Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2236-18
Intern Med 58: 2057-2061, 2019
http://internmed.jp

【 CASE REPORT 】

Disseminated Intravascular Coagulation-like Reaction after Rituximab Infusion in a Patient with Nephrotic Syndrome

Hiroki Nishiwaki[1], Megumi Oikawa[1], Hideto Kajitani[1], Daisuke Komukai[1,2], Yoshihiko Inoue[1] and Fumihiko Koiwa[1]

Abstract:

Several case series have suggested that rituximab is efficacious in adult patients with minimal change disease. We herein report a case of disseminated intravascular coagulation-like reaction after rituximab infusion in a patient with nephrotic syndrome. A 58-year-old Japanese man with minimal change disease diagnosed 15 years earlier was started on rituximab to prevent relapse of nephrotic syndrome when he presented to our clinic with low albuminemia, massive proteinuria, and leg edema. Eleven days after rituximab infusion, he presented with abdominal pain, appetite loss, and tarry stool. A laboratory examination revealed severe thrombocytopenia and coagulopathy, and upper gastrointestinal endoscopy revealed multiple hemorrhagic ulcers in his esophagus and stomach. The patient died two days later. Physicians should consider disseminated intravascular coagulation-like reaction when encountering cases with thrombocytopenia after rituximab infusion for any disease.

Key words: rituximab, nephrotic syndrome, rituximab-induced acute thrombocytopenia, thrombocytopenia, disseminated intravascular coagulation, adult

(Intern Med 58: 2057-2061, 2019)
(DOI: 10.2169/internalmedicine.2236-18)

Introduction

Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen, is commonly used to treat B-cell lymphoma, chronic lymphocytic leukemia, and some autoimmune disorders (1). It has been used successfully in autoimmune diseases targeting the kidney, such as antineutrophil cytoplasmic antibody-associated vasculitis, lupus nephritis, and membranous nephropathy. Recent trials have demonstrated sustained remission and a reduction in relapse rate, as well as a significant reduction in the dose or a discontinuation of steroids and additional immunosuppressive agents in children with steroid-dependent nephrotic syndrome or frequently relapsing nephrotic syndrome (2-4). Some case reports and small case series have suggested that rituximab is efficacious in adult patients with minimal change disease (5-9).

Late-onset pancytopenia, which usually occurs several weeks to months after the administration of rituximab, is also common but is usually self-limiting. However, rituximab-induced acute thrombocytopenia (RIAT) or disseminated intravascular coagulation (DIC)-like reaction, which usually occurs within a few days after the administration of rituximab, is very unusual, and its pathogenesis remains unclear (10-30).

We herein report a case of DIC-like reaction after rituximab infusion in a patient with nephrotic syndrome.

Case Report

A 58-year-old Japanese man was admitted with low albuminemia, massive proteinuria, leg edema. Fifteen years earlier, a percutaneous renal biopsy had been performed, and the pathological diagnosis of minimal change disease was made. After the renal biopsy, he experienced nephrotic syndrome relapses and was diagnosed with steroid-dependent nephrotic syndrome. Thereafter, he had received treatment

[1]Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital, Japan and [2]Division of Nephrology, Kawasaki-Saiwai Hospital, Japan
Received: October 11, 2018; Accepted: January 23, 2019; Advance Publication by J-STAGE: March 28, 2019
Correspondence to Dr. Hiroki Nishiwaki, nwacky1978@yj8.so-net.ne.jp

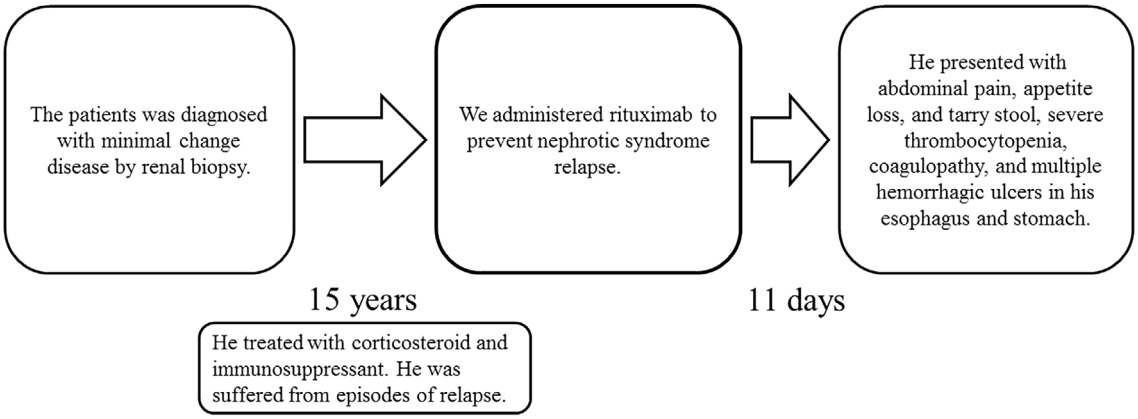

Figure. **Patient's time course.**

Table 1. **Laboratory Findings.**

Total protein	6.1 g/dL	White blood cell	18,410 /μL
Albumin	3.6 g/dL	Seg	80.5 %
Glucose	89 mg/dL	Stab	5.5 %
Blood urea nitro	20.2 mg/dL	Lymph	9.0 %
Uric acid	6.5 mg/dL	Mono	3.0 %
Creatinine	0.91 mg/dL	Meta	1.0 %
Sodium	138 mEq/L	Myelo	1.0 %
Chloride	100 mEq/L	Red blood cell	596×10^4 /μL
Potassium	4.3 mEq/L	Hemoglobin	16.8 g/dL
Calcium	8.3 mg/dL	Hematocrit	51.2 %
Phosphate	4.8 mg/dL	Platelet	7.5×104 /μL
Total bilirubin	0.6 mg/dL		
Aspartate aminotransferase	360 U/L	PT-INR	1.02
Alanine aminotransferase	173 U/L	APTT	21.0 s
Lactate dehydrogenase	1,353 U/L	D-dimer	36.3 μg/mL
Alkaline phosphatase	216 U/L		
gamma-glutamyl transpeptidase	51 U/L	Ferritin	3,094.6 ng/mL
C-reactive protein	0.09 mg/dL		

APTT: activated partial thromboplastin time, PT-INR: international normalized ratio of prothrombin time

with prednisolone and cyclosporine or prednisolone and mizoribine for nephrotic syndrome over the past 15 years (Figure).

He was then admitted to our hospital for the treatment of a nephrotic syndrome relapse. On admission, a physical examination revealed bilateral leg edema. Laboratory investigations showed the following results: proteinuria 4+ (7,150 mg/day) and serum albumin 2.8 g/dL. We administered 30 mg of prednisolone and continued the therapy. Thirteen days later, disease remission occurred. We administered rituximab infusion (375 mg/m^2 of body-surface area, maximum 500 mg) to prevent nephrotic syndrome relapse. Before the rituximab infusion, there had been no notable changes in laboratory values [white blood cell (WBC) 9,410/μL, hemoglobin (Hb) 15.0 g/dL, platelet (PLT) 22.2×10^4/μL]. Three days after the infusion, there were also no notable changes in the laboratory values (WBC 8,660/μL, Hb 15.4 g/dL, PLT 19.3×10^4/μL), and he was discharged the next day.

Eleven days later after rituximab infusion, he presented with abdominal pain and a loss of appetite. Two days later, he presented to the emergency room of our hospital. In addition, he complained of tarry stool. A physical examination revealed blood pressure 165/97 mmHg, pulse rate 60/min, body temperature 36.6℃, respiratory rate 16/min, and multiple oral aphthae. He did not present with altered consciousness. No skin abnormalities or mucosa in the eye or eye lid were noted. Laboratory investigations showed the following results: WBC 18,410/μL (no leukemic cells), Hb 16.8 g/dL, PLT 7.5×10^4/μL, no erythrocyte fragmentation, aspartate aminotransferase 360 U/L, alanine aminotransferase 173 U/L, lactate dehydrogenase 1,353 U/L, and C-reactive protein (CRP) 0.06 mg/dL. His serum creatinine and uric acid levels were normal. A coagulation panel showed an international normalized ratio of prothrombin time (PT-INR) of 1.02 and D-dimer of 3.63 mg/dL (Table 1). Computed tomography with contrast media revealed no thrombosis, solid tumors,

Table 2. Previous Cases of Acute Thrombocytopenia after RTX Infusion.

Age (years), Sex	Disease	RTX infusion times	Platelet count	Liver dysfunction	Splenomegaly	Bleeding	Onset after the infusion of rituximab	DIC-like status	Reference
60 F	LPL	1	7,000	Yes	Yes	Yes (Epistaxis)	a few hours		[10]
57 M	MCL	1	8,000	NS	Yes	NS	1 day		[11]
75 M	PLL	1	7,000	NS	Yes	NS	4 hours		[12]
41 M	HCL	1	7,000	NS	Yes	NS	1 day		[13]
64 M	MCL	1	10,000	NS	NS	NS	1 day		[13]
44 M	HCL	1	6,000	NS	NS	Yes (Mouth, legs and gastrointestinal)	4 hours	Yes	[14]
2 M	AIHA	4	232,000	NS	Yes	Yes (oral and anal ulceration)	1 week		[15]
3M	AIHA	3	7,400	NS	Yes	Yes (Epistaxis)	7 days		[15]
63 M	MCL	5	1,500	NS	NS	NS	1 day		[16]
84 M	MCL	1	15,000	NS	NS	No	1 day		[17]
58 M	MCL	2	9,000	Elevated LDH	Yes	NS	1 day		[18]
71 F	MCL	2	10,000	NS	NS	No	18 hours		[19]
74 M	HCL	1	21,000	NS	Yes	No	1 day	Yes	[20]
73F	MCL	1	14,000	NS	Yes	No	1 day		[21]
83 F	HCL	2	22,000	NS	Yes	No	1 day		[22]
50 M	WM	1	4,800	NS	No	Yes (gastrointestinal)	NS	Yes	[23]
70 M	WM	1	3,000	NS	NS	NS	4 hours	Yes	[24]
66 F	FL	1	16,000	NS	NS	No	a few hours		[25]
63 F	MCL	1	5,000	NS	Yes	No	1 day		[26]
72 M	MCL	1	10,000	NS	Yes	No	1 day		[26]
60 M	MCL	1	11,000	NS	Yes	No	3 days		[26]
64 F	MCL	1	3,000	NS	Yes	No	1 day		[26]
76 M	MCL	1	26,000	NS	Yes	No	1 day		[26]
65 M	FL	1	5,000	NS	Yes	NS	1 day		[27]
59 M	ALL	1	2,000	Rise marginally	No	Yes (gingiva and nose)	1 day	Yes	[28]
74 M	FL	3	14,000	NS	Yes	No	1 day		[29]
72 F	GPA	3	7,000	NS	NS	Yes (bloody stool)	3 days		[30]

AIHA: autoimmune hemolytic anemia, ALL: acute lymphocytic lymphoma, DIC: disseminated intravascular coagulation, F: female, GPA: granulomatosis with polyangiitis, HCL: hairy cell leukemia, FL: follicular lymphoma, LPL: lymphoplasmacytoid lymphoma, M: male, MCL: mantle cell lymphoma, MZL: marginal zone lymphoma, NS: not specified, PLL: prolymphocytic leukemia, RTX: rituximab, WM: Waldenstrom's macroglobulinemia

organic hepatic diseases, or splenomegaly. Blood and urine cultures were negative. Surface antibody and antigen, core antibody and antigen, and deoxyribonucleic acid of hepatitis B were negative. Immunoglobulin M antibody of other viruses, including cytomegalovirus, Epstein-Barr virus, and herpes zoster virus, were negative.

The next day, a physical examination revealed subcutaneous bleeding and intramuscular hematoma. Laboratory tests revealed that the PT-INR had increased to 2.79 from 1.02 while the D-dimer had increased to 206.2 mg/dL from 3.63 mg/dL. The fibrinogen level was 3,727 mg/dL. The PLT dropped to 4.5×10^4/μL from 7.5×10^4/μL. Bone marrow aspiration revealed hypocellular marrow with hematopoietic cells, including mature megakaryocytes, and no evidence of leukemic cells or hemophagocytosis.

Thereafter, the patient started vomiting blood. Upper gastrointestinal endoscopy revealed multiple hemorrhagic ulcers in the esophagus and stomach. It was difficult to stop the bleeding. The patient was transfused with fresh-frozen plasma and received vasopressor therapy; however, his blood pressure gradually decreased, and he ultimately died two days later.

Discussion

We reported a case of DIC-like reaction after rituximab infusion in a patient with nephrotic syndrome. Acute hematologic abnormalities after the administration of rituximab have been reported in patients with hematologic diseases, such as mantle cell lymphoma, hairy cell leukemia, prolymphocytic leukemia, follicular lymphoma, lymphoplasmacytic lymphoma, pre-B acute lymphoblastic leukemia, granulomatosis with polyangiitis, and autoimmune hemolytic anemia (Table 2). To our knowledge, however, this report is the first

case of DIC-like reaction after rituximab infusion in a patient with nephrotic syndrome.

The incidence of rituximab-induced thrombocytopenia (PLT <100,000/μL within 30 days after the administration of rituximab) was reported in a cohort study (31). Among 90 rituximab-treated patients, 27 developed thrombocytopenia (30%). According to that report, most of the thrombocytopenia cases occurred within 1 month, usually within 10 days, after the last administration of rituximab. Among the cases of rituximab-induced thrombocytopenia, several cases of RIAT, which developed within a few days after rituximab administration, have been reported. The onset of RIAT in non-lymphoma cases, in contrast to that in cases with lymphoma, occurred later than that described in previous reports (15, 30). The onset of DIC-like reaction in our case might have been within 10 days after the infusion of rituximab. This was not typically seen in previous RIAT cases. In addition, the previous cases of RIAT presented with severe thrombocytopenia (platelets <10,000/μL), whereas the thrombocytopenia in our case was relatively mild; however, the bleeding symptom was severe, suggesting that the thrombocytopenia had not progressed, but there was activated coagulation and consumption of platelets in the small blood vessels. The differential diagnosis of this case include thrombotic microangiopathy (TMA), an infectious disease related to DIC and Stevens-Johnson syndrome (SJS). First, no erythrocyte fragmentation was confirmed; therefore, typical TMA was not likely. However, as we mentioned, we considered there to be activated coagulation and consumption of platelets in the small blood vessels. There was no kidney dysfunction or psychiatric disturbance, symptoms that are typically seen in cases of thrombotic thrombocytopenic purpura. There was no diarrhea, which is typically seen in cases of hemolytic-uremic syndrome. Second, negative results in laboratory cultures of sputum, urine, and blood were not noted, while CRP was negative in our patient. Therefore, bacterial infection was not likely in this case. Finally, the onset was after the infusion of rituximab, suggesting the possibility of SJS. However, there were no skin abnormalities or abnormalities in the mucosa of the eye or eye lid. The patient had not started any drugs recently except for rituximab, and he had been taking 30 mg prednisolone at the onset. Because the other differential diagnoses were not likely and the onset was after the infusion of rituximab, we diagnosed the patients with DIC-like reaction following rituximab infusion.

Acute thrombocytopenia following rituximab infusion, including RIAT, has been reported as a rare side effect of rituximab administration, and its mechanism and frequency remain unclear. Most of the reported RIAT cases occurred during treatment for lymphoma. The three previous cases and our case were not related to lymphoma and all included bleeding (15, 30). Six cases of acute thrombocytopenia following rituximab infusion with bleeding have been noted in previous case reports (10, 14, 15, 23, 28, 30). Thus, acute thrombocytopenia following rituximab infusion in non-lymphoma cases can be associated with bleeding; however, further studies and case reports are needed to confirm this point.

Rafei et al. summarized the coagulation profile of the previous reports of acute thrombocytopenia following rituximab infusion (28). Five cases documented intravascular fibrinolysis in a DIC-like fashion after the administration of rituximab (14, 20, 23, 24, 28). However, two cases and our present case documented the absence of schistocytes, while the other three did not report the presence or absence of schistocytes. The previous cases had hairy cell leukemia, Waldenstrom's macroglobulinemia, and acute lymphocytic lymphoma, but our patient did not have lymphoma. Therefore, the DIC-like mechanism may be unrelated to the presence of tumor cells.

In conclusion, we reported the case of a patient with nephrotic syndrome who developed DIC-like reaction after the first infusion of rituximab. The DIC-like reaction in our case occurred 11 days after the infusion of rituximab. It may be necessary to change the strategy of laboratory monitoring after rituximab infusion, especially in non-lymphoma cases.

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

References

1. Engelhard M. Anti-CD20 antibody treatment of non-Hodgkin lymphomas. Clin Immunol **172**: 101-104, 2016.
2. KDIGO. clinical practice guideline for glomerulonephritis. Kidney Int Suppl **2**: 1-274, 2012.
3. Prytula A, Lijima K, Kamei K, et al. Rituximab in refractory nephrotic syndrome. Pediatr Nephrol **25**: 461-468, 2010.
4. Ravani P, Magnasco A, Edefonti A, et al. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol **6**: 1308-1315, 2011.
5. Beco A, Castro-Ferreira I, Coentrao L, et al. Rituximab for steroid dependent nephrotic syndrome. Clin Nephrol **74**: 308-310, 2010.
6. Munyentwali H, Bouachi K, Audard V, et al. Rituximab is an efficient and safe treatment in adults with steroid dependent minimal change disease. Kidney Int **83**: 511-516, 2013.
7. Francois H, Daugas E, Bensman A, et al. Unexpected efficacy of rituximab in multi-relapsing minimal change nephrotic syndrome in the adult: first case report and pathophysiological considerations. Am J Kidney Dis **49**: 158-161, 2007.
8. Guitard J, Hebral AL, Fakhouri F, et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. Nephrol Dial Transplant **29**: 2084-2091, 2014.
9. Bruchfield A, Benedek S, Hilderman M, et al. Rituximab for minimal change disease in adults: long-term follow-up. Nephrol Dial Transplant **29**: 851-856, 2014.
10. 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 **15**: 186-187, 2001.
11. Shah C, Grethlein SJ. Case report of rituximab-induced thrombocytopenia. Am J Hematol **75**: 263, 2004.
12. Pamuk GE, Donmez S, Turgut B, Demir M, Vural O. Rituximab induced acute thrombocytopenia in a patient with prolymphocytic leukemia. Am J Hematol **78**: 81, 2005.

13. Otrock ZK, Mahfouz RA, Oghlakian GO, Salem ZM, Bazarbachi A. Rituximab-induced acute thrombocytopenia: a report of two cases. Haematologica **90** (Suppl): ECR23, 2005.
14. Thachil J, Mukherje K, Woodcock B. Rituximab-induced haemorrhagic thrombocytopenia in a patient with hairy cell leukaemia. Br J Haematol **135**: 273-274, 2006.
15. Larrar S, Guitton C, Willems M, Bader-Meunier B. Severe hematological side effects following Rituximab therapy in children. Haematologica **91** (Suppl): ECR36, 2006.
16. Rosado M, Chao H, Rose M. Severe acute thrombocytopenia following rituximab therapy. Leuk Lymphoma **48**: 2239-2240, 2007.
17. Dhand S, Bahrain H. Rituximab-induced severe acute thrombocytopenia: a case report and review of literature. Cancer Invest **26**: 913-915, 2008.
18. Yi JH, Kim SJ, Ahn HK, Lee SJ, Chang MH, Kim WS. Rituximab-induced acute thrombocytopenia: a case report and review of the literature. Med Oncol **26**: 45-48, 2009.
19. Ram R, Bonstein L, Gafter-Gvili A, Ben-Bassat I, Shpilberg O, Raanani P. Rituximab-associated acute thrombocytopenia: an under-diagnosed phenomenon. Am J Hematol **84**: 247-250, 2009.
20. Kotsianidis I, Goutzouvelidis A, Anastasiades A, et al. Severe thrombocytopenia and fibrinolysis mimicking disseminated intravascular coagulation after rituximab infusion. Am J Hematol **85**: 146, 2010.
21. Parajuli R, Hire E, Shah BK. Rituximab-induced acute severe thrombocytopenia. Br J Haematol **149**: 804, 2010.
22. Adiyodi J, Thachil J, Hawkins S, et al. Thrombocytopenia with rituximab treatment -splenomegaly as the risk factor. Ann Hematol **89**: 95-96, 2010.
23. Pilorge S, Park S, Dreyfus F, Bouscary D, Tamburini J. Rituximab-induced life-threatening coagulopathy occurring in a patient with Waldenström macroglobulinemia treated with fludarabine, cyclophosphamide, and rituximab combination. Leuk Lymphoma **51**: 2288-2290, 2010.
24. Novak J, Mocikova H, Pavlicek P, Gaherova L, Kozak T. Rituximab-induced coagulopathy. Leuk Lymphoma **53**: 2299-2301, 2012.
25. El-Osta H, Nair B. Rituximab-induced acute thrombocytopenia: an underappreciated entity. Leuk Lymphoma **54**: 2736-2737, 2013.
26. Sadashiv SK, Rao R, Fazal S, Lister J. Rituximab-induced acute severe thrombocytopenia: a case series in patients with mantle cell lymphoma. Clin Lymphoma Myeloma Leuk **13**: 602-605, 2013.
27. Ureshino H, Nishioka A, Kojima K, et al. Rituximab-induced acute thrombocytopenia in high tumor burden follicular lymphoma. Intern Med **55**: 2061-2064, 2016.
28. Rafei H, Nassereddine S, Garcia IF. Disseminated intravascular coagulation-like reaction following rituximab infusion. BMJ Case Rep **8**: 1-6, 2017.
29. 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 **57**: 1151-1154, 2018.
30. Endo Y, Koga T, Ishida M, et al. Rituximab-induced acute thrombocytopenia in granulomatosis with polyangiitis. Intern Med **57**: 2247-2250, 2018.
31. Giezen TJ, Mantel-Teeuwisse AK, ten Berg MJ, et al. Rituximab induced thrombocytopenia: a cohort study. Eur J Haematol **89**: 256-266, 2012.