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**Title:** Late onset absolute neutropenia following ocrelizumab treatment in Multiple Sclerosis

**Running Title:** A case report from San Raffaele hospital

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**Background:** B cell depletion is a powerful therapeutic strategy for Multiple Sclerosis (MS). Ocrelizumab is a monoclonal antibody that selectively targets CD20, a membrane glycosylated protein expressed on B-lymphocytes. Ocrelizumab structure and mechanism of action are related to rituximab. Late-onset neutropenia (LON) is an absolute neutrophil count (ANC)  $<1.5 \times 10^9/L$ , occurring  $>4$  weeks following the last dose, without other identifiable cause, preceded by a normal ANC. LON could be a rare complication of rituximab-treatment.

**Methods:** We described a case of LON occurred 105 days after last ocrelizumab infusion in a Relapsing Remitting MS patient.

**Results:** A 26-year old naïve MS-patient received her third ocrelizumab infusion, 600 mg, on April 15<sup>th</sup> 2019. She had no other medical illness and did not take any concomitant medications. Pre-infusion biochemical analysis, immunoglobulins and blood counts were normal. On July 30<sup>th</sup> 2019 she reported pain in her mouth, headache and fever evolving over a 2-day period to transient loss of consciousness. She had aphthous stomatitis and a normal neurologic exam except for mild lethargy. Body temperature was 39°C, white blood cell count, absolute lymphocyte count (ALC), ANC and absolute monocyte count (AMC) were  $1.1 \times 10^9/L$ ,  $0.3 \times 10^9/L$ ,  $0.0 \times 10^9/L$  and  $0.8 \times 10^9/L$ . C-reactive protein (CRP) and procalcitonin (PCT) were 36 U/L and 1.0 U/L. She was treated with acyclovir and ceftriaxone. Brain computed tomography, chest x-ray, abdominal ultrasound, cultures of blood and urine and lumbar puncture, included molecular studies for viruses, were negative. Symptoms improved two days after treatment started and ANC, ALC, CRP and PCT returned to normal.

**Conclusions:** In clinical trials, transient neutropenia was found in 13% of ocrelizumab-patients. In literature, there is only one reported case of LON following ocrelizumab treatment in MS. Our case highlights the importance of serial monitoring of blood count after ocrelizumab and prompts further investigations to unravel underneath causes.