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LETTER TO THE EDITORS

Cutaneous diseases related to a hyperactive T-cell response in ocrelizumab-treated multiple sclerosis patients

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Dear Sirs,

Whereas, B-cell depletion has proven very efficient at controlling disease activity in several auto-immune diseases, including MS, long-term or rare side effects of the treatment remain unknown. Adverse events related to B-cell depletion are notably an increase in the risk of shingles, herpesvirus infection or hypogammaglobulinemia [1]. Palmo-plantar pustulosis (PPP) and oral lichen planus (OLP) are T-cell-mediated cutaneous diseases that have been associated with rituximab. We report the occurrence of these cutaneous diseases in two multiple sclerosis patients treated with ocrelizumab.

Case no 1

PPP is a variant of psoriasis, affecting the extremities, related to a hyperactive T-cell response [2]. We report the case of a 60-year-old female patient, suffering from relapsing–remitting multiple sclerosis for 11 years. She had no familial or personal history of psoriasis or psoriatic arthritis. She was previously treated with natalizumab and switched to ocrelizumab, because of JCV seropositivity. 15 days after the second course (half-dose) of ocrelizumab, she presented painful PPP, unresponsive to topical corticosteroids nor to acitretin (Fig. 1A, B). The patient was not rechallenged with ocrelizumab. Currently, PPP is slowly healing using topical calcipotriol and betamethasone.

Case no 2

OLP is a T-cell-mediated disease, characterized by painful oro-pharyngeal ulcers, resulting from a $CD8^+$ T-cell-mediated reaction against epithelial basal cells [3]. We describe the case of a 52-year-old male patient with primary progressive MS diagnosed 7 years earlier. 5 years following diagnosis, ocrelizumab infusions were started. After 2,5 years of treatment (five infusion cycles), he presented increasing odynophagia, with burning sensations in the oral cavity and on the tongue, preventing proper feeding and hydration. Examination revealed erosive lichenus-like lesions on the tongue, gums, and between the base of the tongue and the epiglottis. Biopsy confirmed erosive lichen planus (Fig. 1C). Ocrelizumab was not reinfused and the patient slowly recovered 6 months after, with vitamin C and salicylic acid topical solution.

We describe the emergence of two dermatological immune-mediated diseases, namely PPP and OLP, in MS patients treated with ocrelizumab. Of note, both diseases are thought to be caused by a hyperactive T-cell response. Although a direct causal link is not proven, as patients were not rechallenged with ocrelizumab, it is likely that the T- and B-cell imbalance was triggered by the B-cell depleting therapy. Similar cases have been described following treatment with another anti-CD20 agent, rituximab [4–8]. The rituximab-associated adverse events resolved upon treatment interruption and administration of topical steroids for both diseases. In some cases of PPP, oral immunosuppressants such as methotrexate or apremilast, a phosphodiesterase 4 inhibitor for PPP were also used with success. In the case of OLP, intralesional injection of triamcinolone acetonide were also administered.

From an immunological point of view, these cases highlight the delicate balance needed between T- and B-cell responses to maintain homeostasis, with B-cells playing a role as antigen-presenting cells, but on the other hand having regulatory functions by controlling excessive T-cell activity

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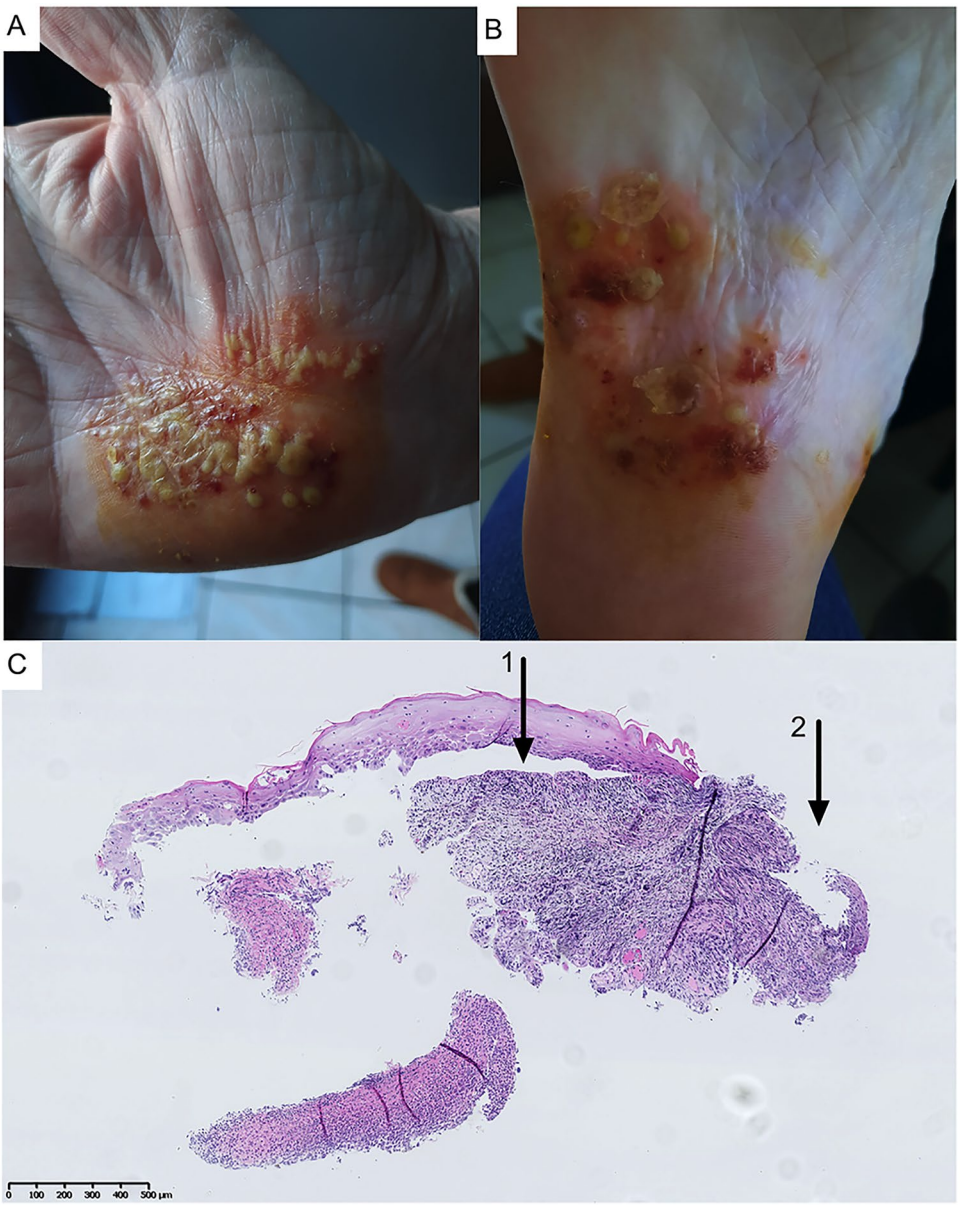

Fig. 1 Illustration of immune-mediated dermatological adverse events. **a**, **b** Photographies of the characteristic cutaneous lesions of palmoplantar pustulosis: presence of several blisters filled with a yellow turbid liquid on the palm **a** of the hand and sole of the foot **b** of case no 1. **c** Biopsy of a fragment of the oral mucosa (HE stain, original magnification X5) showing the characteristic features of erosive oral lichen planus of case no 2: parakeratosis, acanthosis and lymphohistiocytic infiltrates at the dermal-epidermal interface. A sub-basal separation (1) and an ulceration (2) are shown with the corresponding arrows

in the setting of cutaneous immune-mediated diseases such as PPP or OLP.

As of April 2020, more than 160,000 patients with relapsing and primary progressive MS have been treated with ocrelizumab, resulting in over 200,000 patient-years of exposure (Roche, data on file, 31 March 2020). Due to increased use of the drug, rarer adverse events, not captured within the setting of randomized controlled trials, can occur. This highlights the need for clinician alertness, pharmacovigilance reporting and finally participation to real-world observational studies or registries to collect such data.

Declarations

Conflicts of interest The authors declare no competing interests.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to publish Signed informed consent for publication was obtained from both patients.

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