Dear Editors,

The recently published AWMF guideline [1] on the diagnosis and treatment of pemphigus and bullous pemphigoid supports first-line use of monoclonal CD20 antibody rituximab in moderate to severe pemphigus vulgaris/foliaceus. These recommendations are certainly justified by the excellent efficacy [2–5], mostly beneficial safety profile, and recent approval of rituximab for the treatment of pemphigus vulgaris by both the US Food and Drug Administration (2018), and the European Medicines Agency (2019). National [1] and international [6] pemphigus treatment guidelines refer to infections as a significant adverse effect of rituximab, but fail to mention late-onset neutropenia (LON) as a possibly under-estimated trigger of infectious complications. Late-onset neutropenia was observed following administration of rituximab regardless of the underlying disease [7–13] and has clearly been documented in pemphigus patients [14]. Dermatologists, however, are commonly unaware of this potentially serious condition.

A 31-year-old man presented to our department in April 2014 with a new onset of scaly plaques and flaccid blisters. Pemphigus foliaceus was diagnosed based on histology, immunofluorescence, and ELISA detection of IgG autoantibodies against desmoglein-1 (Figure 1). Clinical and serological response to dexamethasone pulses was incomplete, and steroid-sparing immunosuppressive therapy proved challenging as the patient was planning to father another child. Respective doses of 1,000 mg rituximab were given in a two-week interval in November 2014. Following a period of complete remission, skin lesions relapsed in 2016. Another series of dexamethasone pulses and medication with mycophenolate mofetil (2 g/d) – family planning was by then completed – led to temporary disease control, but another relapse occurred in 2018. A second cycle of rituximab in September 2018 enabled complete remission. Routine laboratory examinations in January 2019, 134 days after administration of rituximab, revealed a new onset of neutropenia (780/μL). The patient had recently recovered from an obstinate cold, but felt otherwise healthy. He denied any recent comedication with common elicitors of neutropenia (e. g. metamizole). Mycophenolate mofetil was discontinued, but neutrophils dropped to 210/μL within the next week and subsequently reached a nadir of 48/μL. He developed subfebrile temperatures, was admitted to his hometown hospital, and received filgrastim at daily doses of 300 μg. Following a period of reactive leukocytosis, neutrophils returned to normal levels within two weeks. Mycophenolate mofetil was re-administered under close monitoring of neutrophil counts which remained within the normal range for several months. A relapse of neutropenia (minimum 170/μL) occurred in August 2019 in the aftermath of another common cold; swift recovery was documented following re-administration of filgrastim and temporary discontinuation of mycophenolate mofetil.

Late-onset neutropenia has been defined as neutrophil counts of less than 1,500/μL occurring at least four weeks after rituximab treatment [8, 11]. The time to its onset commonly ranges between five and six months [8, 11, 13], but may amount to over a year [11]. Spontaneous recovery is commonly observed within a few weeks, but relapses following neutrophil reconstitution – as observed in our patient – may exceptionally occur [11]. In contrast to general assumptions, LON is not infrequent. Its incidence is estimated at approximately 6.0 % [9, 11, 12], but might vary within a broad range (1.3 % [13]–29.9 % [8]). The risk of LON possibly depends on the underlying disease, and is supposed to be highest in coexisting lupus erythematosus [8]. Comedication with disease-modifying antirheumatic drugs does not seem to influence its incidence [13]. The frequently asymptomatic course accounts for a substantial risk of under-detection. Severe infectious complications [7, 8, 10, 11, 13] including fatalities [12], however, may occur. Administration of filgrastim was demonstrated to shorten the time to recovery, but did not affect overall outcomes [11]. Despite a certain risk of relapse, only a relatively small proportion of patients with a history of LON will develop recurring neutropenia upon re-challenge with rituximab [10, 11, 13].

Hypotheses regarding the pathomechanisms of LON include an immune dysregulation during B-cell recovery which coincides with an excess of B-cell activating factor (BAFF) [10] and leads to a promotion of B-cell lymphopoiësis over granulopoiesis [8, 15]. High pre-treatment levels of a proliferation-inducing ligand (APRIL) [8], and certain single-nucleotide polymorphisms in the Fcγ receptor gene [9] were suggested to be predictive of LON. These considerations, however, do not fully explain its infrequent occurrence, and commonly self-limiting course. We assume that exogenous pro-inflammatory factors including viral infections such as our patient’s “common colds” might trigger LON in predisposed individuals. As predisposing and triggering factors remain ill-defined, monthly complete blood counts, and close monitoring for infection are advisable over a period of at least six months following administration of rituximab.

The benefits of rituximab for guideline-directed treatment of pemphigus clearly outweigh its risks [3–5]. Information about LON, however, ought to be implemented in future treatment guidelines.
Conflict of interest
None.

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Figure 1 Neutrophil count, anti-desmoglein-1 (anti-Dsg-1) antibodies, and treatment in the course of time. Blue dotted line: 1,500 neutrophils/μL, defining threshold of neutropenia. Excess neutrophils (maximum 53,000/μL) following administration of filgrastim are not depicted. A spontaneously resolving period of neutropenia (minimum 780/μL) in summer 2017 was retrospectively considered an earlier episode of LON following the first administration of rituximab.
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