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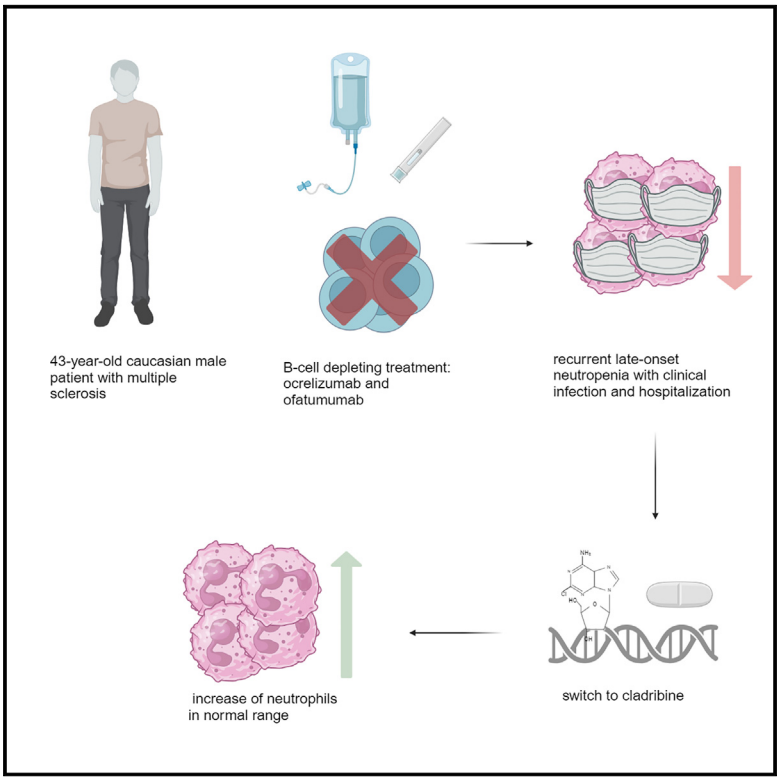
Case report

Recurrent late-onset neutropenia following treatment with different B cell-depleting strategies in multiple sclerosis

Graphical abstract



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In brief

This case report presents the first documented occurrence of late-onset neutropenia (LON) in a multiple sclerosis (MS) patient treated with ocrelizumab and subsequently ofatumumab. The findings underscore the need for close monitoring of MS patients undergoing B cell-depletion therapy, with treatment decisions after LON remaining challenging.

Highlights

- Late-onset neutropenia is a rare side effect of B cell-depletion therapy
- We describe the first case of late-onset neutropenia after ofatumumab
- Highlights disease activity risk after receiving granulocyte-colony-stimulating factor
- Close monitoring and careful therapy decisions are important in late-onset neutropenia

Translation to Patients

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Case report

Recurrent late-onset neutropenia following treatment with different B cell-depleting strategies in multiple sclerosis

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CONTEXT AND SIGNIFICANCE Late-onset neutropenia (LON) is a delayed drop in neutrophil count associated with an increased risk of infection and is a rare side effect of B cell-depletion therapy in multiple sclerosis (MS). Since B cell-targeting therapies are broadly used in MS, it is crucial to monitor for long-term side effects. Here, Protopapa et al. report recurrent LON in a patient after switching from ocrelizumab to ofatumumab, causing infection and hospitalization. This case highlights the importance of close monitoring and careful management of patients on B cell treatment. Switching treatment can be challenging as LON recurred after switching between B cell treatments. In this case, treatment with cladribine did not cause blood abnormalities after nine months.

SUMMARY

Background: As B cell-depleting therapies in multiple sclerosis (MS) have gained significant importance in the last several years, their long-term safety profile is of considerable clinical interest. Late-onset neutropenia (LON) is a rare, but potentially severe, adverse event that was first described in patients with rheumatic disorders under therapy with rituximab. Ofatumumab was approved in 2021 for the treatment of relapsing-remitting multiple sclerosis (RRMS). Neutropenia occurred in 0.2% of patients in clinical phase 3 trials, and to date, no cases of LON have been reported under ofatumumab treatment.

Methods: Here, we report a case of repetitive symptomatic LON under ocrelizumab as well as ofatumumab treatment. Additionally, we review the literature on rare occurrences of LON in patients with MS, neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) undergoing B cell-depleting therapies, including rituximab, ocrelizumab, ofatumumab, inebilizumab, and ublituximab.

Findings: In our case, the patient presented with repetitive symptomatic LON under ocrelizumab as well as ofatumumab treatment leading to febrile infections, subsequent use of antibiotics, and application of granulocyte-colony-stimulating factor. After repetitive episodes of LON under both B cell-depleting strategies, cladribine was subsequently initiated. A nine-month follow-up showed a normal neutrophil count and no evidence of disease activity.

Conclusions: This case highlights the significance of symptomatic late-onset blood count changes under both ocrelizumab and ofatumumab and emphasizes the importance of continuous monitoring of the differential blood count under B cell-depleting treatment.

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INTRODUCTION

B cell-depletion therapy is highly effective in people with multiple sclerosis (pwMS). Several different B cell therapies are available for MS and related disorders, including rituximab, ocrelizumab, ofatumumab, ublituximab, and inebilizumab, each of which has a slightly different mechanism of action. In 2021, the European Medicines Agency approved ofatumumab, a subcutaneous anti-CD20 monoclonal antibody that selectively depletes B cells, for the treatment of adults with relapsing-remitting multiple sclerosis (RRMS). In two double-blind phase 3 trials, ASCLEPIOS I and ASCLEPIOS II, ofatumumab was associated with a lower annualized relapse rate than teriflunomide.[1,2] Regarding safety, ofatumumab showed manageable adverse events with more frequent injection-related systemic reactions, predominantly with the first injection.[1] The occurrence of infection was similar in both treatment groups. With respect to the blood cell count, neutropenia occurred more frequently in the teriflunomide (0.43%) than in the ofatumumab (0.2%) group.[1,2] Neutropenia following subcutaneous ofatumumab in MS may also be less common (0.3%) and to a lesser extent (typically grade 2 or less) than following ocrelizumab (4.4%–4.6%, typically grade 2 or more).[3,4]

Considering the increasing number of patients remaining on B cell-depleting therapies for years, it is important to recognize and manage long-term side effects. Late-onset neutropenia (LON) is defined as an absolute neutrophil count (ANC) <1.5 cells/nL that develops between 4 and 6 weeks after the last drug administration.[5,6] The ANC must be in the normal range before treatment initiation and other causes must be ruled out.[7,8] There are several cases describing LON in pwMS after other B cell-depletion treatments like rituximab[8–11] or ocrelizumab.[12–17] However, no case reports describe an LON after ofatumumab treatment; there were no cases of LON in the approval trials.[2] According to previous case series and studies, the incidence of LON with rituximab in non-neurological diseases varied from 1.3% to 27%,[5,10,18] with the assumption of higher incidence if a laboratory follow-up 4 weeks after administration[19–23] was done. However, the data in MS cohorts are still insufficient.

Since LON can be accompanied by severe infections leading to hospitalization and prolonged treatment, it is of the utmost importance to detect LON early. Here, we present the case of a patient with MS who developed recurrent episodes of LON after treatment with ocrelizumab and ofatumumab. In addition, we review the literature on rare cases of LON in patients with MS, neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) undergoing B cell-depleting therapies (rituximab, ocrelizumab, ofatumumab, inebilzumab, ublitixumab).

RESULTS

Case report

We report the case of a 43-year-old male patient, diagnosed with RRMS in 2005 and treated with different disease-modifying therapies (DMTs). Initial treatment with interferon-β was discontinued due to breakthrough disease activity. Afterward, he was switched to natalizumab, which was stopped because of an increasing risk of progressive multifocal leukoencephalopathy after 3 years of treatment due to a rising titer of John Cunningham virus. Fingolimod was then initiated and later terminated due to recurrent lymphopenia and fungal infection. In 2015, an attempt with dimethyl fumarate was made, resulting in subclinical activity evidenced by new periventricular lesions with gadolinium (Gd^+) enhancement.

As a result of breakthrough disease activity under basic/moderate DMT and moderate lymphopenia under fingolimod, the patient received his first ocrelizumab infusion in April 2018. In May 2022 (173 days after ocrelizumab infusion) and in September 2022 (72 days after ocrelizumab infusion), the patient demonstrated low ANCs (May 2022: 1.1 cells/nL; September 2022: 0.59 cells/nL) (Figure 1). During these episodes, the patient reported frequent skin infections and infections of the upper respiratory tract. Due to the two symptomatic neutropenic episodes under ocrelizumab, we opted for an intra-class switch to ofatumumab. The first administration in December 2022 was well tolerated.

At the end of March 2023 (41 days after the last ofatumumab administration), the patient presented with clinical signs of infection along with high C-reactive protein in the serum. An oral antibiotic and antiviral therapy was administered; absolute blood count showed leuko-, lympho-, and neutropenia (leukocytes 1.3/nL, lymphocytes 0.49/nL, neutrophils 0.09/nL) (Figure 1). The last ofatumumab administration had been more than 4 weeks prior, so an LON was diagnosed. Due to severe neutropenia, the patient received granulocyte-colony-stimulating factor (G-CSF) stimulation with filgrastim (30 MU subcutaneously). Within 2 weeks, the absolute counts of neutrophils, leukocytes, and lymphocytes increased to the normal range.

Unfortunately, 1 month later the patient reported new neurological symptoms such as dizziness and gait disturbance. He was hospitalized for further diagnostics since he presented with signs of infection that included fever, weakness, and vomiting. A cranial MRI displayed a new lesion in the middle cerebellar peduncle. Therefore, we started a 3-day high-dose corticosteroid pulse therapy (1 g/day methylprednisolone). The symptoms were continuously remitting over a few weeks, so we discussed the possible DMT alternatives. Again (112 days after the last ofatumumab administration), laboratory tests showed a new leuko-, lympho-, and neutropenia (leukocytes 1.6/nL, lymphocytes 0.6/nL, neutrophils 0.7/nL). In line with these poor blood count results, the patient again showed clinical signs of infection. The patient was rehospitalized for antibiotics, acyclovir and G-CSF administration. Based on the repetitive neutropenia even after ofatumumab discontinuation, a bone marrow biopsy was performed. The biopsy showed reduced granulopoiesis and no indications of malignancies. Due to the breakthrough activity under mild/moderate DMTs on the one hand and lymphopenia under S1P receptor modulator on the other hand, we decided to initiate an induction treatment with cladribine. At 37 days after the last LON, the cell counts had normalized (leukocytes 4.4/nL, lymphocytes 1.3/nL, neutrophils 2.6/nL), so we initiated the cladribine treatment. A 9-month follow-up showed a normal neutrophil count and no evidence of clinical or subclinical disease activity.

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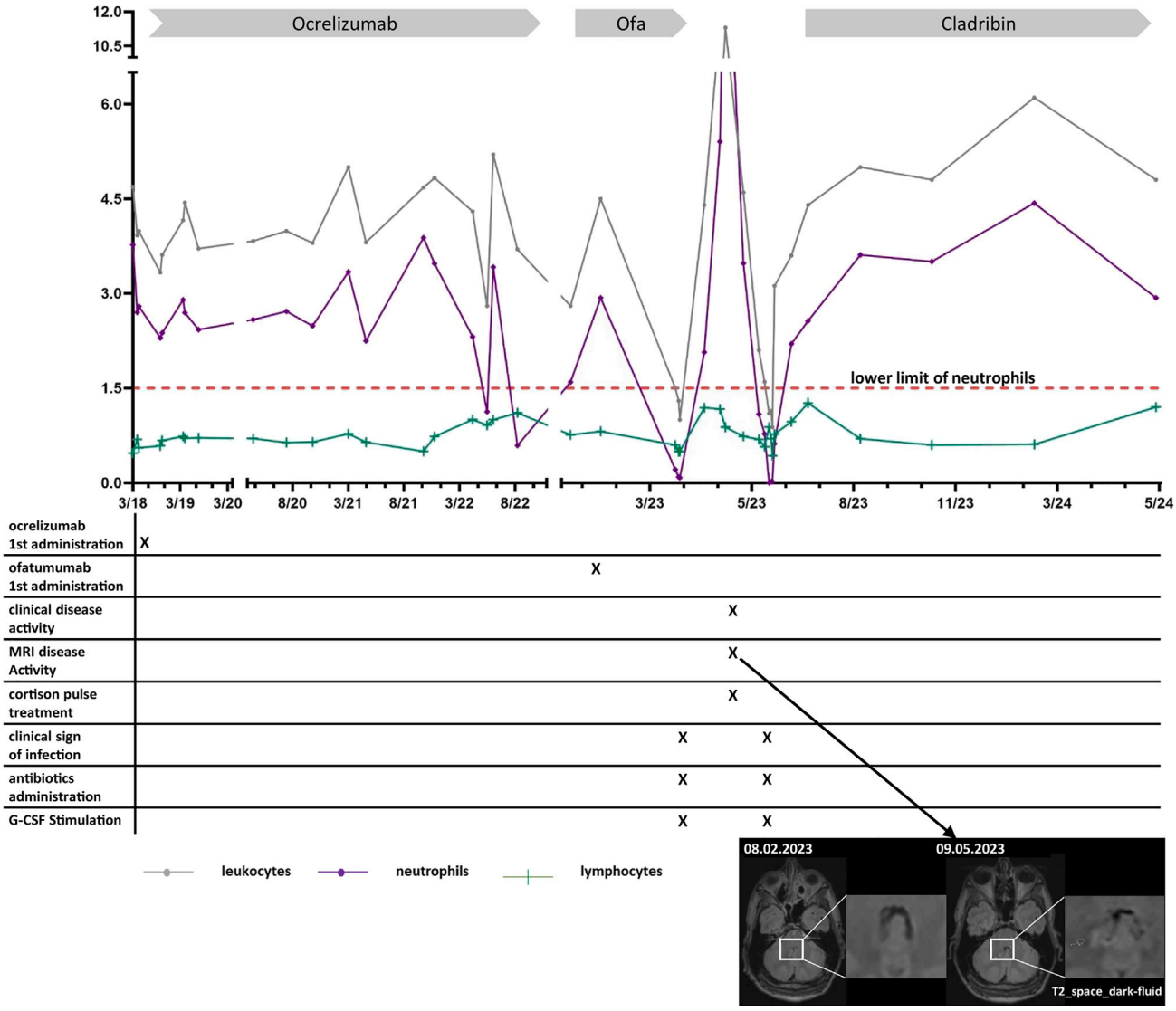

Figure 1. Overview of blood cell counts, therapy, and clinical incidents

Trajectory of the blood cell count (gray: leukocytes, purple: neutrophils, green: lymphocytes). The lower limit of neutrophils is depicted by the dotted red line. Top bars indicate disease-modifying treatment and duration over the course of treatment. The bottom table shows significant clinical events over the observation period. Ocr, ocrelizumab; Ofa, ofatumumab.

Literature review results

Although several cases of LON after treatment with rituximab have been reported in rheumatology and hematology, there are considerably fewer cases describing LON in patients with MS, MOGAD, or NMOSD after the administration of ocrelizumab or rituximab. According to our literature review, we did not identify any case with LON associated with ofatumumab, ublituximab, and inebilizumab.

The first case describing LON associated with ocrelizumab was published in 2019 by Cohen et al.[16] In total, we identified 30 cases with LON (Table 1) from patients with RRMS (n = 18), primary progressive multiple sclerosis (PPMS; n = 3), NMOSD (n = 3), or MOGAD (n = 6). Out of these 30 cases, 17 led to hospitalization with the administration of antibiotics and 21 received G-CSF. Conversely, several cases were associated with asymptomatic and self-limiting neutropenia.[8,24]

A relatively large retrospective analysis by Rigal et al.[27] of 385 patients with LON after rituximab identified 10 patients with MS, MOGAD, or NMOSD. A total of 80% of these were re-exposed to rituximab after recovery, with only one of them experiencing repetitive LON. Furthermore, the authors observed that the occurrence of LON was more frequent in NMOSD and MOGAD than in MS.

Beigneux et al.[7] described three cases with LON in patients treated with ocrelizumab. In these cases, as well as in one case from Maniscalco et al.,[29] the authors observed a recurrence of symptomatic agranulocytosis after continued treatment with ocrelizumab.[7] Cases reported by Auer et al.[17] and Marrodan

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Table 1. Literature review: Patient characteristics with late-onset neutropenia after treatment with B cell-depletion therapies in MS, MOGAD, and NMOSD

No.	Author	Year	No. of cases	Diagnosis	B cell-depletion treatment	Prior treatments	Lowest ANC, cells/nL	Days to neutropenia	Hospitalization	G-CSF	Antibiotics	Continuing treatment	Recurrence of neutropenia	DMT switch
1	Plate et al.[24]	2014	1	NMO	RTX	AZA	0.41	90	no	no	no	yes	no	no
2	Rissanen et al.[25]	2018	1	RRMS	RTX	IFN-β1a, NZB	0.02	90	yes	yes	yes	no	no	DMF
3	Biotti et al.[26]	2018	2	MOGAD (1 + 2)	RTX (1 + 2)	–	0 (1 + 2)	90 (1 + 2)	yes (1 + 2)	yes	yes	1. yes 2. no	1. no 2. –	1. RTX 2. TOC
4	Cohen[16]	2019	1	RRMS	OCR	GA, IFN-β1a, DMF	0	79	yes	yes	yes	NR	NR	NR
5	Zanetta et al.[12]	2020	1	RRMS	OCR	–	0.0	106	yes	no	yes	NR	no	NR
6	Auer et al.[17]	2020	1	RRMS	OCR	RTX	0.1	128	no	no	yes	no	no	NR
7	Rigal et al.[27]	2020	10	MOGAD (4), NMOSD (2), RRMS (4)	RTX	none	0.03 (median)	119.7 (median)	yes (6)	yes (6)	yes (6)	yes (8)	yes (1)	TOC (2)
8	Marrodan et al.[28]	2021	1	RRMS	1. RTX 2. OCR	IFN-β1a, FNG, DMF	1. 0.038 2. 0.24	1. 2 and 60 2. 30	1. yes 2. NA	1. yes 2. yes	1. yes 2. NA	1. No 2. yes	yes	1. OCR
9	Maniscalco et al.[29]	2021	1	RRMS	OCR	IFN-β1a, GA, NZB, FNG	0.7 0.9	49 77	NR	yes	yes	yes	yes	NR
10	Baird-Gunning et al.[14]	2021	1	PPMS	OCR	none	0.0	42	yes	yes	yes	no	no	no
11	Alba Suárez et al.[30]	2021	1	PPMS	OCR	none	0.34	19	yes	no	yes	no	no	NR
12	Kermode et al.[31]	2021	1	RRMS	OCR	IFN-β1a	0.29	70	yes	Yes	yes	yes	no	no
14	Rauniyar et al.[15]	2022	1	PPMS	OCR	none	0.0	90	yes	yes	yes	no	yes	NR
15	Rigal et al.[8]	2022	2	1. MOGAD 2. RRMS	1. RTX 2. OCR	NA	1. 0.07 2. 0.67	1. 70 2. 119	no	1. yes 2. no	no	yes	yes	1. RTX 2. OCR
16	Hess et al.[13]	2023	2	1. RRMS 2. RRMS	OCR	1. IFN-β1a, DMF, NZB 2. DMF	1. 0.47 2. 0.1	1. 66	1. yes 2. NR	1. yes 2. yes	1. yes 2. no	1. no 2. no	1. no 2. no	1. NZB 2. OFA
17	Beigneux et al.[7]	2024	3	1. RRMS 2. RRMS 3. RRMS	OCR	1. DMF 2. NZB, FNG 3. none	1. 0.32 2. 0.03 3. 0.02	1. 56 2. 43 3. 31	1. NR 2. NR 3. no	1. no 2. yes 3. yes	1. yes 2. no 3. no	1. yes 2. no 3. yes	3. yes 4. yes 5. yes	1. NZB 2. OFA 3. NZB
18	Alabdulqader et al.[32]	2024	1	RRMS	OCR	NA	0.0	46	yes	yes	yes	NR	no	NR

ANC, absolute neutrophil count; AZA, azathioprine; DMF, dimethyl fumarate; DMT, disease-modifying therapy; FNG, fingolimod; GA, glatiramer acetate; G-CSF, granulocyte-colony-stimulating factor; IFN-β1a, interferon-β1a; MMF, mycophenolate; MOGAD, myelin oligodendrocyte glycoprotein antibody; NMOSD, neuromyelitis optica spectrum disorder; NR, not reported; NZB, natalizumab; OCR, ocrelizumab; OFA, ofatumumab; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; RTX, rituximab; TOC, tocilizumab.

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et al.[28] describe the occurrence of LON after switching treatment from rituximab to ocrelizumab.

In 2022, Rigal et al.[8] presented the first prospective study for monitoring LON after anti-CD20 therapy in patients with inflammatory disorders of the CNS.[8] Within 6 months, 2 out of 152 (1.32%) patients experienced an LON. One patient had a recurrence of neutropenia after continuing the B cell-depletion treatment. In these cases, patients showed no clinical signs of infection, thus underscoring the existing recommendation to perform blood sampling at least 3 months after the last infusion.[8,33]

In contrast to the other cases, Marrodan et al.[28] and Alba Suárez et al.[30] described, in addition to LON, the occurrence of an early-onset neutropenia developing between 2 and 19 days since the last infusion with clinical signs of infection.

Interestingly, Biotti et al.[26] described two cases of LON associated with neurological relapse in MOGAD patients. Comparable with our reported case, one of the two patients suffered from a new clinical relapse with new MRI lesions after G-CSF stimulation. In an effort to understand the cause of LON and exclude other possible causes in their case, Kermode et al.[31] performed a bone marrow biopsy, which showed a myeloid maturation arrest.

After the resolution of LON, it remains challenging to decide between re-exposure or an alternative treatment. Several groups report the continuation of rituximab or ocrelizumab or the switch to another B cell-depletion treatment,[13,17,28] while other groups tried a de-escalation of the DMT.[25]

DISCUSSION

Following the approval of ocrelizumab for RRMS and PPMS in 2016, ofatumumab was the second B cell-depletion drug approved for MS. The short-term adverse effects of both DMTs seem to be manageable and especially patients using ofatumumab tolerate the therapy quite well. However, the long-term adverse effects are still unknown.

LON has been repeatedly investigated during therapy with rituximab[8–11] and ocrelizumab.[12–17] However, it has not been described with the newest B cell therapy for MS, ofatumumab. Herewith, we describe a case of a patient with LON after treatment with both ocrelizumab and ofatumumab.

The underlying pathomechanism of LON after B cell depletion remains unclear. Previous studies suggested an excess of T cell large granular lymphocytes in the bone marrow and peripheral blood, which can lead to the apoptosis of neutrophils.[34] Additionally, there is evidence of the production of autoantibodies binding to the neutrophil surface, an imbalance between B cell lymphopoiesis and granulopoiesis, and elevated levels of B cell activation factor[35] following B cell depletion favoring B cell repletion. Furthermore, CD20-depleting treatment could result in the decreased production of granulocyte-macrophage-CSF after the permanent depletion of naive and memory B cells.[36,37] It is worth noting that likely more than one mechanism contributes to the development of neutropenia.[4] However, in our view, studies focusing specifically on LON in patients with MS under B cell-depleting therapies are important, as the patient profile in hematologic diseases differs from that of patients with MS.

In addition, we suggest laboratory assessment 4–6 weeks after initiation of a B cell-depleting therapy. If LON occurs, then patients should be closely monitored for the appearance of clinical signs of infection, such as fever. A consultation with the hematology department is in these cases required. In cases of clinical signs of infection or a persistence of the neutropenia, a G-CSF stimulation should be considered.

An underestimated problem is the increased risk of disease activity after G-CSF stimulation.[38] In our case and in the case of Biotti et al.,[26] a clinical relapse and new MRI lesions occurred after the administration of G-CSF. Similarly, Rust et al.[39] presented a case with MS and breast cancer after chemotherapy who received G-CSF stimulation. Three months later, this patient experienced a new relapse, 7 years after the last relapse. In animal studies, it has been shown that G-CSF-deficient mice are resistant to the induction of experimental autoimmune encephalitis.[40,41] Furthermore, MS patients showed an increased number of G-CSF-producing T helper cells, and patients under immunomodulatory treatment showed a decreased number compared to untreated patients.[42] However, the indication for G-CSF stimulation should be made with caution and in consultation with the hematologist.

A further noteworthy aspect is the cumulative impact of prior immunomodulatory treatments on the development of LON. In our case, the patient previously received five DMTs with different modes of action, including high-efficacy DMTs like fingolimod and ocrelizumab, both of which resulted in significant alterations in the blood count (fingolimod:lymphopenia, ocrelizumab:lymphopenia, and neutropenia). The number of prior immunomodulatory treatments may be a possible risk factor for the occurrence of LON and could be an interesting approach for further investigation. Finally, when exhibiting recurrent cellular alterations leading to increased susceptibility to infections, particularly prior to initiating immunomodulatory treatment, it is important to consider underlying immunodeficiency conditions such as severe combined immunodeficiency (SCID)-like traits or adenosine deaminase deficiency. The observed depletion of both lymphocytes and neutrophils raises the possibility of an SCID-like phenotype, which could complicate treatment choices.

However, in the context of highly active MS courses, a highly efficient DMT is deemed mandatory. A mild to moderate DMT resulted in breakthrough disease activity in our case. Some authors recommend an intra-class switch to another B cell-depletion treatment[13,17,28] or natalizumab. However, many cases lack information regarding neutrophil count in the post-switch phase. Notably, we observed the repeated occurrence of neutropenia after switching from ocrelizumab to ofatumumab. This specific observation led us to question the recommendation to switch to another B cell-depleting therapy after LON. In our case, 9 months after initiating cladribine, the patient demonstrated a stable clinical and radiological disease course, along with a neutrophil count within the normal range. Certainly the use of natalizumab, in particular, if the John Cunningham virus titer is negative, seems to be a good alternative in cases with LON.

In conclusion, we report the first case of repeated LON after treatment with ofatumumab leading to hospitalization, use of antibiotics, and application of G-CSF. Further multicentric

observational trials are needed to identify patients at risk of developing LON under B cell-depleting therapy, in particular, ofatumumab.

Limitations of the study

While this case report contributes valuable insights, some limitations must be considered when interpreting the findings. First, it is uncertain whether our patient's LON was solely due to ofatumamab or if the prior ocrelizumab treatment had an additive effect. Second, the patient's past lymphocyte drop, although not severe, suggests a possible genetic susceptibility for lymphopenia. Third, as this case report is based on a single patient, the generalizability of the results is limited.

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to and will be fulfilled by the lead contact, Stefan Bittner (stefan.bittner@unimedizin-mainz.de).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.P., V.F., and S.B.; statistical analysis, M.P.; writing – original draft, M.P.; writing – review & editing, M.S., L.S., F.S., V.F., F.Z., and S.B.; funding acquisition, F.Z., V.F., and S.B. All authors had unrestricted access to all data. All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility for its content, including the accuracy of the data and its statistical analysis.

DECLARATION OF INTERESTS

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STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODELS AND SUBJECT DETAILS
  - Informed consent/ethical approval
- METHOD DETAILS
  - Laboratory and imaging details
  - Literature review

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
GraphPad Prism 9.5.1	Graphstats Technologies	graphpad.com
BioRender	BioRender	biorender.com

EXPERIMENTAL MODELS AND SUBJECT DETAILS

The case reports a 43-year old Caucasian male patient with RRMS presenting to our outpatient clinic at the University Medical Center Mainz since 2012. The patient was diagnosed with RRMS in 2005 and treated with different disease-modifying therapies (DMT). After disease duration of 13 years, a B-cell-depleting therapy was initiated in 2018. Participant information on sex, age, and race was self-reported. Information on gender and socioeconomic status was not collected. The patient was treated at the Department of Neurology at the University Medical Center of the Johannes Gutenberg University Mainz by MP and VF and SB as resident and senior physicians, respectively.

Informed consent/ethical approval

The patient provided written informed consent for sharing clinical data and consented to publication of this case report. The study was approved by the local ethics committee (Landesärztekammer Rheinland-Pfalz, ethics vote n° 2020–15206_1).

METHOD DETAILS

Laboratory and imaging details

Laboratory measurements were carried out in the central laboratory of our university hospital as part of routine monitoring under disease-modifying therapy. The following parameters were analyzed: blood count, including leukocytes, lymphocytes and neutrophils. Structural MRI was performed on a 3-Tesla MRI scanner with a 32-channel receive-only head coil at the University Medical Center Mainz. In this patient, the sequences included a sagittal 3D T1-weighted magnetization-prepared rapid gradient echo sequence and a sagittal 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence.

GraphPad Prism (Version 9.5.1) was used for graphical depiction of laboratory results. Graphical abstract was created using biorender.com.

Literature review

We performed a literature review by searching PubMed for studies and case reports that reported LON in patients with MS, NMOSD or MOGAD after B-cell depletion therapies (rituximab, ocrelizumab, ofatumumab, inebilizumab, ublituximab). Concretely, we searched for ‘‘late-onset neutropenia’’, ‘‘delayed neutropenia’’, ‘‘rituximab’’, ‘‘ocrelizumab’’, ‘‘ofatumumab’’ ‘‘inebilizumab’’, ‘‘ublituximab’’ ‘‘multiple sclerosis’’, ‘‘neuromyelitis optica spectrum disorder’’, ‘‘NMOSD’’, ‘‘MOGAD’’ and combinations thereof. We chose only cases with MS, NMOSD or MOGAD. Ultimately, we identified 18 studies and case series that matched our search criteria (Table 1).