A case of late-onset neutropenia secondary to rituximab in a patient with mucous membrane pemphigoid

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INTRODUCTION

Rituximab (RTX) is increasingly used in the treatment of autoimmune blistering disorders (AIBDs). Neutropenia associated with RTX has been reported in the treatment of hematologic and rheumatic conditions,[1,2] occurring both shortly after treatment and weeks to months later. Definitions of early-onset neutropenia (EON) and late-onset neutropenia (LON) have been variable in the literature (Table I), with presentation ranging from an asymptomatic laboratory test value to critical illness. Few cases of RTX-associated neutropenia in the setting of AIBDs have been reported.[3-6] Here, we present a case of LON secondary to RTX occurring in a patient with mucous membrane pemphigoid (MMP), a condition in which RTX-associated neutropenia has not been reported to our knowledge.

CASE REPORT

A 70-year-old woman was diagnosed with MMP in 2013 by hematoxylin-eosin and immunofluorescence. She was initially treated with dapsone, prednisone, and intravenous immunoglobulin. Due to progressive disease, she was switched to cyclophosphamide in June 2014. She then developed pancytopenia secondary to cyclophosphamide in June 2015, from which she had recovered by August 2015 after cessation of the drug. In June 2016, she began RTX monotherapy.

Abbreviations used:

AIBD:	autoimmune blistering disorder
ANC:	absolute neutrophil count
EON:	early-onset neutropenia
G-CSF:	granulocyte-colony stimulating factor
LON:	late-onset neutropenia
MMP:	mucous membrane pemphigoid
RTX:	rituximab

Sixty-three days after her second cycle of RTX, the patient's absolute neutrophil count (ANC) was incidentally noted to be 1.0×10^9/L, without associated anemia or thrombocytopenia (Fig 1). She was asymptomatic, with no intervention required. Her isolated neutropenia was still present before her third cycle of RTX, when ANC was 1.1×10^9/L. At 134 days after her third cycle of RTX, her ANC further decreased to 0.2×10^9/L. She was initially asymptomatic but then developed respiratory symptoms with an ANC of $<0.1 \times 10^9$/L, and doxycycline was prescribed. Twenty-two days later, she developed a fever and was admitted to the hospital, where she received antibiotics for pneumonia and urinary tract infection. Her ANC at this time was 0.9×10^9/L, and she received 3 doses of granulocyte-colony stimulating factor (G-CSF). Her ANC normalized after 14 days. She has not been rechallenged with RTX, and her ANC remains normal.

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Table I. Neutropenia definitions

Term	Definition
Neutropenia	
Mild	ANC $\geq$ 1.0 and $<$ 1.5 $\times$ 10^9/L
Moderate	ANC $\geq$ 0.5 and $<$ 1.0 $\times$ 10^9/L
Severe	ANC $<$ 0.5 $\times$ 10^9/L
Late-onset neutropenia	
Hematology literature[1]	ANC $<$ 0.5 to 1.5 $\times$ 10^9/L occurring more than 4* weeks after the last infusion of rituximab in the absence of any other identifiable cause
Rheumatology/autoimmune literature[2,10]	ANC $<$ 1.0 to 1.5 $\times$ 10^9/L occurring more than 4 weeks after the last dose of rituximab without another identifiable cause
Early-onset neutropenia	
Rheumatology/autoimmune literature[3,8]	Neutropenia (not further quantified) occurring within 4 weeks of treatment initiation

ANC, Absolute neutrophil count.
*Two reports included cases that occurred within 2 to 3 weeks of the last rituximab infusion.

DISCUSSION

Neutropenia is a now well-established effect that can occur after RTX therapy. LON has been reported more frequently than EON, but EON is likely underreported because neutropenia occurring within 4 weeks of RTX was excluded from previous trials.[1] Only 5 cases of RTX-associated neutropenia have been reported in the setting of AIBDs,[3-6] including the present case (Table II); as such, it is difficult to draw definitive conclusions regarding incidence, prognosis, and management in patients with dermatologic disorders. Inferences can best be drawn from populations with rheumatic disorders, whose clinical characteristics and treatments likely have the greatest overlap with AIBDs, but current knowledge is limited.

In populations with rheumatic and hematologic disorders, the frequency of occurrence of LON is reported to be 1.3% to 29.9%.[7] True incidence is confounded, however, by the retrospective nature of studies, varying definitions of LON used, and diverse populations. The incidence of EON is difficult to assess because there have been only 8 reported cases[3,8] and 1 indeterminate case.[6] The mechanism of RTX-associated neutropenia is unknown, and the heterogeneity of cases precludes conclusive assessment of contributing factors.[1]

LON can occur after any cycle of RTX[2,7,9] and may be more common with higher cumulative doses of RTX.[1,7] It has been reported in the setting and absence of concurrent immunosuppressants,[2,7,9] with the contribution of concurrent or prior immunosuppression variably reported to have an association on its development.[7,9] A history of neutropenia before RTX has not been associated with development of LON.[7] Although many patients with RTX-associated neutropenia have been female,[2,3,8] no association between LON and sex has been found.[7] LON has been associated with an immunoglobulin G Fc receptor polymorphism, which may lead to enhanced neutrophil destruction.[1]

In patients with rheumatic disorders, the average onset of LON after RTX is approximately 5 months (range, 40-366 days).[2,9] Its duration has been reported to last between 3 and 45 days,[2,9] with an outlier of 270 days in which neutropenia was improved after 60 days.[2] Recurrence rates upon rituximab rechallenge are variable, ranging from 0% to 50%.[2,7,9] Treatment recommendations are unclear, with G-CSF reported to shorten time to ANC recovery but leading to no change in clinical outcome.[2]

Although traditionally viewed as a benign adverse event with frequent self-resolution,[1,2] LON has also been suggested to be more severe in patients with rheumatic disorders, with rates of infectious symptoms necessitating hospitalization or intravenous antibiotics varying between 28% and 85%.[2,7,9] These rates are notably higher than the 17% reported in patients with hematologic disorders.[1] In both populations, concurrent or prior immunosuppression was common, and its contribution to infections cannot be excluded. In the majority of cases, patients with neutropenia recovered.[1,2,7,9] One death was reported in a patient with lymphoma,[1] and 1 death was reported 24 months after LON in a patient with granulomatosis with polyangiitis who later developed myelodysplasia.[10] Of the cases of EON, only 1 was associated with sepsis, and no deaths were reported.[3,8]

Based on analysis of the cases of RTX-associated neutropenia in association with AIBDs (Table II), the nadir of neutropenia in our case is similar to that of cases reported in the literature. The duration in

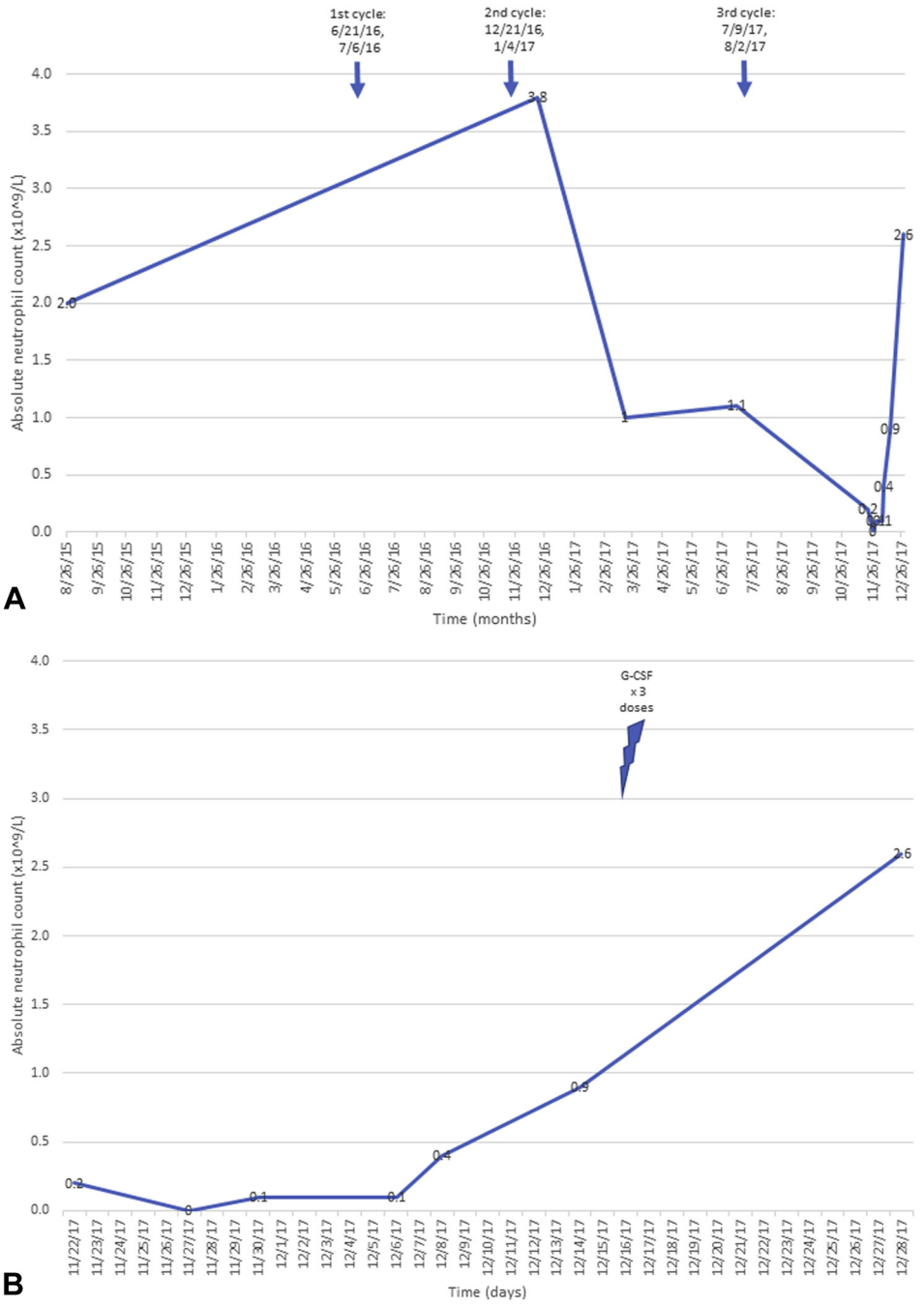

Fig 1. **A,** Absolute neutrophil count over time in the reported case, with the *x*-axis reported in months. Arrows denote cycles of rituximab with corresponding dates. **B,** Absolute neutrophil count over time in the reported case, with the *x*-axis reported in days. Lightning bolt denotes administration of 3 doses of G-CSF. *G-CSF*, Granulocyte-colony stimulating factor.

previously reported cases was much shorter than in our case, although our case is confounded by neutropenia that persisted between multiple cycles of rituximab. All patients who developed RTX-associated neutropenia in AIBDs ultimately required hospitalization, antibiotics, and G-CSF,[3-6] although our patient did well with neutropenia for 281 days. Although this could point toward more serious consequences of RTX-associated neutropenia in the setting of AIBDs, it may be attributable to sampling bias because patients with infectious symptoms are likely to be tested, whereas complete

Table II. Reported cases of rituximab-associated neutropenia in autoimmune blistering disorders

Reference	Patient no.	Age, years	Sex	Condition treated	Concurrent immunosuppression	RTX dosing	Type of neutropenia	Time to onset of neutropenia	Nadir ANC, $\times 10^9$/L	Duration of neutropenia, days	Hospitalization/ antibiotics/G-CSF and other notes	Recurrence
Goh et al, 2007[4]	1	48	M	PV	Prednisolone, cyclosporine, mycophenolate mofetil	375 mg/m^2 weekly × 4 weeks	LON	133 days after last RTX infusion	0.6	10	Yes/yes/yes Treated for PNA	Unknown
Rios-Fernandez et al, 2007[5]	2	27	F	PV	Azathioprine, prednisone	375 mg/m^2 weekly × 4 weeks	LON	191 days after last RTX infusion	0.36	5	Presumed yes as was given IV antibiotics/ yes/yes Episode of fever	Unknown
Adler et al, 2018[3]	3	46	F	BP	Mycophenolate mofetil	375 mg/m^2 weekly × 4 weeks	EON	18 days after first RTX infusion	0.0	~12	Yes/yes/yes Initially found incidentally (ANC, 0.9 × 10^9/L); then patient presented with fever and respiratory symptoms (ANC, 0.0 × 10^9/L) No source of infection identified	Unknown
Khosravi et al, 2017[6]	4	66	F	BP	Prednisolone	RTX biosimilar (Reditux, Dr Reddy's Laboratories, Hyderabad, India) 500-mg weekly infusions × 4 weeks	Indeterminate	18 days after last RTX infusion	0.44	~5	Yes/yes/yes Patient presented with fever No source of infection identified	No recurrence with different RTX biosimilar (Zytux, AryoGen, Tehran, Iran)
Current case	5	70	F	MMP	None	1000 mg × 2 doses spaced 2 weeks apart	LON	63 days	After 1st cycle: 1.0 After 2nd cycle: 0.0	295	After 2nd cycle: No/no/no After 3rd cycle: Yes/ yes/yes Treated for PNA, UTI	Unknown

ANC, Absolute neutrophil count; *BP,* bullous pemphigoid; *EON,* early-onset neutropenia; *F,* female; *G-CSF,* granulocyte-colony stimulating factor; *IV,* intravenous; *LON,* late-onset neutropenia; *M,* male; *MMP,* mucous membrane pemphigoid; *PNA,* pneumonia; *PV,* pemphigus vulgaris; *RTX,* rituximab; *UTI,* urinary traction infection.

blood count monitoring may not otherwise be performed.

In summary, we present a case of LON secondary to RTX in a patient with MMP that developed after her second cycle of RTX and worsened after their third cycle, ultimately requiring hospitalization, antibiotics, and G-CSF but leading to no long-term sequelae. We review the literature for other cases of RTX-associated neutropenia associated with AIBDs and draw attention to this adverse effect that we may see in clinical practice, especially as use of RTX increases. Future reporting may lead to enhanced understanding of its pathophysiology and more definitive screening and management recommendations.

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