug-bound immunoglobulins, and the fluorescence values obtained in the presence and absence of drug were compared. A fluorescence ratio of ≤2.0 was the cutoff for the detection of drug-dependent antiplatelet antibodies. IgM and IgG antiplatelet antibodies for diphenhydramine, acetaminophen, naproxen, and rituximab were negative.

A diagnosis of rituximab-induced acute thrombocytopenia (RIAT) was made. The patient was managed conservatively and monitored for the development of potential clinical complications.

**Discussion**

This report presented a case of rituximab-induced acute thrombocytopenia (RIAT) in a 46-year-old woman with splenic marginal zone lymphoma (SMZL) who had a history of chronic hepatitis C virus (HCV) infection. A previously reported cohort study on the mechanisms involved in RIAT showed an incidence of 3% in clinical trials, but in a post-marketing drug study, the incidence was higher, at 20% with a platelet count of <49,000/μl within 30 days following rituximab infusion [6,7]. Giezen et al. showed that most cases of RIAT occurred within the first ten days after rituximab administration [7]. In 2018, a case report of RIAT and review of the literature published by Omura et al. found that acute thrombocytopenia could occur with rituximab reinfusion, but the incidence and the factors involved in recurrence remain unknown [8]. Ram et al. reported that most cases of RIAT developed on average at 19 hours after rituximab infusion and spontaneous resolution of thrombocytopenia occurred at an average of four days [9].

The mechanisms involved in the development of RIAT remain to be elucidated. Proposed mechanisms include the presence of CD20 antigen (FcγRIIa) on the platelet surface [8,10], the presence of soluble anti-CD20 antigen in the plasma [11], leading to immune complex formation followed by complement activation and binding of rituximab to Cq1, resulting in the release of cytokines, including tumor necrosis factor-a (TNF-a) [9,12]. Although a previous case report identified the presence of antibodies to rituximab [9], none were detected in the serum of the patient described in the present case report. This finding suggests that a variety of possible mechanisms may lead to RIAT in individual cases. Although the effects of rituximab in our patient were self-limited, there have been previously reported significant adverse effects associated with RIAT, including epistaxis and gastrointestinal bleeding [13,14].

**Conclusions**

This report presented a case of rituximab-induced acute thrombocytopenia (RIAT) in a woman with splenic marginal zone lymphoma (SMZL) who had a history of chronic hepatitis C virus (HCV) infection. RIAT is a rare complication of treatment with rituximab and may be poorly recognized. Further studies are needed to determine the incidence and causes of thrombocytopenia in patients treated with rituximab and the possible association with chronic viral infections, including HCV. Because rituximab treatment is often given as an outpatient, blood counts are not routinely examined after rituximab infusion but are usually obtained at weekly or monthly intervals, which means that RIAT may be under-diagnosed. Also, the remaining uncertainties about the incidence and risk factors for RIAT have significant clinical implications, including reluctance to use rituximab and to continue to treat patients with drugs that may have a worse toxicity profile.

**Conflict of interest**

None.

**References:**

1. Pierpont TM, Limper CB, Richards KL: Past, present, and future of rituximab – the world’s first oncology monoclonal antibody therapy. Front Oncol, 2018; 8: 163
2. Ramos-Casals M, Garcia-Hernandez FJ, de Ramon E et al: Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol, 2010; 28(4): 468–76
3. Storz U: Rituximab: How approval history is reflected by a corresponding patent filing strategy. MAbs, 2014; 6(4): 820–37
4. Tsutsumi Y, Yamamoto Y, Ito S et al: Hepatitis B virus reactivation with a rituximab-containing regimen. World J Hepatol, 2015; 7(21): 2344–51
5. Ennishi D, Maeda Y, Niiitsu N et al: Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: A Japanese multicenter analysis. Blood, 2010; 116(24): 5119–25
6. Giezen TI, Mantel-Teeuwisse AK, ten Berg MJ et al: Rituximab-induced thrombocytopenia: A cohort study. Eur J Haematol, 2012; 89(3): 256–66
7. McLaughlin P, Grillo-Lopez AJ, Link BK et al: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. J Clin Oncol, 1998; 16(8): 2825–33
8. Omura Y, Shimazu H, Takahashi T: Rituximab-induced acute thrombocytopenia in a patient with follicular lymphoma: A case report and review of the literature. Intern Med, 2018; 57(8): 1151–54
9. Ram R, Bonstein L, Gafter-Gvili A et al: Rituximab-associated acute thrombocytopenia: an under-diagnosed phenomenon. Am J Hematol, 2009; 84(4): 247–50
10. Qiao J, Al-Tamimi M, Baker RI et al: The platelet Fc receptor, Fcgamma RIIa. Immunol Rev, 2015; 268(1): 241–52
11. Manshouri T, Do KA, Wang X et al: Circulating CD20 is detectable in the plasma of patients with chronic lymphocytic leukemia and is of prognostic significance. Blood, 2003; 101(7): 2507–13

12. Michelmann I, Bockmann D, Nurnberger W et al: Thrombocytopenia and complement activation under recombinant TNF alpha/IFN gamma therapy in man. Ann Hematol, 1997; 74(4): 179–84

13. Rigamonti C, Volta C, Colombi S et al: Severe thrombocytopenia and clinical bleeding associated with rituximab infusion in a lymphoma patient with massive splenomegaly without leukemic invasion. Leukemia, 2003; 15(1): 186–87

14. Thachil J, Mukherje K, Woodcock B: Rituximab-induced haemorrhagic thrombocytopenia in a patient with hairy cell leukaemia. Br J Haematol, 2006; 135(2): 273–74