

Psoriasiform dermatitis following ocrelizumab in relapsing-remitting multiple sclerosis: case report and literature review.

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Abstract

We present a case of a 30-year-old man with relapsing-remitting multiple sclerosis who developed psoriasiform dermatitis following his second course of ocrelizumab. This resolved with topical therapies and discontinuation of treatment. Cases of psoriasiform rashes have been increasingly reported in the use of ocrelizumab and are possibly due to B-cell (CD20) depletion and T-cell overregulation. Nevertheless, skin-related adverse reactions are not yet considered in the risk management plans of anti-CD20 treatments in multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune condition of the central nervous system for which disease-modifying treatment (DMT) options have increased rapidly in recent years. The anti-CD20 monoclonal antibody ocrelizumab is an effective treatment for relapsing-remitting MS¹ and primary progressive MS². As it becomes more widely used, more side effects are being described.

We describe a case of psoriasiform dermatitis following a second course of ocrelizumab. In this case, informed consent was gained.

Case report

A 30-year-old male presented to our attention in June 2020 after two relapses in the previous year. The MRI scan showed brain and spinal cord demyelinating lesions with dissemination in space, and the CSF analysis showed unmatched oligoclonal bands. He did not report any relevant family or past medical history, except for smoking history and sinus bradycardia attributed to high vagal tone.

Because of the presence of spinal cord lesions and male sex, he was estimated to be at high risk for future relapses, and we recommended ocrelizumab as a high-efficacy DMT. Treatment was then delayed for patient's personal reasons.

He received his first course of ocrelizumab in November-December 2021. Pretreatment blood tests were unremarkable, including total blood count, liver and renal function, and viral screen.

In February 2022, he developed colicky flank pain. Blood tests showed an eGFR of 33 mL/min/1.73 m² and a serum creatinine of 223 µmol/L. Urine microscopy was unremarkable. The patient was not on any other medication and had no recent contrast imaging. The pain had resolved by the time he was assessed, and renal function improved with hydration. Computed tomography of the kidneys, ureters and bladder was normal. The presumptive

discharge diagnosis was of kidney stones that may have been expelled before assessment. Most recent blood tests show normal and serum creatinine.

We could not establish a clear link between this event and ocrelizumab, and a second course was administered in June 2022 with no immediate complications.

In December 2022, he presented to his GP with a rash. This had begun with erythematous patches on his palms and soles, which blistered. The rash then generalised with papules over his arms and his torso, face, and legs. He reported, with hindsight, that the rash may have developed in January 2022 following the first course of ocrelizumab and had progressively worsened since then. Bacterial and fungal cultures were negative. A punch biopsy showed parakeratosis and psoriasiform epidermal hyperplasia with patchy spongiosis, suggesting psoriasiform dermatitis (Figure 1). Autoimmune screening was unremarkable: ANA screen was negative, complement levels were normal, and anti-TTG antibodies were negative. He was given three days of oral prednisolone, followed by topical steroids, antihistamines, and emollients. Ocrelizumab was discontinued.

The rash was resolving at clinic follow-up 12 months later, and by March 2023, it had completely resolved. Patient is awaiting to start diroximel fumarate and will have dermatological examinations at regular intervals.

Discussion

Ocrelizumab is a humanised monoclonal antibody to CD20 with a generally good safety profile.^{1,2}

As use widens, skin-related adverse events (AEs) are being reported³, such as psoriatic dermatoses, at various ages and stages of treatment (see Table 1). Two case reports describe patients who developed psoriasiform dermatitis on ocrelizumab.^{4,5} Three case reports describe patients who developed a pustular form of psoriasis, like our patient's rash, that had also begun with a blistering rash on the hands and soles.⁶⁻⁸

Other inflammatory rashes, such as nummular eczema⁸ and pyoderma granulosum⁹, are also described. The latter led to a young patient having multiple disfiguring surgeries and ultimately requiring a catheter and stoma.⁹

Finally, a recent analysis of FDA data showed that psoriasis was more frequently reported in patients with MS treated with anti-CD20 therapies.¹⁰

It is difficult to establish a causal relationship, whether this is a drug reaction, an unmasking of a previous vulnerability, or secondary autoimmunity. Psoriasis characteristically presents at age 15-20, with a second peak in incidence between 50-60 years, and follows a relapsing and remitting course. Our patient had no relevant personal or family history of psoriasis. Infective causes were ruled out, and there were no other triggers in the environment or medication history.

Psoriasis is not more common in people with MS¹¹, although shared genetic factors have been suggested¹². Inflammation in plaque psoriasis is maintained via distinct T-cell subsets¹³, Th17, which activate keratinocyte proliferation. There are several mechanisms by which anti-CD20 therapy could induce psoriasis. Secondary autoimmunity on anti-CD20 therapy has been described previously with patients developing inflammatory bowel disease (IBD).¹⁴ IBD and psoriasis share pathophysiological features, including the Th-17 cell dysregulation¹³ that may be induced by B-cell depletion. Other pathways, including TNF-alpha, IL-12 and IL-23 signalling, may be involved.¹³

Finally, a possible hypothesis is that anti-CD20 treatments may dysregulate the expression of B-lymphocyte induced maturation protein 1 (BLIMP-1). BLIMP-1 depletion can cause an increased IL-9 secretion by Th-9 cells¹⁵ contributing to the pathogenesis of psoriatic skin lesions.¹⁶

After discontinuing ocrelizumab, we proceeded with diroximel fumarate since it may regulate the Th17 population and improve psoriasis.¹⁷ We excluded Sphingosine-1-phosphate receptor modulators due to the history of sinus bradycardia, and natalizumab as it has been associated

with psoriasis variants³ and JCV-serostatus is less reliable following B-cell-depletion. If a psoriasis relapse occurs, we will discuss the combination of diroximel fumarate with secukinumab, which has been shown to have good efficacy and safety outcomes.¹⁸ In case of MS activity, we will suggest the patient switch to cladribine. Initially, we approached this drug with caution due to its known association with severe skin reactions¹⁹. However, to date, there have not been any cases of association with psoriasis reported, so that we will advise cladribine as an alternative DMT.

Conclusion

Our case and literature review suggest that ocrelizumab may be associated with inflammatory skin conditions, particularly psoriasis, and there are plausible mechanisms for this. We recommend that anti-CD20 surveillance plans should include skin examinations at regular intervals.

Declaration of Conflicting Interests: EC, VP, HH, AH and MS have nothing to disclose. FDA has received speaker honoraria from Neurology Academy, Janssen, Merck, Novartis, Sanofi and served in an advisory board for Novartis, Sanofi and Coloplast. She received congress fees from Janssen, Novartis, Roche and Merck. She is a regional coordinator for the Oratorio Hand Trial (Hoffmann-La Roche) an PI of commercial and academic trials included CHARIOT-MS, ALITHIOS (Novartis), O'HAND (Roche). SC has received speaker honoraria from Merck.

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Article	Diagnosis	Age	Sex	MS subtype	Duration of treatment when developed rash	Biopsy findings	Treatment	Follow-up
Darwin E. et al. <i>Dermatology Online Journal</i> 2018 ⁴	Psoriasisiform dermatitis	68	F	RRMS	2 courses	Psoriasisiform epidermal hyperplasia + eosinophil infiltrate	Continued	Clobetasol ointment for rash, Ocrelizumab continued
Sankari, S.E. et al. <i>Journal of Neurology</i> 2021 ⁶	Palmo-plantar pustulosis	60	F	RRMS	2 courses	Not biopsied	Discontinued	Topical calcipotriol and betamethasone.
Sankari, S.E. et al. <i>Journal of Neurology</i> 2021 ⁶	Oral lichen planus	52	M	PPMS	2.5 years	Not biopsied	Discontinued	Topical vitamin C and salicylic acid. Lesions resolved
Jakob Brecl G. et al. <i>International Journal of Dermatology</i> 2022 ⁵	Psoriasisiform dermatitis	66 ⁴	F	PPMS	2 courses	Psoriasisiform hyperplasia, covered with thin confluent parakeratosis and hypogranulosis in the central part of the epidermis	Discontinued	Topical therapy
Jakob Brecl G. et al. <i>International Journal of Dermatology</i> 2022 ⁵	Pustulosis psoriasis	40 ⁴	F	PPMS	1 course	Thickened cornea with parakeratosis, neutrophils, and more scarce leukocyte-fibrin crusts, focally	Discontinued	Given 'oral and topical drugs' with moderate improvement.

						reduced granular layer, predominant type of psoriatic acanthosis		
Lappi A. et al. <i>Italian Journal of Dermatology and Venerology</i> 2022 ⁷	Palmoplantar pustular psoriasis	38	F	Not specified	1 course	Not biopsied	Not specified	Given phototherapy (NB-UVB) and topical calcipotriol and betamethasone, lesions resolved
Sirbu, C.A. et al. <i>Journal of Clinical Medicine</i> 2022 ⁸	Nummular eczema	42	M	PPMS	2 years	Hyperkeratosis, epidermal hyperplasia with spongiosis, hypergranulosis	Continued	Topical steroids, antihistamines, oral antibiotics, topical crystal violet solution. Resolved but ongoing relapses which respond to crystal violet solution
Porwal, M.H. et al. <i>Multiple Sclerosis and Related Disorders</i> 2022 ⁹	Pyoderma granulatum	23	F	RRMS	2.5 years	Small granulomas, neutrophilic granulocytes	Discontinued	IVIg, cyclosporin, surgical debridement

Table 1. – Characteristics of inflammatory rashes developed on ocrelizumab

Abbreviations: RRMS: relapsing-remitting multiple sclerosis; PPMS: primary-progressive multiple sclerosis

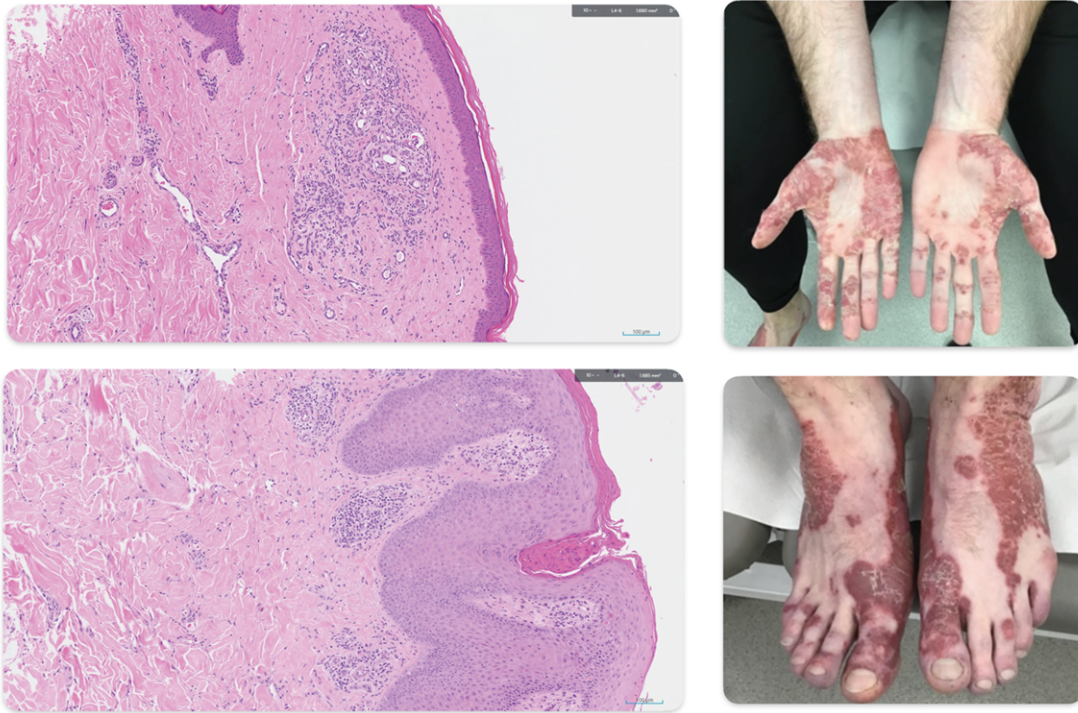


Figure 1. Histopathology results and clinical pictures

On the left, images from the punch biopsy taken from the affected areas showing parakeratosis and psoriasiform epidermal hyperplasia with patchy spongiosis, suggestive of psoriasiform dermatitis. On the right, pictures of the erythematous patches with blisters on patient's palms and soles.