Late onset absolute neutropenia following ocrelizumab treatment in Multiple Sclerosis: a case report and review of the literature

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Introduction and Aim

Ocrelizumab is a recombinant humanized monoclonal antibody approved for the treatment of Multiple Sclerosis (MS) directed against CD20, a membrane glycosylated protein expressed on B-lymphocytes, but not plasma cells or neutrophils. Ocrelizumab structure and mechanism of action are related to rituximab, which has been used for years in the treatment of rheumatoid arthritis. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects are not fully elucidated but, likely, CD20 binding leads to antibody-dependent cellular cytolysis and complement-mediated lysis of CD20 expressing cells [1].

In January 2018, ocrelizumab has been approved in Europe for the treatment of both Relapsing Remitting (RRMS) and Primary Progressive MS (PPMS) and it is administered intravenously every six months. Infusion reactions, infections and a small proportion of malignancies are the main side effects that have been reported in clinical trials [2].

The aim of this work is to describe a case of absolute neutropenia in a naïve patient affected by RRMS and treated with ocrelizumab at San Raffaele Multiple Sclerosis Center, Milan, Italy.

Results

A 26-year old naïve woman was diagnosed with RRMS in August 2018 (***Figure 1***) and started ocrelizumab 600 mg, administered as two separate infusions over a period of two weeks, on October 2018. She had no other medical illness and did not take any concomitant medications.

She received her third cycle of ocrelizumab, the first as a single 600 mg infusion, on April 15th 2019. Pre-infusion biochemical analysis, immunoglobulin A (IgA), G (IgG), M (IgM) and blood counts were normal and she did not experience any infections prior to the infusion.

On July 30th 2019 she reported pain in her mouth, headache and fever with chills evolving over a 2-day period and presented to the Emergency Room (ER) on August 1st 2019 for transient loss of consciousness. On physical examination, she had aphthous stomatitis on tongue and pharynx and a normal neurologic examination except for mild lethargy (***Figure 2***). She had no evidence of organomegaly or skin rash.

On August 1st, body temperature was 39°C, white blood cell count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC) and absolute monocyte count (AMC) were 1.1x109/L, 0.3x109/L, 0x109/L and 0.8x109/L, respectively. C-reactive protein (CRP) and procalcitonin (PCT) were 36 U/L and 1.0 U/L. Full blood examinations are summarized in ***Table 1***.

In the ER, she performed an otorhinolaryngology evaluation that demonstrated aphthous lesions on left margin of the tongue and epiglottis and white spots on palatine tonsils (***Figure 2***). Brain computed tomography and investigations for infections as chest x-ray, abdominal ultrasounds, cultures of blood and urine were negative. Considering the presence of headache, high body temperature and lethargy, she subsequently underwent a lumbar puncture: physical-chemical analysis of cerebrospinal fluid was normal and molecular tests for viruses, including Epstein Barr Virus, Cytomegalovirus, Human Herpes Simplex 1 and 2 and Varicella-zoster virus were negative.

She was hospitalized and empirically treated with acyclovir at the dosage of 10 mg/kg three times a day and ceftriaxone 2 g/day, intravenously, starting from August 1st 2019. Symptoms started improving two days after treatment started and ANC, ALC and CRP returned to normal. She was discharged on August 6th 2019: headache and fever were completely resolved and patient displayed exclusively a mild stomatitis. Blood tests performed 14 days after discharge were normal (***Table 1***).

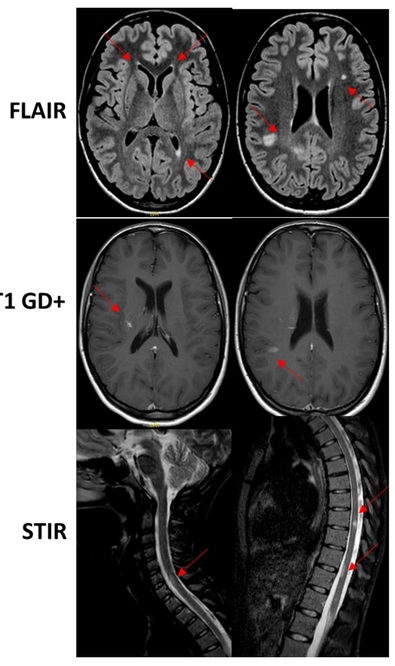

Figure 1. **Brain Magnetics Resonance Imaging of our MS patient**

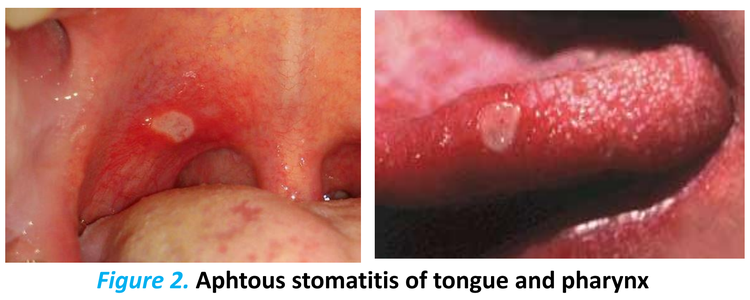

Figure 2. **Aphtous stomatitis of tongue and pharynx**

DATE	WBC	ALC	ANC	AMC	PLT	INR	CRP	PCT
September 8, 2018	5.7	2.5	2.5	0.5	318	1.1	N.T.	N.T.
April 2, 2019	5.8	1.6	3.6	0.4	263	N.T.	N.T.	N.T.
August 1, 2019	1.1	0.3	0.0	0.8	160	1.2	22	1.0
August 2, 2019	2.0	0.7	0.2	1.1	190	2.0	N.T.	N.T.
August 3, 2019	4.6	1.8	1.3	1.3	200	N.T.	29	6.0
August 4, 2019	4.9	2.3	1.8	0.6	210	N.T.	14	N.T.
August 6, 2019	6.2	2.8	2.6	0.6	340	1.0	3.0	0.5
August 20, 2019	6.6	2.3	3.6	0.5	340	N.T.	0.09	N.T.

Table 1. **Table 1: Serial blood cell levels prior to and following ocrelizumab infusion on April 15, 2019**

Abbreviations: WBC = white blood cells, ALC = absolute lymphocyte count, ANC = absolute neutrophil count, AMC = absolute monocyte count, PLTI= platelets, NR= international normalized ratio, CRP= C-reactive protein, PCT= procalcitonin, N.T. = not tested.

All values are ×10^3/µL (10^9/L). Treatment with acyclovir 10 mg/kg three times a day and ceftriaxone 2 g/die was on August 1, 2019.

Discussion

Late-onset neutropenia (LON) is defined as an ANC of <1.5 × 109/L that develops > 4 weeks after last drug administration, preceded by a normal neutrophil count, without other identifiable causes. LON has emerged as a possible adverse event of rituximab treatment and its incidence, as calculated from various studies, ranges from 3% to 27% [3]. Causes of LON following rituximab are poorly understood and many mechanisms such as infectious etiology, antibody-mediated destructions, neutrophil apoptosis triggered by the FAS/FAS ligand pathway, low granulocytic progenitor cell reserve and abnormal localization of immature precursors in the bone marrow have been postulated [3].

Clinical issues following LON, including infectious risk and rituximab re-treatment, are of outstanding importance as they may affect treatment strategy and final patient outcome. Individual rates of infections in literature range from 0-20% and they usually are mild and self-limited [4]. The use of granulocyte colony-stimulating factor, filgrastim, seems to minimally affect the course of LON, speeding rather than altering LON resolution [3].

In the RRMS clinical trial, neutropenia was found in 14.7% of ocrelizumab patients, compared to 40.9% of interferon beta-1a patients. In the PPMS trial, neutropenia occurred in 13% of ocrelizumab-treated patients compared to 10% in placebo. The majority of decreased neutrophil counts were transient and ANC were between 1.5x109/L and 1.0x109/L. Only 1% of patients displayed an ANC< 1.0x109/L and none of those cases was associated with infections. Only two patients who respectively displayed 0.5<ANC<1.0 x109/L and ANC<0.5 x109/L needed a specific treatment with filgrastim. All of those patients continued with ocrelizumab treatment after neutropenia resolved [2].

There is only one reported case of LON developing 73 days after ocrelizumab infusion in a MS patient, who was previously treated with glatiramer acetate, interferon-β-1a and dimethyl fumarate [5]. Patient developed fever, mild lethargy and mucositis and her ANC and ALC were 0.0 and 0.3×109/L, respectively. She was treated with cefepime and acyclovir and she was given a single dose of filgrastim 300 µg and methylprednisolone 1000 mg with net improvement of both ANC and ALC, which returned to normal values.

Conclusions

In our case, absolute neutropenia could be directly correlated with ocrelizumab action, likely through an immune-mediated mechanism that could resemble the one involved in rituximab LON, or, alternatively, could be a consequence of a viral infection such as Human Herpes Virus, that we were not able to detect.

Overall, this case highlights the importance of serial monitoring of blood count after ocrelizumab, rises questions regarding the continuation of ocrelizumab use and prompts further investigations in order to unravel underneath causes.

Bibliography

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