Rituximab-induced Acute Thrombocytopenia in High Tumor Burden Follicular Lymphoma

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Abstract

Rituximab-induced acute thrombocytopenia (RIAT), a rare complication of rituximab administration, has not yet been described in follicular lymphoma (FL). A 65-year-old man received rituximab for the treatment of high tumor burden follicular lymphoma in the leukemic phase. The next day, his platelet count abruptly dropped from 85,000 to 5,000/μL, which spontaneously recovered in a few days without specific treatment. We speculate that the occurrence of infusion-related cytokine release syndrome in rituximab-sensitive high tumor burden FL contributed to the development of RIAT. Frequent monitoring of the platelet count is advisable for select patients considered to be at a high risk for RIAT.

Key words: rituximab, thrombocytopenia, follicular lymphoma

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Introduction

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody widely used for the treatment of B cell lymphoproliferative disorders (1). Rituximab, either as a single agent or in combination with chemotherapy, has significantly improved the survival outcome for patients diagnosed with B cell non-Hodgkin’s lymphomas (NHL) (2-4). The administration of rituximab is well tolerated, however, it is often associated with infusion reactions that involve a fever, chills, rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension (5). These symptoms typically occur within a few hours after the start of rituximab infusion. Neutropenia, anemia and thrombocytopenia have been described as hematological toxicities that generally occur during a 10- to 14-day window after the infusion.

Rituximab-induced acute thrombocytopenia (RIAT) that occurs within a few days of rituximab administration has been rarely reported in patients with NHL (6-16). A total of 15 such cases have been reported in the literature. Interestingly, RIAT has been described almost exclusively in patients with mantle cell lymphoma (MCL) (6-14). MCL is a rare subtype of NHL, accounting for only 5% of NHL cases. Rituximab is more frequently used in patients with diffuse large B cell lymphoma (DLBCL; the most common type of aggressive NHL) and follicular lymphoma (FL; the most common type of indolent NHL) (1-3). Nevertheless, RIAT has not been described in association with these lymphoma types.

We herein report a case of RIAT that developed after rituximab administration in a patient with high tumor burden follicular lymphoma (FL).

Case Report

A 65-year-old man presented with abdominal fullness, lymphadenopathy and pedal edema. On physical examination, huge splenomegaly and generalized lymphadenopathy were noted. The hemoglobin (Hb) level was 9.1 g/dL, white blood cell count (WBC) 189,800/μL with 92% abnormal lymphocytes, and platelet count (PLT) 88,000/μL. Circulating lymphocytes were small cells with rounded to slightly irregular nuclei, which indicated lymphoma cells. A computed tomographic scan revealed systemic lymphadenopathy, pleural effusion, ascites and massive splenomegaly (22 cm in the long axis) (Fig. 1). A biopsy of the left axillary...
lymph node revealed the histologic features of grade 2 FL. Immunohistchemistry revealed that the lymphoma cells were positive for CD20, CD79a, CD10 and BCL-2 and negative for CD3 and CD5. A minority of the lymphoma cells were positive for the proliferation marker MIB-1 (-10%). Identical immunophenotypes were observed in circulating lymphocytes. A chromosome analysis revealed a t(14;18)(q32;q21) in the tumor. The presence of an IGH-BCL2 fusion gene was confirmed by a fluorescence in situ hybridization analysis. According to these findings, a diagnosis of FL in the leukemic phase was made.

After discussing treatment options, the patient was scheduled to receive cyclophosphamide (CHOP) chemotherapy (750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin and 1.4 mg/m² vincristine on day 1, and 1 mg/kg prednisolone on days 1-5) followed by rituximab. CHOP treatment brought the regression of lymph node lesions by more than 50% and the disappearance of pleural effusion, ascites and pedal edema within 2 weeks. The effect on reducing the spleen size was modest. On day 19 of CHOP chemotherapy, the patient received rituximab 375 mg/m² intravenously over 4 hours. Before the rituximab administration, the Hb level was 8.1 g/dL, WBC 12,000/μL with 87% abnormal lymphocytes, and PLT 85,000/μL. Within 2 hours, he developed infusion-related hypersensitivity reactions consisting of a fever, chill and nausea, which were resolved by 125 mg methylprednisolone administration. The next day (day 20), his PLT count abruptly dropped to 5,000/μL, which was verified on a peripheral smear and repeat complete blood count. The WBC also dropped to 2,200/μL with 59% abnormal lymphocytes, along with an asymptomatic elevation of lactate dehydrogenase from 278 to 412 IU/L (normal: 130-220 IU/L). Serum levels of uric acid (6.7 mg/dL, normal 2.5-7.0 mg/dL), potassium (4.2 mEq/L, normal 3.6-4.9 mEq/L) and creatinine (0.82 mg/dL, normal 0.4-0.7 mg/dL) were within the normal limits, arguing against the notion that thrombocytopenia developed in association with tumor lysis syndrome. The prothrombin time-international normalized ratio and the fibrinogen level were within normal limits. The fibrin/fibrinogen degradation product (FDP) level was increased from 15.2 to 38.5 μg/mL (normal <5 μg/mL), and the D-dimer level from 5.1 to 15.9 μg/mL (normal <1.0 μg/mL). The patient did not meet the diagnostic criteria for disseminated intravascular coagulation (DIC) proposed by the Japanese Ministry of Health, Labour and Welfare (17), although an increased fibrinolytic activity was observed. He received a 10-unit platelet transfusion, and the 24-hour post-transfusion PLT count was 30,000/μL. His platelet counts spontaneously recovered without treatment (Fig. 2). Rituximab was omitted from subsequent cycles of treatment to avoid a risk of life-threatening bleeding (16, 18).

**Figure 1.** 3D reconstruction from computed tomography scans showing massive splenomegaly.

RITAN has been rarely described in patients with NHL (6-16). A total of 15 such cases have been reported; 13 cases had MCL (6-14), one small lymphocytic lymphoma (15) and one lymphoplasmacytic lymphoma (16). Therefore, the mechanism of RITAN remains unclear. Given the low incidence of MCL (-5%) and widespread use of rituximab in various B cell lymphomas, the exclusive occurrence of RITAN in MCL may suggest that MCL-specific clinical and/or pathological features are involved in the pathogenesis of RITAN. RITAN has been frequently associated with infusion-related cytokine release syndrome (6, 9, 11-14) and high tumor burden lymphoma (in the leukemic phase or with massive splenomegaly) (6, 9-14). It is of interest that RITAN has been also reported in rare cases of hairy cell leukemia (a chronic B-cell lymphoid leukemia) (18) and autoimmune hemolytic anemia (19), in which splenomegaly was observed.

Despite the widespread use of rituximab in the treatment of FL, RITAN has not been reported in patients with FL. We speculate that high tumor burden, high sensitivity of FL cells to rituximab and the occurrence of infusion reactions might have contributed to the development of RITAN in our case. Our case had pleural effusion, ascites, massive splenomegaly, cytopenia, and circulating lymphoma cells, all indicating high tumor burden FL (20). Considering that massive splenomegaly is very rare in FL (21, 22), the patient appeared to bear enormous tumor burden. Furthermore, circulating lymphoma cell counts rapidly decreased in response to rituximab treatment, suggesting high sensitivity to rituximab. Finally, the patient developed infusion-related cytokine release syndrome. Some investigators have described that rituximab-induced systemic fibrinolysis, not necessarily in relation to DIC, may trigger RITAN (23, 24). Taken together, we speculate that the mechanism of RITAN in our case may be as follows: (1) FL cells massively infiltrated into the spleen (and other organs) and induced structural alterations in the endothelium and subendothelial space, (2) rituximab rapidly eradicated lymphoma cells and the subendothelium
was exposed to flowing blood, (3) cytokines released from normal and neoplastic lymphocytes and endothelial cells affected the integrity of the endothelial barrier, and (4) endothelial disruption induced platelet activation and aggregation, leading to transient acute thrombocytopenia, which recovered with endothelial repair (18, 23, 24). Increased levels of FDP and D-dimer would support this hypothesis. As the red pulp of the spleen is composed of splenic vascular sinuses and the cords of Billroth, Adiyodi et al. (18) have suggested a potential association of RIAT development with severe splenic architectural alterations with a red pulp involvement and subendothelial exposure after treatment.

From the clinical viewpoint, RIAT has generally shown a benign clinical course, being self-resolving, but occasionally it has been associated with major clinical bleeding (16, 18). Considering that RIAT often occurs within a few days after rituximab infusion, frequent monitoring of platelet counts during this period is advisable for select patients considered to be at a high risk for RIAT. As of September 2015, rituximab is indicated for the treatment of patients with CD20-positive B-NHL, CD 20-positive immunodeficiency-associated B-lymphoproliferative disorders, granulomatosis with polyangiitis, microscopic polyangiitis and idiopathic nephrotic syndrome in Japan. A greater accumulation of clinical data would help to determine whether RIAT is a lymphoma-specific complication or whether it can occur in various disease conditions.

We herein reported a case of RIAT that developed after rituximab administration in a patient with high tumor burden FL. Monitoring of the platelet count for a few days after rituximab infusion is advisable for select patients considered to be at a high risk for RIAT.

The authors state that they have no Conflict of Interest (COI).

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