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

Brittney Schultz, MD,a and Donna Culton, MD, PhDb

Minneapolis, Minnesota and Chapel Hill, North Carolina

Key words: neutropenia; pemphigus; pemphigoid; rituximab.

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.

Sixty-three days after her second cycle of RTX, the patient’s absolute neutrophil count (ANC) was incidentally noted to be $1.0 \times 10^9/L$, 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 $1.1 \times 10^9/L$. At 134 days after her third cycle of RTX, her ANC further decreased to $0.2 \times 10^9/L$. 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 $0.9 \times 10^9/L$, 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.

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

From the Departments of Dermatology and Internal Medicine, University of Minnesota, Minneapolisa and Department of Dermatology, University of North Carolina, Chapel Hill.b

Funding sources: None.

Disclosure: Dr Culton has given educational talks on rituximab and has been compensated by Genentech. Dr Schultz has no conflicts of interest to declare.

Displayed as a poster presentation at the 2019 Medical Dermatology Society Annual Meeting, Washington, DC, on February 28, 2019, under the title “Rituximab-Associated Neutropenia in Autoimmune Blistering Disorders: A Case Report, Review of the Literature, and Proposal for Management.” Also presented at the University of Minnesota Dermatology Research Day on April 10, 2019 in Minneapolis, MN, and at the Minnesota Dermatologic Society Meeting on May 17, 2019 in Minneapolis, MN.

Correspondence to: Brittney Schultz, MD, Department of Dermatology, University of Minnesota, 4-240 Phillips-Wangensteen Building, 516 Delaware St Southeast, Minneapolis, MN 55455. E-mail: bschultz@umn.edu.

JAAD Case Reports 2019;5:715-9.

2352-5126

© 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jdcr.2019.06.009
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 under-reported because neutropenia occurring within 4 weeks of RTX was excluded from previous trials. Only 5 cases of RTX-associated neutropenia have been reported in the setting of AIBDs, 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%. 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 and 1 indeterminate case. The mechanism of RTX-associated neutropenia is unknown, and the heterogeneity of cases precludes conclusive assessment of contributing factors.

LON can occur after any cycle of RTX and may be more common with higher cumulative doses of RTX. It has been reported in the setting and absence of concurrent immunosuppressants, with the contribution of concurrent or prior immunosuppression variably reported to have an association on its development. A history of neutropenia before RTX has not been associated with development of LON. Although many patients with RTX-associated neutropenia have been female, no association between LON and sex has been found.

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

Although traditionally viewed as a benign adverse event with frequent self-resolution, 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%. These rates are notably higher than the 17% reported in patients with hematologic disorders.

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

| Table I. Neutropenia definitions |
|----------------------------------|
| Term                            | Definition                                                                 |
| Neutropenia                     | ANC ≥ 1.0 and < 1.5 \times 10^9/L                                         |
| Mild                            | ANC ≥ 1.0 and < 1.5 \times 10^9/L                                         |
| Moderate                        | ANC < 0.5 \times 10^9/L                                                  |
| Late-onset neutropenia          | 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 |
| Hematology literature           | ANC < 0.5 to 1.5 \times 10^9/L occurring more than 4 weeks after the last dose of rituximab without another identifiable cause |
| Rheumatology/autoimmune literature | 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.
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, 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

![Image of graphs A and B]

**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.
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 \(^5\)          | 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                            | Initially found incidentally (ANC, 0.9 $\times$ $10^9$/L); then patient presented with fever and respiratory symptoms (ANC, 0.0 $\times$ $10^9$/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 Patient presented with fever No source of infection identified | No recurrence with different RTX biosimilar (Zytux, AryoGen, Tehran, Iran) | Unknown    |
| 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: 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.

REFERENCES
1. Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine (Baltimore). 2010;89(5):308-318.
2. Monaco WE, Jones JD, Rigby WF. Rituximab associated late-onset neutropenia—a rheumatology case series and review of the literature. Clin Rheumatol. 2016;35(10):2457-2462.
3. Adler BL, Crew AB, Woodley DT. Early-onset neutropenia after rituximab therapy for bullous pemphigoid. Clin Exp Dermatol. 2018;44(3):334-336.
4. Goh MS, McCormack C, Dinh HV, Welsh B, Foley P, Prince HM. Rituximab in the adjuvant treatment of pemphigus vulgaris: a prospective open-label pilot study in five patients. Br J Dermatol. 2007;156(5):990-996.
5. Rios-Fernández R, Gutierrez-Salmerón MT, Callejas-Rubio JL, Fernández-Pugnaire M, Ortego-Centeno N. Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. Br J Dermatol. 2007;157(6):1271-1273.
6. Khosravi H, Abdollahi M, Badakhsh M, et al. Rituximab induced neutropenia in a patient with bullous pemphigoid. Arch Med. 2017;9:2. https://doi.org/10.21767/1989-5216.1000208.
7. Parodis I, Söder F, Faustini F, et al. Rituximab-mediated late-onset neutropenia in systemic lupus erythematosus—distinct roles of BAFF and APRIL. Lupus. 2018;27(9):1470-1478.
8. Shah S, Kavadichanda CG, Belani P, Ganesh RN, Negi VS. Early onset neutropenia and thrombocytopenia following rituximab in lupus nephritis. Int J Rheum Dis. 2019;22(5):946-950.
9. Knight A, Sundström Y, Börjesson O, Bruchfeld A, Malmström V, Gunnarsson I. Late-onset neutropenia after rituximab in ANCA-associated vasculitis. Scand J Rheumatol. 2016;45(5):404-407.
10. Besada E, Koldingsnes W, Nossent J. Characteristics of late onset neutropenia in rheumatologic patients treated with rituximab: a case review analysis from a single center. QJM. 2012;105(6):545-550.