

**Rituximab-induced acute thrombocytopaenia in an African lupus patient: A case report**Akpabio A A¹, Nga C N¹, Udofia U K¹, Asuka E S¹, Orji P N²¹Department of Internal Medicine, University of Uyo Teaching Hospital, Uyo – Nigeria²Excel Children Medical Centre, Dolphin Estate, Ikoyi, Lagos - Nigeria**Abstract**

Drug-induced acute thrombocytopaenia (DITP) is a complication of various medications resulting in a platelet count $<50 \times 10^9/L$ from prior normal levels. It typically occurs within 1-2 weeks post-administration but can occur rapidly within 1-3 days with previous exposure. Rituximab (an anti-CD20 antibody) used to treat many autoimmune cytopaenias, has been reported to cause thrombocytopaenia mostly in lymphoma patients.

Reports in lupus are rare possibly because of off-label use. We hereby highlight the case of a 39-year old African lady who developed acute thrombocytopenia 12 days post-rituximab. Frequent monitoring of blood counts will enhance identification and treatment of this complication.

Keywords: Rituximab, acute thrombocytopenia, lupus, case report, African

Introduction

Drug induced thrombocytopaenia (DITP) is a clinical condition that can occur from various medications resulting in a platelet count $<50 \times 10^9/L$ from prior normal levels. It is thought to occur in two main ways: decreased production (from marrow suppression) and accelerated destruction (immune-mediated).¹ It typically occurs within 1-2 weeks after initiating a new medication or rapidly (1-3 days) if the drug has been taken before. Recovery subsequently occurs 10 or more days following drug cessation.^{1,2}

Common medications identified include: heparin, quinine, carbamazepine, vancomycin, sulphonamides and cimetidine among others.³ Interestingly, rituximab (an anti-CD20 antibody) has also been mentioned in several reports⁴⁻⁶ as a cause of thrombocytopenia despite being an

effective treatment for many primary autoimmune cytopaenias as well as refractory thrombocytopenia associated with systemic lupus erythematosus (SLE).⁷

Rituximab-induced thrombocytopenia (RIT) is mostly reported in patients with lymphoma,^{4,6} though cases have been noted in those with vasculitis⁸ and autoimmune hemolytic anaemia.⁹ Despite its frequent off-label use and efficacy in SLE, reports of rituximab-induced thrombocytopenia among lupus patients are sparse^{10,11} with none among blacks despite having the highest incidence and prevalence of lupus worldwide.¹² We hereby report a case of rituximab-induced acute thrombocytopenia in a 39 year old African lady following therapy for bullous SLE.

Case Summary

Mrs FCB a 39-year-old Nigerian lady was first diagnosed by a Physician with lupus in November 2017 after a month history of recurrent fever, fatigue, hair loss, polyarthritis, frothy urine as well as facial and leg swelling. She also noticed generalized bullous rashes, oral ulcers,

Corresponding Author: Dr Akpabio, Akpabio Akanimo

Internal Medicine Department,
University of Uyo Teaching Hospital, Uyo,
Akwa Ibom State, Nigeria.

E-mail: petersakpabio@yahoo.com, Phone: +2348039272954

photosensitivity and two left leg ulcers occurring at herbal incision sites. Investigations at diagnosis showed ESR 90mm/hr, ANA 1:5120 (speckled pattern), dsDNA 300IU/ml (>18) and mild pericardial effusion on echocardiography. She was commenced on oral prednisolone, hydroxychloroquine (HCQ) and sunscreen with improvement in symptoms.

After 6 months on treatment, she discontinued her medications thinking she was cured but had a flare 2 months later (July 2018). Following re-appearance of generalized bullous rashes in addition to the poorly healing leg ulcers that was unresponsive to her previous medications, she was referred to a rheumatologist for further care. Examination findings on presentation at the rheumatology clinic in November 2018 revealed an obese lady (BMI 29.3Kg/m²), with mild pallor, facial puffiness and bilateral pitting leg edema. No fever, oral ulcers, synovitis or asterixis was noted. She had a pulse rate of 72b/min, blood pressure 120/80mmHg, and respiratory rate 20c/min with normal findings on cardiovascular and chest exams respectively.

Multiple small bullae (1cm diameter, in various stages of healing) were seen over the arms, legs, chest and back with facial sparing as shown in Figure 1. Two ulcers were also noted – a larger 8cm x 6cm oval ulcer on the medial third of the leg and a smaller 1cm x 1cm round ulcer on the dorsum of the foot both with unhealthy granulation tissue and slough. An impression of SLE flare with bullous lupus, nephritis and infected vasculitic ulcers was made.

Investigation results obtained showed: PCV 35%, WBC 9800/mm³, Platelets 295,000/mm³, ESR = 48mm/hr, creatinine 53µmol/l, urea 4.2mmol/l, sodium 137mmol/l, potassium 3.7mmol/l, chloride 102mmol/l and bicarbonate 27mmol/l. She had a normal urinalysis and abdominal ultrasound with urine protein-creatinine ratio (UPCR) of 124mg/day (<15) and estimated GFR (CKD-EPI) of 115mls/minute. Renal biopsy revealed a mild patchy active chronic interstitial nephritis with essentially normal glomeruli on light and immunofluorescence microscopy. A skin biopsy was in keeping with systemic lupus erythematosus (SLE). The ulcers were infected with *Staphylococcus aureus* that was sensitive to clindamycin, meropenem and imipenem.

While saving funds to purchase rituximab, she was re-started on tabs mycophenolate mofetil (MMF) 1g twice daily, oral prednisolone 20mg daily, tabs HCQ 200mg daily, tabs dapsone 50mg daily, tabs lisinopril 5mg daily, betamethasone cream twice daily, sunscreen SPF 50 as well as daily wound dressing and twice daily oral clindamycin 600mg. Bullae persisted despite above therapies for 3 months with at least 10 new bullae appearing daily (figure 1). She finally purchased and received IV rituximab (Mabthera® Roche) in February 2019 at a dose of 500mg 2 weeks apart (due to cost constraints). A full blood count done 2 days pre-rituximab showed a PCV of 36%, WBC 7500/mm³, Platelets 272,000/mm³ and ESR = 51mm/hr.

She developed mild hematuria and blood-stained stools but no other signs of bleeding about 9 days after the first rituximab dose. Her platelet count declined from a pre-treatment baseline of 272,000/mm³ to a nadir of 59,000/mm³ from a blood count done 12 days after the first dose. The 2nd dose of rituximab given two weeks after the first dose was uneventful with patient declining to have a blood transfusion as platelet infusions were unavailable. Her clotting profile was normal and she received a single 10mg dose of parenteral vitamin K with subsequent resolution of bleeding. Platelet count slowly improved to 87,000/mm³ a week after the 2nd dose, stabilizing at a normal level of 185,000/mm³ one month after the second dose (see figure 3). Her platelet counts have remained stable in the last 1 year with a recent value of 290,000/mm³. Table 1 summarizes her full blood count results at different points in her management.

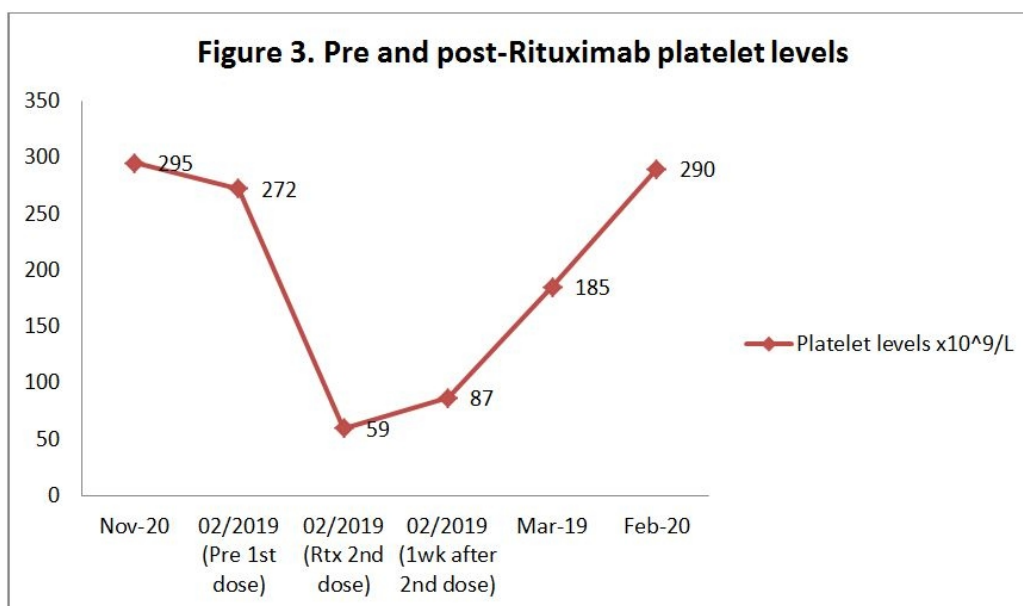
Skin lesions resolved completely 3 months post-rituximab with residual hyperpigmentation and have remained stable 1 year post-treatment (see figure 2). Ulcers improved after rituximab and a venous stripping procedure was done to treat incompetent veins. Her current medications include: tabs MMF 1g twice daily, hydroxychloroquine 200mg daily, prednisolone 10mg daily among others. Latest blood tests show: normal urinalysis, electrolytes (Creatinine 88µmol/l), normal complement [C3=101.1mg/dl (90-180), C4 = 26mg/dl (10-40)], HBA_{1c} 4.8%, PCV 34%, ESR = 45mm/hr. Patient is on regular clinic follow-up with rheumatology and dermatology.

Table 1: Full blood count parameters during patient’s management

DATE	PCV (%)	WBC (x 10 ⁹ /l)	PLT (x 10 ⁹ /l)	ESR
5/11/2018 (3 months pre-treatment)	35	9.8	295	48
4/2/2019 (2 days before 1 st dose)	36	7.5	272	51
18/2/2019 (12 days after 1 st dose)	33	4.6	59	42
27/2/2019 (1 week after 2 nd dose)	34	5.2	87	39
29/3/2019 (1 month after 2 nd dose)	35	7.9	185	37
10/2/2020 (1 year post-treatment)	34	8.6	290	45



Figures 1 and 2: Pre and post-treatment bullous SLE



*1st and 2nd rituximab doses were 2 weeks apart

Discussion

Rituximab-induced acute thrombocytopenia (RIAT) is a complication of rituximab therapy mostly reported in lymphoma patients and rarely in patients with autoimmune disease. Risk factors in cancer patients include: pre-treatment platelet $<100 \times 10^9/L$, splenomegaly, marrow involvement¹³ and concurrent chemotherapy.¹⁴ A cumulative incidence of 20% (for platelet count $<50 \times 10^9/L$) was noted among a Dutch cohort (85% cancer patients, 15% autoimmune) demonstrating a higher prevalence in clinical practice compared to clinical trial reports (1.7%).¹⁴

Rituximab-induced acute thrombocytopenia is often undiagnosed because most patients do not get immediate post-therapy blood counts and are usually on multiple immunosuppressive medications.^{6,13} Proposed mechanisms include; (i) CD20 antigen causing antigen-antibody immune-mediated cell lysis by complement activation, (ii) CD20 antigen on the platelet surface, (iii) platelet binding of a soluble anti-CD20/rituximab complex, and (iv) intravascular fibrinolysis.⁶ Overall, immune-mediated thrombocytopenia can have an abrupt onset, while thrombocytopenia from marrow suppression usually runs a gradual course two or more weeks after drug administration.¹⁴

Although the platelet count in our index patient was slightly above $50 \times 10^9/L$, RIAT was the most likely cause in view of a sudden sharp decline in platelet levels following drug administration with no other identifiable cause. Reports in SLE are rare (despite frequent off label use) with none noted among blacks who are mostly affected by lupus worldwide.¹⁰⁻¹² We came across two reports of RIAT in lupus patients^{10,11}: the first a 36 year old Hispanic lady who received a total of 1.5g (375mg x 4) of rituximab for severe nephritis and hemolytic anaemia while the second was a 35 year old Indian who was treated with 2g (1000mg x 2) rituximab for lupus nephritis. In both cases platelet counts fell within a week of medication onset and recovered within 2-4 weeks of cessation.

Our index case had a similar age to the other two women (36 years) though her indication was different as she was treated for severe bullous SLE and vasculitis. Compared to the others, our African patient received low dose rituximab (500mg x 2) due to cost constraints and developed

thrombocytopaenia which was only noted 12 days after the first dose. Although the duration noted is longer than the other 2 reports, it is possible that our index patient developed acute thrombocytopenia days before bleeding was noticed. Development of RIAT following low dose rituximab could indicate an idiosyncratic mechanism rather than a dose-dependent one.

Some authors have reported relatively mild manifestations of RIAT despite low platelet counts^{4,5} with recovery at the end of treatment as also seen in our index case. Other supportive care could include platelet transfusions or where indicated plasmapheresis, intravenous immunoglobulin etc.¹⁵ With rituximab maintaining a better safety profile than most other immunosuppressive agents⁷ and its widespread use in lupus and other conditions, it is essential to anticipate occurrence of rituximab-induced acute thrombocytopenia and frequently monitor blood counts before and after treatment.

In conclusion, we have reported a case of rituximab-induced acute thrombocytopaenia in a known lupus patient. Our case management was limited by the absence of bone marrow aspiration cytology to exclude other causes of thrombocytopenia as well as the relatively infrequent full blood count checks mainly due to the fact that patient was travelling from a neighbouring state to access rheumatology care. Acute thrombocytopaenia can result from medications like rituximab, though commoner causes should be first excluded.

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