CASE REPORT

Rituximab-induced Acute Thrombocytopaenia in a Patient with Mixed Connective Tissue Disease: A Case-based Review.

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Abstract

Rituximab-induced acute thrombocytopaenia (RIAT) is a potential adverse drug reaction associated with the use of this therapeutic agent. Majority of the reported cases involved patients with haematological malignancies and its occurrence in autoimmune connective tissue diseases is rare. The pathogenesis of RIAT remains unclear but immune-mediated pathway has been implicated in the mechanism. RIAT runs a benign course and recovery ensues after its onset. Although life-threatening haemorrhage is uncommon, the risk remains significant with severe thrombocytopaenia. Despite being rare, the clinicians should be aware of this phenomenon. Post-administration monitoring of blood counts is pivotal in order to identify its occurrence. This report aims to highlight a case of RIAT with bleeding tendency in a woman with active mixed connective tissue disease.

Keywords: *Bleeding, mixed connective tissue disease, rituximab-induced acute thrombocytopaenia.*

Introduction

Rituximab, a chimeric anti-CD20 monoclonal antibody, has an established role in the treatment of lymphoid malignancies and certain autoimmune diseases. Peripheral blood cytopaenia, both late-onset and acute-onset, is a recognized side effect associated with the use of rituximab [1]. Late-onset cytopaenia (pancytopaenia, isolated neutropaenia, thrombocytopaenia or anaemia) develops several weeks to months after the administration of rituximab and is relatively common with Cattaneo et al reporting an overall frequency of 29.8% [2]. On the contrary, acute cytopaenia occurring within a few hours to a few days following the administration of rituximab is rare and of which, thrombocytopaenia is the commonest abnormality reported [3,4]. It is evident that patients with haematological malignancies had a higher risk to develop rituximab-induced thrombocytopaenia compared to patients with autoimmune diseases [5]. Rituximab has been shown to be an effective treatment option for autoimmune inflammatory rheumatic diseases which are resistant to conventional immunosuppressants [6,7]. With the increasing usage of rituximab, more cases of rituximab-induced acute thrombocytopaenia (RIAT) in patients with autoimmune connective tissue diseases are anticipated despite RIAT being a rare adverse drug reaction.

Case report

A 48-year-old woman presented with progressively worsening arthritis involving both knees and shoulders. She had mixed connective tissue disease (MCTD) with predominant systemic lupus erythematosus (SLE) features for 14 years. Her disease had become increasingly refractory to conventional disease-modifying antirheumatic drugs (DMARDs) and she experienced recurrent debilitating arthritis in recent months. Her latest serological profile showed raised titre of antinuclear factor (ANF 1:320 cytoplasmic, speckled), strongly positive anti-Jo-1, anti-nRNP, and anti-Ro52, positive anti-Sm, anti SSA/Ro and anti-double-stranded DNA (64 IU/L).

Upon review, active synovitis was noted at her shoulder and knee joints. There was no fever, joint deformity or mucocutaneous lesions. Examination of other organ systems was unremarkable. Investigations revealed elevated erythrocyte sedimentation rate (ESR 49 mm/Hr) and C-reactive protein (CRP 47.7mg/L). Her full blood counts (FBC), liver function test (LFT), renal profile (RP), and urine microscopy were normal. Determined to be having active MCTD, she was initiated on intravenous (IV) parecoxib, IV methylprednisolone, hydroxychloroquine (HCQ) and mycophenolate mofetil (MMF) alongside intra-articular triamcinolone acetonide for the knees. The methotrexate (MTX) was continued. Her knee arthritis improved but the left shoulder remained in pain, albeit of lesser degree. The plan to step up therapy to rituximab was discussed prior to discharge.

She was readmitted two weeks later with persistent left shoulder inflammation despite on prednisolone, HCQ, MTX, MMF, and analgesics. She consented to treatment with rituximab. Her baseline investigations prior to receiving rituximab revealed a total white cell count (TWBC) of 11.6 x 10^9/L, haemoglobin (Hb) of 13.7 g/dL, and platelet (PLT) count of 139 x 10^9/L. Following the premedication of paracetamol, IV chlorphenamine, and IV methylprednisolone, IV rituximab 1000mg was given. The infusion process was uneventful. The patient requested to be discharged after the treatment as she claimed to feel better.

However, she was readmitted after a day when she developed spontaneous bruises on her body. On examination, multiple purpuric and ecchymotic lesions were noted on her limbs and abdominal wall alongside subconjunctival haemorrhage at the right eye (Figure 1). She was haemodynamically stable and there were no clinical signs of gastrointestinal, urogenital, or

intracranial bleed. Immediate repeat PLT count was 40 x 10^9/L which further dropped to 3 x 10^9/L within 12 hours. The TWBC was 13 x 10^9/L and Hb was 15.1 g/dL. Coagulation profile was normal with international normalized ratio at 0.96 and activated partial thromboplastin time at 36 seconds. Considering the temporal relationship between the rituximab infusion and the drastic decrease in PLT count, the diagnosis of rituximab-induced acute thrombocytopaenia (RIAT) was made. She was transferred to intensive care unit (ICU) for close monitoring. A three-day course of intravenous methylprednisolone one gram daily was initiated. All other immunosuppressant agents were withheld. Eight units of platelet concentrates were transfused in a span of two days. Further evaluation showed elevated CRP at 114.5 mg/L, a negative Coombs test, normal complement C3 and C4 level (1.0 g/L and 0.21 g/L respectively), normal RP and LFT. Peripheral blood film revealed thrombocytopaenia but no platelet clumps or abnormal cells seen. She remained stable in ICU. The post-transfusion PLT count was 23 x 10^9/L.

On day 3 after the onset of RIAT, she decided to self-discharge against medical advice and sought treatment in other healthcare facilities for monitoring of the blood counts at her own discretion and risk. The course of the intravenous methylprednisolone was interrupted with the third dose administered on day 4 after the onset of RIAT, along with platelet transfusion when she presented again with thrombocytopaenia (PLT count of 11 x 10^9/L). Despite her frequent movement, she did not develop any further bleeding complications. Her subsequent PLT counts gradually improved. During her follow-up review 12 days after the onset of RIAT, all the haemorrhagic manifestations had resolved. Her PLT count had returned to baseline level (134 x 10^9/L). Anticipating the possible recurrence of RIAT with the risk of life-threatening haemorrhage, the clinical decision was to discontinue the subsequent dose of rituximab.

Discussion

Rituximab-induced acute thrombocytopaenia (RIAT) is rare in autoimmune connective tissue diseases (CTD) [8,9,10,11]. Majority of the cases were reported in patients with haematological malignancies (Table 1). The pathogenesis of RIAT has not been fully elucidated. Kong et al identified the presence of rituximab-dependent anti-platelet antibodies in three lymphoma patients who developed RIAT following the first exposure to the drug, suggesting an immune-mediated pathogenetic pathway [12]. Other proposed mechanisms of RIAT observed in patients with haematological malignancies include cytokine release syndrome with endothelial damage followed by platelet aggregation resulting in thrombocytopaenia, binding of circulatory CD20 antigen to platelet causing immune-mediated cell destruction, and disseminated intravascular coagulopathy-like reaction causing platelet consumption [13,14,15]. Massive tumour burden, bone marrow invasion, splenomegaly, a relatively low platelet count prior to the administration of rituximab, and a high platelet distribution width have been linked to a higher risk of developing thrombocytopaenia in patients with haematological malignancies while advanced age and chronic kidney disease are significant risk factors in patients with autoimmune bullous diseases [5,13,14,16]. As for autoimmune CTD, the evidence is still lacking and more robust clinical trials are needed to establish the pathogenesis and to determine the risk factors of RIAT in these patients.

RIAT has been reported when rituximab is used in various settings. It can arise when rituximab is given as a monotherapy or in combination with a chemotherapy regimen [3,4,8,9,11,13]. It may occur following the first dose of rituximab as in this case or only appear after repeated exposure to the drug [8,9,11,13,14,17]. In RIAT, the thrombocytopaenia develops early, usually in a few hours after the administration of rituximab, and typically reaches a nadir within a day [3,4,18,19,20]. Its abrupt onset can be missed if

the blood counts are not monitored particularly when rituximab is administered in an out-patient setting, hence possibly leading to underdiagnosis of this event. At present, there remains no clear recommendation for the frequency of blood count monitoring during the immediate post-transfusion period when rituximab is utilized in rheumatic diseases [21]. While the platelet count in RIAT can decline rapidly to a critical level, haemorrhagic manifestations are not common [3,4,13,14,17,18,19,20,22]. Nonetheless, the risk of major bleeding remains high when the platelet count is less than 20 x 10^9/L [23]. Hence, platelet transfusion is often given as a precautionary measure in severe thrombocytopaenia. Interestingly, when the cases of RIAT in autoimmune inflammatory rheumatic diseases were analysed, haemorrhagic manifestations seemed to be more frequently reported (mucosal bleed, haematuria, bloody stool) [8,9,11]. This patient had also developed mucocutaneous bleeding along with the thrombocytopaenia. This observation may suggest that even though RIAT is uncommon in autoimmune CTDs, there may be a higher tendency for patients to develop bleeding complications when it does occur. Besides the low platelet counts, other determinants of the bleeding risk need to be explored, particularly those contributing to platelet dysfunction [24].

RIAT is a transient event and resolution within one to two weeks with gradual recovery of platelet counts is expected in most cases [3,8,11,13,17,20,22]. The principal management strategies include close observation for any bleeding tendencies, intensive monitoring of the blood counts, and platelet transfusion when indication arises. The usage of corticosteroids and intravenous immunoglobulins has been implicated in the treatment of RIAT, by promoting the recovery of the platelet counts [8,25]. Some authors reported the recurrence of RIAT with reinitiation of rituximab [8,13,18,19]. In other cases, the patients continued to receive the subsequent cycles of chemotherapy regimen with rituximab safely without any recurrence [3,17]. At present, there is no plausible explanation to this peculiar nature of RIAT.

Conclusion

Despite RIAT being a rare phenomenon, the emerging reports of this condition in autoimmune connective tissue diseases should raise awareness among clinicians regarding this adverse effect of rituximab. Close monitoring of blood counts after the administration of rituximab is crucial in order to capture its occurrence and minimize the possibility of catastrophic haemorrhage. Future development of expert consensus on the management of RIAT is highly anticipated.

Conflict of Interest and financial disclosures
None

Informed Consent
Written informed consent was obtained from the patient for the publication of this report and the accompanying images.

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Authors contribution:
LHS: Manuscript writing and formatting
WS: Ideas, case management, data collection, and review of the manuscript

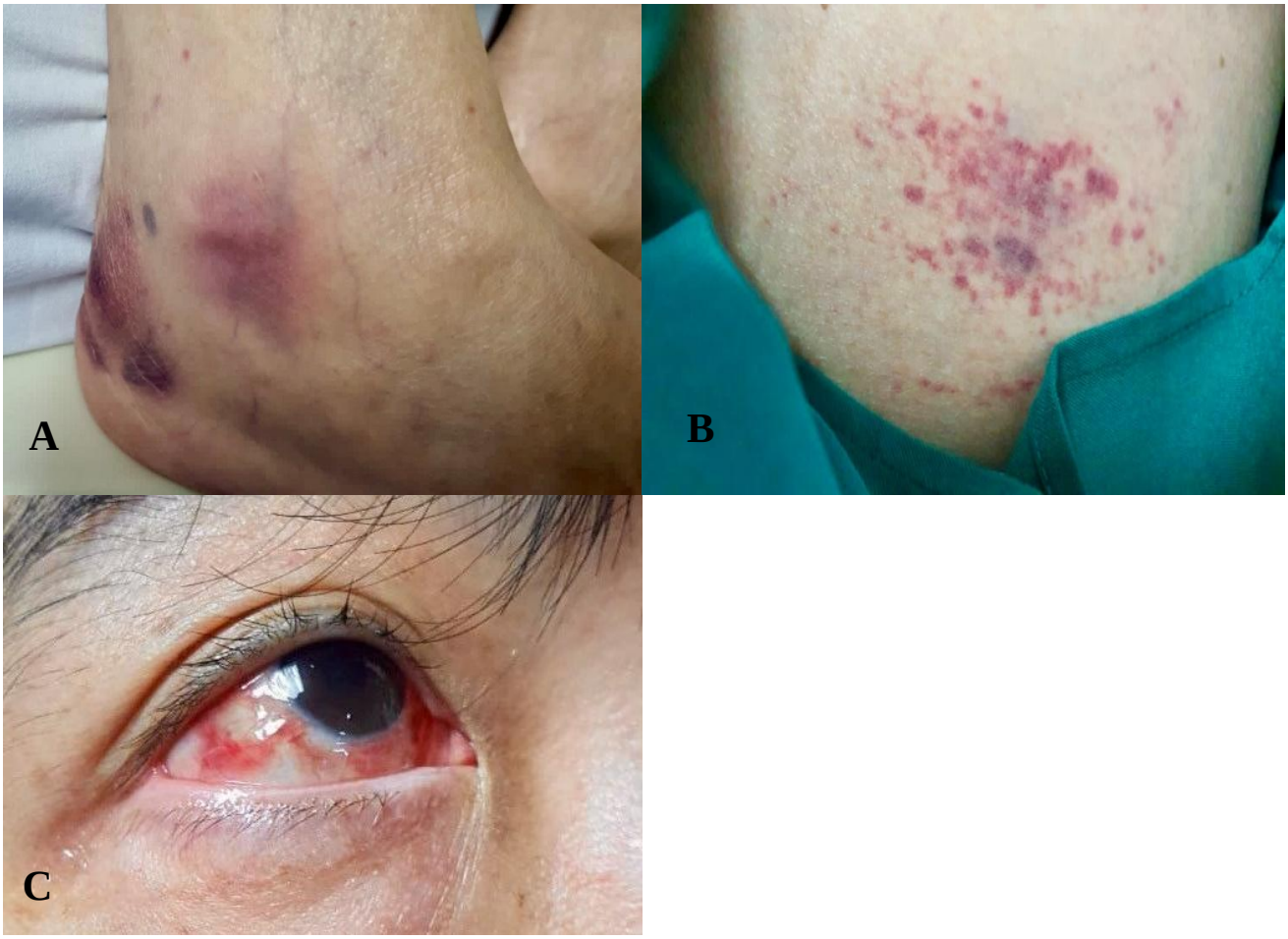

Figure 1. A. Ecchymotic patches on the right ankle. B. Purpuric spots on the abdominal wall. C. Subconjunctival haemorrhage at the right eye.

Table 1. Summary of case reports of rituximab-induced acute thrombocytopaenia (RIAT)

Study	Age (Y) /Sex	Indication of rituximab	Occurrence with first use	Treatment regimen	Time interval*	PLT nadir ($X10^9$/L)	Bleeding / PLT transfusion	PLT recovery	Recurrence with subsequent use
El-Osta et al [3]	66; F	MCL	Yes	Combination	Within hours	16	No / No	6 days	No
Ram et al [4]	71; F	MCL	No	Combination	8 hours	10	No / No	5 days	Not known
Yudhishdran et al [8]	36; F	SLE	Yes	Single agent	10 days	5	Yes / Yes	10 days	Yes
Akpabio et al [9]	39; F	SLE	Yes	Single agent	12 days	59	Yes / No	7 days	Not known
Shah et al [10]	35; F	SLE	Yes	Single agent	3 days	41	No / No	10 days	Yes
Endo et al [11]	72; F	GPA	No	Single agent	3 days	7	Yes / Yes	2 weeks	Not known
Omura et al [13]	74; M	FL	No	Combination	1 day	14	No / Yes	Within 1 week	Yes
Jiang et al [14]	56; F	FL	No	Combination	1 day	26	No / No	Within 1 week	Yes
	63; F	SMZL	Yes	Combination	1 day	25	No / No	Within 1 week	Yes
Sadashiv et al [17]	63; F	MCL	Yes	Combination	1 day	5	No / Yes	4 days	No
	72; M	MCL	Yes	Combination	1 day	10	No / Yes	5 days	No
	60; M	MCL	No	Combination	3 days	11	No / Yes	4 days	No
	64; F	MCL	Yes	Combination	1 day	3	No / Yes	13 days	No
	76; M	MCL	Yes	Combination	1 day	26	No / No	4 days	Not known
Yi et al [18]	58; M	MCL	Yes	Combination	1 day	24	No / No	3 weeks	Yes
Rosado et al [19]	63; M	MCL	No	Combination	1 day	15	No / Yes	3 days	Yes
Ureshino et al [20]	65; M	FL	Yes	Combination	1 day	5	No / Yes	Within 1 week	Not known
Otrock et al [22]	41; M	HCL	Yes	Combination	1 day	7	No / Yes	1 week	Not known
	64; M	MCL	Yes	Single agent	1 day	10	No / Yes	A few days	Not known
This study	48; F	MCTD	Yes	Single agent	1 day	3	Yes / Yes	12 days	Not known

M: male, F: female, Y: years, PLT: platelet, MCL: mantle cell lymphoma, SLE: systemic lupus erythematosus, GPA: granulomatosis with polyangiitis, FL: follicular lymphoma, SMZL: splenic marginal zone lymphoma, HCL: hairy cell leukaemia, MCTD: mixed connective tissue disease

*Time interval to documentation of thrombocytopaenia after rituximab administration

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