CASE REPORT

Disseminated intravascular coagulation-like reaction following rituximab infusion

Hind Rafei,[1] Samah Nassereddine,[1] Ivan F Garcia[2]

[1]Department of Internal Medicine, George Washington University School of Medicine & Health Sciences, Washington, DC, USA
[2]Department of Medicine, Inova Fairfax Hospital, Falls Church, Virginia, USA

Correspondence to
Dr Hind Rafei, hindrafei@gwu.edu

SUMMARY

Rituximab generally is a well-tolerated medication used in a variety of haematological and autoimmune conditions. The safety profile of the medication has been reviewed in the literature. Infusion reactions due to cytokine release are the most common side effects. With the increased use of rituximab, there is an increase incidence of cytopenias, most commonly thrombocytopenia and leucopenia. Coagulopathy is quite rare, reported previously in four cases in the literature. We highlighted the clinical course of a 39-year-old patient with precursor B-cell acute lymphoblastic leukaemia who was started on rituximab infusion. The patient developed a cytokine-release syndrome with haemodynamic instability, followed by rapid-onset cytopenias and disseminated intravascular coagulation abnormalities characterised by coagulopathy with fibrinolysis and mucocutaneous bleeding. The report is followed by a review of the literature. It is important to recognise rituximab-induced coagulopathy early as part of the differential diagnosis of thrombocytopenia and disseminated intravascular coagulation following rituximab administration.

BACKGROUND

Rituximab is a chimeric anti-CD20 monoclonal antibody that is commonly used to treat different lymphoproliferative diseases and autoimmune conditions. It is relatively very well tolerated. With the increased use of rituximab, an increasing number of serious complications related to rituximab infusions have been noted. These complications encompass an array of presentations and affect different systems. The severity of reactions and side effects of rituximab are reported based on the grading system for reporting adverse effects from chemotherapy. Grade 3–4 represent moderate to severe adverse events and grade 5 represents fatalities.[1] The most common reactions (incidence of at least 25%) in patients receiving rituximab monotherapy are infusion reactions.[2] The infusion reactions noted are usually mild to moderate (grade 1 or 2); grade 3–4 reactions are rare and dose dependent.[3 4] Cytopenias are other complications of rituximab therapy.[5] Grade 3 and 4 cytopenias lasting ~2 weeks have been seen in 48% of patients who had non-Hodgkin lymphoma and who received rituximab monotherapy, lymphopenia being the most common.[2 3]

Coagulopathy has been rarely described in the literature as a complication of rituximab infusion. A literature review showed four previously reported cases with coagulopathy following rituximab

infusion. In this review, we report the case of a patient with precursor B-cell acute lymphoblastic leukaemia who developed a disseminated intravascular coagulation (DIC) picture after rituximab infusion. We will briefly summarise the potential side effects of rituximab infusion and review the previously reported cases with rituximab-associated coagulopathy.

CASE PRESENTATION

A 39-year-old man with no medical history presented to the emergency room with severe, diffuse body pain. At admission, he endorsed pain in his chest, thighs, legs and back, as well as generalised abdominal discomfort, and he reported many months of drenching night sweats. Presenting vital signs were significant for tachycardia, and physical examination was remarkable only for generalised rib tenderness to moderate palpation and the absence of palpable splenomegaly. Relevant admission laboratory results included leucocytosis of 99 950/mm^3 (segmented neutrophils 17%, band neutrophils 8%, blasts 55%), haemoglobin 14.7 g/dL and platelet count 58 000/mm^3. Flow cytometry analysis of peripheral blood and bone marrow biopsy were consistent with the diagnosis of precursor B-cell acute lymphoblastic leukaemia ('pre-B-cell acute lymphoblastic leukaemia (pre-B-ALL)'; negative to weak expression of CD45; positive expression of CD10, CD19, CD20, CD79a, TdT and CD34; aberrant expression of CD33 and CD61; MPO stain negative). Fluorescence in situ hybridisation was positive for the ABL1-BCR fusion gene (Philadelphia chromosome positive). The decision was made to induce the patient on hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone), with rituximab 375 mg/m^2 prescribed on days one and 11 of the first cycle of chemotherapy. He was maintained on fluids and initiated on routine tumour lysis prophylaxis. Follow-up preinduction blood work was obtained and was remarkable for leucocytosis of 63 910/mm^3 (blasts 78%), haemoglobin 13 g/dL and platelet count 14 000/mm^3. Coagulation panel showed international normalised ratio (INR) of 1.1, fibrinogen 612 mg/dL and D-dimer 4770 mg/dL. Basic metabolic panel and liver tests were grossly unremarkable (potassium 3.1 mmol/L, phosphorus 2.4 mmol/L), and lactate dehydrogenase (LDH) was 1005 U/L. Uric acid was normal.

On day one of chemotherapy, ~150 min after rituximab infusion, the patient evolved fever of 102.4 F with rigors, nausea, vomiting, pronounced sinus tachycardia (approximate rate of 150),

tachypnoea and profound hypotension to 82/51, consistent with a severe cytokine-release syndrome. He was haemodynamically stabilised and rituximab infusion was held. Five hours later, significant coagulation abnormalities and relative cytopenias evolved in the setting of clinically significant mucocutaneous bleeding (gingival and nasal bleeding), and in the absence of schistocytes on peripheral blood smear. INR rose to 1.9 from 1.1, D-dimer rose to >20 000 mg/dL from 4770 mg/dL and fibrinogen dropped to 422 mg/dL from 612 mg/dL, with further drop to 71 mg/dL after 96 hours. Platelet and white cell count dropped dramatically (14 000/mm^3 to 2000/mm^3 and 63 910/mm^3 to 10 420/mm^3, respectively), while haemoglobin dropped to 11.8 g/dL from 13 g/dL. LDH level rose prominently. Uric acid level remained relatively unchanged, and liver tests rose marginally (aspartate transaminase (AST) to 649 U/L from 23 U/L, alanine transaminase (ALT) to 50 U/L from 14 U/L, alkaline phosphatase to 272 U/L from 102 U/L). Figure 1A–C illustrate the evolution of the patient's coagulopathy over the first 96 hours of chemotherapy (figure 1).

In this setting, the patient was transfused with one pool of cryoprecipitate and with platelets. Fibrinogen levels increased to 138 mg/dL, with subsequent stability; however, he required additional platelet transfusions to maintain stability. After further clinical recovery, the patient resumed his chemotherapy and received his second rituximab infusion on day 11, complicated by recurrent thrombocytopenia (14 000–5000/mm^3). However, the postinfusion coagulation profile, including INR, D-dimer and fibrinogen level, was not suggestive of DIC, and there was no objective manifestation of haemodynamically significant cytokine-release syndrome. Figure 2 illustrates the patient's recovery from coagulopathy in the period between the first and second rituximab doses, in the setting of persistent thrombocytopenia (figure 2).

OUTCOME AND FOLLOW-UP
After receiving the second infusion of rituximab, the patient completed his chemotherapy induction without further complications, and was discharged in a good clinical condition to be followed as outpatient.

DISCUSSION
A PubMed database search using the terms: rituximab AND fibrinolysis, rituximab AND coagulation, and rituximab AND thrombocytopenia was conducted. Papers specifically addressing acute haematological adverse effects of rituximab were reviewed. The search yielded one cohort study and 16 case reports.[6–22] In total, 22 patients were addressed in these case reports, and 29 rituximab infusions associated with haematological adverse reactions were reported between 2001 and 2013. Patients' characteristics and clinical courses (not including our patient) are summarised in table 1.

Among the 22 patients, 14 were male patients and eight were female patients. There were 13 mantle cell lymphomas (MCL), four hairy cell leukaemias (HCL), two Waldenstrom's macroglobulinemia, one lymphoplasmacytic lymphoma, one B-cell prolymphocytic leukaemia, and one marginal zone lymphoma. There were no cases of pre-B-ALL. In all studies where the dose of rituximab was reported, the dose infused was 375 mg/m^2.

The median time to development of adverse events related to rituximab infusion was 24 hours, the fastest occurring within 2 hours of start of infusion. Clinically evident cytokine-release syndrome was commonly found, occurring in 14 cases (absent in five; not reported on in the remainder), and with similar manifestations to that presented in our case, including fever, chills, severe rigors and tachycardia, but without profound hypotension except in one case where the reaction was severe.[19] Postinfusion thrombocytopenia was documented in all cases reviewed (mean preinfusion level of 116 000+/−38 581, and postinfusion level of 22 379+/−18 076). Ten cases reported on post-transfusion leucopenia (mean preinfusion count 31 449 +/−43 818 and postinfusion count 8032+/−7767).

Importantly, only eight cases reported on the coagulation profile of their patients, and only four documented intravascular fibrinolysis in a DIC-like fashion.[10 15 21 22] In the first of these cases,[10] the D-dimer and INR increased to 33 020 mg/dL and 1.2, respectively, and fibrinogen decreased to 410 mg/dL (starting level not specified for any of the three tests), and there was no report on the presence of schistocytes or change in LDH. In the second case,[15] the D-dimer and INR increased to 15 470 mg/dL and 2.43, respectively, and fibrinogen decreased to 127 mg/dL (again, starting level not specified for any of the three tests). However, the absence of schistocytes was documented, and LDH level increased to two times above the upper limit of normal. In the two latter cases,[21 22] the D-dimer increased from an unspecified starting level and 420 ng/mL to 110 400 ng/L and 9670 ng/mL, respectively; prothrombin ratio (PR) decreased from 92% to 50% in the third case and INR increased from 1.31 to 1.78 in the fourth case; and fibrinogen decreased from 380 mg/dL and 290 mg/dL to 50 mg/dL and 180 mg/dL, respectively. There was again no mention of the presence or absence of schistocytes in neither of these last two cases. Interestingly, in the second case fibrinolysis and thrombocytopenia occurred within hours of rituximab infusion, and fibrinogen continued to decrease in the 96 hours postinfusion (89 mg/dL). Collectively, the findings in these four cases are the most representative of a DIC-like abnormality across all cases reviewed. One study documented a patient with a normal coagulation profile after rituximab infusion despite development of thrombocytopenia and a twofold increase in AST, ALT and LDH,[6] and two other studies excluded DIC as the source for post-transfusion thrombocytopenia.[12 14] Another study did not comment on the presence of DIC, though an abnormal coagulation profile postinfusion was reported.[16]

Rituximab is a chimeric monoclonal antibody that targets CD20 and is used in a variety of conditions including lymphoproliferative and autoimmune diseases.[23 24] It has a relatively favourable toxicity profile; the most common adverse effects include an acute infusion reaction consisting of fever, chills, rigors, rash and occasionally bronchospasm and hypotension. This effect is known as a 'cytokine-release syndrome', and is thought to be due to robust cytokine release,[25–27] in the presence of circulating tumour cells.[28]

Delayed-onset cytopenias are the most common haematological adverse reactions associated with rituximab, and most often appear several weeks after rituximab infusion. In one analysis conducted on 77 courses of rituximab,[5] delayed-onset cytopenias were documented in 29.8% of the cases, including neutropenia (27.3%) at a median of 10 weeks, thrombocytopenia (10.4%) at a median of 4 weeks, and anaemia (5.2%) at a median of 5 weeks. Another study reported on cytopenias in 53 patients, most of whom received rituximab for non-Hodgkins' lymphoma.[29] In this series eight episodes of grade 4, neutropenia were detected between 1 and 5 months after rituximab infusion; five of these occurred when rituximab was used as single agent and the other three when rituximab was used in combination with other agents.[29] In our case, the patient experienced a dramatic drop in total white cell count within 5 hours of infusion, with rituximab as a single agent.
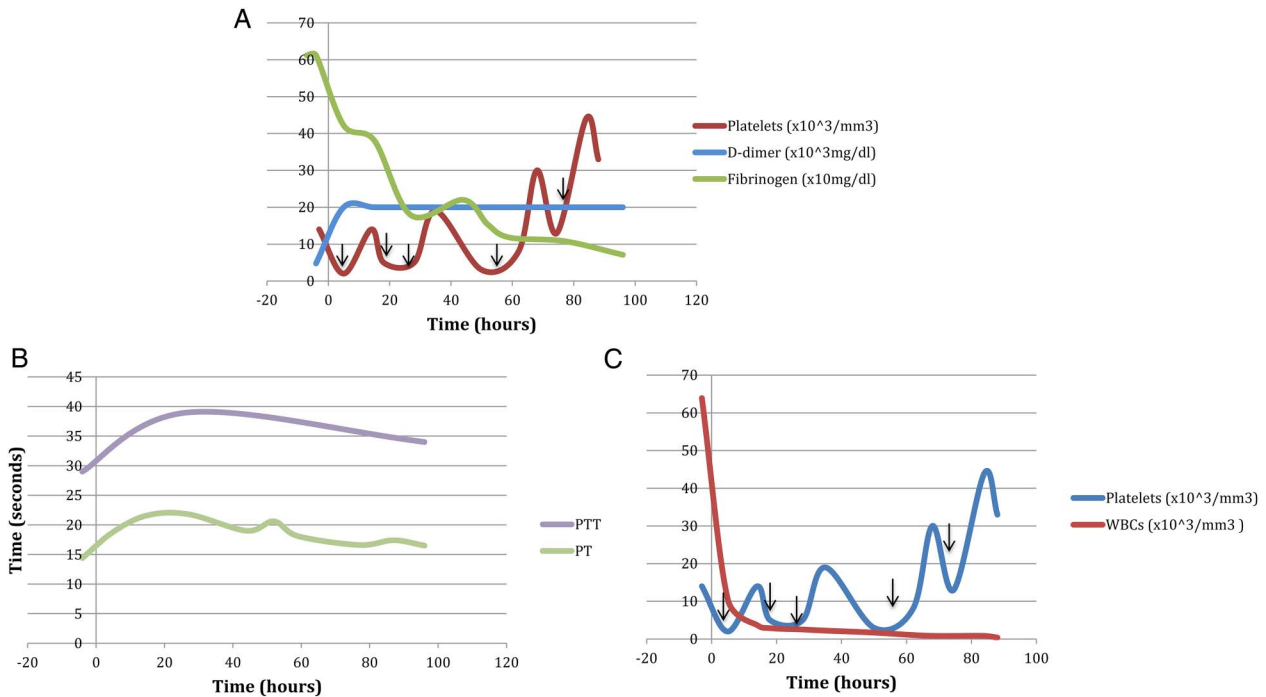
Figure 1 (A) Coagulation profile during initial rituximab infusion from a few hours prior to the start of infusion until 96 hours after infusion. Time 0 corresponds to the start of rituximab infusion. The black arrows indicate platelet transfusion. (B) Prothrombin time and partial thromboplastin time during initial rituximab infusion from a few hours prior to the start of infusion until 96 hours after infusion. Time 0 corresponds to the start of rituximab infusion. (C) Evolution of rapid-onset relative cytopenias from a few hours prior to the start of infusion until 96 hours after infusion. Time 0 corresponds to the start of rituximab infusion. The black arrows indicate platelet transfusion.
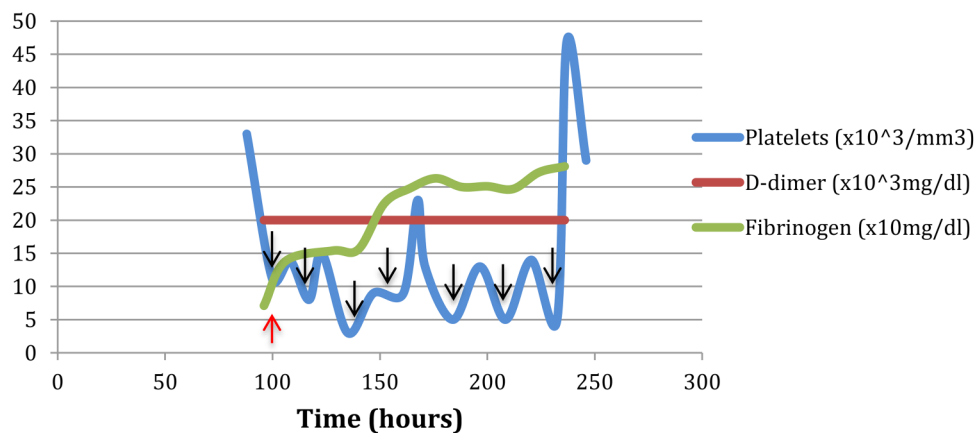

Figure 2 Coagulation profile between rituximab dose 1 and 2, after transfusion of one pool cryoprecipitate and five units of platelets. Time 0 corresponds to the start of rituximab infusion. The black arrows indicate platelet transfusion and the red arrow indicate platelet transfusion.

In contrast, reports of cytopenias with coagulopathy and temporal association with rituximab infusion are uncommon in the literature. Indeed, the acute, postinfusion thrombocytopenia associated with laboratory evidence of coagulopathy and fibrinolysis (rapid rise in D-dimer and prothrombin time, and drop in fibrinogen) presented in our case seems quite rare (reported only in four cases;[10 15 21 22] and is suggestive of DIC or a DIC-like abnormality, despite the absence of schistocytes on peripheral blood smear. Further, there are no reported cases of these abnormalities as sequelae to a haemodynamically significant cytokine-release syndrome with clinical manifestations of bleeding in a patient with pre-B-ALL. The presence of these attributes together makes the patient in our case unique. Only the case reported by Kotsianidis *et al* is similar when one

considers the chronological progression of the adverse events and the nature of the coagulation abnormalities, including the lack of schistocytes, but this case did not involve haemodynamically significant cytokine-release syndrome, mucocutaneous bleeding or pre-B-ALL.[15]

The mechanism underlying the coagulopathy associated with rituximab may not be concluded from the case report per se. We hypothesise, however, a few mechanisms based on observations from our case report as well as review of the literature. A rituximab infusion associated with a severe cytokine-release syndrome with rapid-onset cytopenias and a DIC-like syndrome, like the one seen in our patient, may reflect a relationship between profound cytokine release and activation of the complement cascade.[14] Consider that a postinfusion drop in total

Table 1 Summary of cases of haematological adverse effects following rituximab

Pt#	Author (year)	Infusion	G	Age	Haematological disease	Splenomegaly	Preplatelets	Preleukocytes	Pre-Hb	Pre-D-dimer	Pre-fib	Pre-INR	Pre-LDH	Rituximab dose	Hours to ADR	Postplatelets	Postleukocytes	Post-Hb	Post-D-dimer	Post-fib	Post-INR	Post-LDH	CRS	Intravascular fibrinolysis	Shistocytes
1	Rigamonti (2001)	1	F	60	LPL	Yes	86 000	1100	9.7	NS	NS	NS	NS	375 mg/m²	5	7000	1100	9.7	Normal	Normal	Normal	2×up	Yes	No	NS
2	Shah (2004)	1	M	57	MCL	Yes	151 000	10 800	9.4	NS	NS	NS	NS	375 mg/m²	24	8000	6000	7.7	NS	NS	NS	NS	Yes	NS	NS
3	Pamuk (2005)	1	M	75	B-cell PLL	Yes	92 000	160 000	7.7	NS	NS	NS	NS	375 mg/m²	4	7000	12 000	7.4	NS	NS	NS	NS	NS	NS	NS
4	Otrock (2005)	1	M	41	HCL	Yes	85 000	2800	9.5	NS	NS	NS	NS	375 mg/m²	24	7000	NS	NS	NS	NS	NS	NS	Yes	NS	NS
5	Otrock (2005)	1	M	64	MCL	NS	90 000	90 200	10.5	NS	NS	NS	NS	375 mg/m²	24	10 000	NS	NS	NS	NS	NS	NS	Yes	NS	NS
6	Thachil (2006)	1	M	44	HCL	NS	31 000	1400	9.4	NS	NS	NS	NS	NS	5	6000	NS	NS	33 020 ng/ml	410	1.2	NS	No	Yes	NS
7	Rosado (2007)	1	M	64	MCL	NS	175 000	NS	NS	NS	NS	NS	NS	375 mg/m²	24	22 000	NS	NS	NS	NS	NS	NS	NS	NS	No
7	Rosada (2007)	2	M	64	MCL	NS	135 000	NS	NS	NS	NS	NS	NS	375 mg/m²	18	11 000	NS	NS	NS	NS	NS	NS	NS	NS	No
8	Yi (2009)	1	M	58	MCL-BV	Yes	132 000	NS	NS	NS	NS	NS	994	375 mg/m²	24	24 000	NS	NS	Normal	Normal	Normal	3018	Yes	No	NS
8	Yi (2009)	2	M	58	MCL-BV	Yes	139 000	NS	NS	NS	NS	NS	NS	375 mg/m²	8	48 000	NS	NS	NS	NS	NS	NS	Yes	NS	NS
9	Dhand (2008)	1	M	84	MCL	NS	121 000	NS	NS	NS	NS	NS	NS	375 mg/m²	24	15 000	NS	NS	NS	NS	NS	NS	No	NS	NS
10	Ram (2009)	1	F	71	MCL	NS	63 000	80 000	10.5	NS	NS	NS	NS	375 mg/m²	18	10 000	1000	NS	NS	NS	NS	NS	Yes	No	No
11	Kotsianidis (2009)	1	M	74	Atypical HCL	Yes	127 000	49 700	13.7	NS	NS	NS	NS	375 mg/m²	24	21 000	28 000	NS	15 470 mg/dL	127	2.43	2×ULN	No	Yes	No
12	Adiyodi (2010)	1	F	83	HCL	Yes	74 000	NS	NS	NS	NS	NS	NS	NS	12	22 000	NS	NS	High	Normal	Normal	NS	Yes	NS	NS
13	Adiyodi (2010)	1	F	79	MZL	Yes	162 000	NS	8.4	NS	NS	NS	NS	375 mg/m²	24	43 000	NS	NS	NS	NS	NS	NS	Yes	NS	NS
14	Parajuli (2010)	1	F	73	MCL	Yes	85 000	NS	NS	NS	NS	NS	NS	NS	24	14 000	NS	NS	NS	NS	NS	NS	Yes	NS	NS
14	Parajuli (2010)	2	F	73	MCL	Yes	100 000	NS	NS	NS	NS	NS	NS	NS	24	54 000	NS	NS	NS	NS	NS	NS	NS	NS	NS
14	Parajuli (2010)	3	F	73	MCL	Yes	126 000	NS	NS	NS	NS	NS	NS	NS	24	27 000	NS	NS	NS	NS	NS	NS	NS	NS	NS
14	Parajuli (2010)	4	F	73	MCL	Yes	123 000	NS	NS	NS	NS	NS	NS	NS	24	49 000	NS	NS	NS	NS	NS	NS	NS	NS	NS
14	Parajuli (2010)	5	F	73	MCL	Yes	103 000	NS	NS	NS	NS	NS	NS	NS	24	27 000	NS	NS	NS	NS	NS	NS	NS	NS	NS
15	Pilorge (2010)	2	M	50	WM	No	144 000	3800	11.8	NS	380	PR=92%	347	375 mg/m²	2	48 000	NS	11.4	110 400 ng/L	50	PR=50%	NS	Yes	Yes	NS
16	Novak (2012)	1	M	70	WM	NS	171 000	2900	8.4	420 ng/mL	290	1.31	NS	375 mg/m²	4	30 000	NS	NS	9670 ng/mL	180	1.78	NS	No	Yes	NS
17	El-Osta (2013)	1	F	66	MCL	NS	175 000	18 400	NS	NS	NS	NS	Normal	NS	3	16 000	NS	NS	NS	NS	NS	NS	NS	NS	NS
18	Sadashiv (2013)	1	F	63	MCL	Yes	133 000	9990	8.6	NS	NS	NS	NS	NS	24	5000	7640	7.4	NS	NS	NS	NS	Yes	NS	NS
18	Sadashiv (2013)	2	F	63	MCL	Yes	149 000	NS	NS	NS	NS	NS	NS	NS	24	5000	NS	NS	NS	NS	NS	NS	NS	NS	NS
19	Sadashiv (2013)	1	M	72	MCL	Yes	33 000	26 260	9.4	NS	NS	NS	NS	NS	24	10 000	5730	9.1	NS	NS	NS	NS	No	NS	NS
20	Sadashiv (2013)	1	M	60	MCL	Yes	146 000	12 320	10.1	NS	NS	NS	NS	NS	72	74 000	3860	8.8	NS	NS	NS	NS	NS	NS	NS
21	Sadashiv (2013)	1	F	64	MCL	Yes	91 000	13 070	8.6	NS	NS	NS	NS	NS	24	3000	6180	8.5	NS	NS	NS	NS	Yes	NS	NS
22	Sadashiv (2013)	1	M	76	MCL	Yes	122 000	20 440	14.1	NS	NS	NS	NS	NS	24	26 000	8810	13.4	NS	NS	NS	NS	Yes	NS	NS

2×ULN, two times upper limit of normal; 2×up, twofold increase; ADR, adverse reactions in hours; BV, Blastoid variant; CRS, cytokine-release syndrome; F, female; fib, fibrinogen; G, gender; Hb, haemoglobin; HCL, hairy cell leukaemia; INR, international normalised ratio; LDH, lactate dehydrogenase; LPL, lymphoplasmacytoid lymphoma; M, male; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NS, not specified; PLL, prolymphocytic leukaemia; PR, Prothrombin ratio; Pt#, Patient number; WM, Waldenstrom's macroglobulinemia.

white cell count is a common, expected occurrence with rituximab, likely due to the binding by rituximab to CD20 positive B lymphocytes, activating the complement cascade and cell lysis. Whether the extent of complement-mediated lymphocyte destruction is proportional to the severity of a preceding cytokine-release syndrome would be a matter for further study. Only three reported cases of rituximab-associated fibrinolysis before ours were accompanied by cytokine-release syndrome while the fourth was not; which suggests that the two phenomena might not be mechanistically linked. Another theory would be related to the burden of disease whereby rituximab causes rapid and dramatic tumour destruction regardless of complement activity. The massive destruction products lead to coagulopathy in a DIC-like picture. The observation that our patient well tolerated subsequent infusions of rituximab without developing this coagulopathy might be as well related to the decreased burden of disease after initial infusion.

Learning points

- This is a case report of a patient who developed acute haematological abnormalities including thrombocytopenia as well as fibrinolysis and coagulation abnormalities very similar to disseminated intravascular coagulation (DIC) shortly after the first infusion of rituximab.
- Rituximab-associated coagulopathy in a DIC-like fashion seems to be a very rare phenomenon.
- It is extremely important to recognise this phenomenon early as part of the differential diagnosis of thrombocytopenia and DIC following rituximab administration.
- We recommend laboratory monitoring shortly after rituximab infusion and thereafter to detect these abnormalities and initiate supportive treatment early.

REFERENCES

1 US Department of Health and Human Services 2010. Common terminology criteria for adverse events v4. 03.
2 *Rituxan [package insert].* South San Francisco, CA: Genentech, Inc., 2011.
3 Kasi PM, Tawbi HA, Oddis CV, et al. Clinical review: serious adverse events associated with the use of rituximab-a critical care perspective. *Critical Care* 2012;16:1.
4 Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188–95.
5 Cattaneo C, Spedini P, Casari S, et al. Delayed-onset peripheral blood cytopenia after rituximab: frequency and risk factor assessment in a consecutive series of 77 treatments. *Leuk Lymphoma* 2006;47:1013–17.
6 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* 2001;15:186.
7 Shah C, Grethlein SJ. Case report of rituximab-induced thrombocytopenia. *Am J Hematol* 2004;75:263.
8 Pamuk GE, Donmez S, Turgut B, et al. Rituximab-induced acute thrombocytopenia in a patient with prolymphocytic leukemia. *Am J Hematol* 2005;78:81.
9 Otrock ZK, Mahfouz RA, Oghlakian GO, et al. Rituximab-induced acute thrombocytopenia: a report of two cases. *Haematologica* 2005;90(Suppl):ECR23.
10 Thachil J, Mukherje K, Woodcock B. Rituximab-induced haemorrhagic thrombocytopenia in a patient with hairy cell leukaemia. *Br J Haematol* 2006;135:273–4.
11 Rosado M, Chao H, Rose M. Severe acute thrombocytopenia following rituximab therapy. *Leuk Lymphoma* 2007;48:2239–40.
12 Yi JH, Kim SJ, Ahn HK, et al. Rituximab-induced acute thrombocytopenia: a case report and review of the literature. *Med Oncol* 2009;26:45–8.
13 Dhand S, Bahrain H. Rituximab-induced severe acute thrombocytopenia: a case report and review of literature. *Cancer Invest* 2008;26:913–15.
14 Ram R, Bonstein L, Gafter-Gvili A, et al. Rituximab-associated acute thrombocytopenia: an under-diagnosed phenomenon. *Am J Hematol* 2009;84:247–50.
15 Kotsianidis I, Goutzouvelidis A, Anastasiades A, et al. Severe thrombocytopenia and fibrinolysis mimicking disseminated intravascular coagulation after rituximab infusion. *Am J Hematol* 2010;85:146.
16 Adiyodi J, Thachil J, Hawkins S, et al. Thrombocytopenia with rituximab treatment —splenomegaly as the risk factor. *Ann Hematol* 2010;89:95–6.
17 Parajuli R, Hire E, Shah BK. Rituximab-induced acute severe thrombocytopenia. *Br J Haematol* 2010;149:804.
18 El-Osta H, Nair B. Rituximab-induced acute thrombocytopenia: an underappreciated entity. *Leuk Lymphoma* 2013;54:2736–7.
19 Sadashiv SK, Rao R, Fazal S, et al. Rituximab-induced acute severe thrombocytopenia: a case series in patients with mantle cell lymphoma. *Clin Lymphoma Myeloma Leuk* 2013;13:602–5.
20 Giezen TJ, Mantel-Teeuwisse AK, ten Berg MJ, et al. Rituximab-induced thrombocytopenia: a cohort study. *Eur J Haematol* 2012;89:256–66.
21 Pilorge S, Park S, Dreyfus F, et al. Rituximab-induced life-threatening coagulopathy occurring in a patient with Waldenström macroglobulinemia treated with fludarabine, cyclophosphamide, and rituximab combination. *Leuk Lymphoma* 2010;51:2288–90.
22 Novak J, Mocikova H, Pavlicek P, et al. Rituximab-induced coagulopathy. *Leuk Lymphoma* 2012;53:2299–301.
23 Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. *Arthritis Rheum* 2007;56:3896–908.
24 Avilés A, Nambo MJ, Neri N, et al. Dose dense (CEOP-14) vs dose dense and rituximab (CEOP-14+R) in high-risk diffuse large cell lymphoma. *Med Oncol* 2007;24:85–9.
25 Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* 2010;14:E10.
26 Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *J Clin Oncol* 2001;19:2153–64.
27 Winkler U, Jensen M, Manzke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999;94:2217–24.
28 Byrd JC, Waselenko JK, Maneatis TJ, et al. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. *J Clin Oncol* 1999;17:791.
29 Chaiwatanatorn K, Lee N, Grigg A, et al. Delayed-onset neutropenia associated with rituximab therapy. *Br J Haematol* 2003;121:913–18.