Fulminant *Demodex folliculitis* in a patient with ulcerative colitis treated with tofacitinib

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INTRODUCTION

Janus kinase (JAK) inhibitors (JAKi) are a rapidly growing new drug class with efficacy in various disorders. The United States Food and Drug Administration approved tofacitinib in 2012 for the treatment of rheumatoid arthritis.[1] Currently, the initial authorization of tofacitinib has been expanded in the United States and Europe to include psoriatic arthritis, ulcerative colitis (UC), juvenile idiopathic arthritis, and ankylosing spondylitis.[1,2] The anti-inflammatory effects of tofacitinib are based on a preferential inhibition of JAK-1 and JAK-3.[2]

Acneiform eruptions and exacerbations of acne have been reported with JAKi treatment. The etiology of these cutaneous adverse reactions is poorly understood, and their optimal management is not yet established.[3,4]

Here, we report about a patient with UC, refractory to various immunosuppressants and biopharmaceuticals, who developed severe *Demodex folliculitis* while treated with tofacitinib. The cutaneous eruption responded well to a combination of lymecycline and ivermectin while continuing tofacitinib, with sustained disease control of colitis.

Abbreviations used:

ANA: antinuclear antibodies
JAK: janus kinase
JAKi: janus kinase inhibitor
UC: ulcerative colitis

CASE REPORT

A 37-year-old woman presented to our department with fever and an extensive papulopustular eruption on the face (Fig 1, *A*). The skin lesions had started about 2 weeks ago and had worsened with topical metronidazole gel.

Her medical history was remarkable for the diagnosis of UC in 2009, which has since been proven to be refractory to azathioprine, tumor-necrosis-factor-alpha inhibitors (adalimumab, golimumab, and infliximab), vedolizumab, and ustekinumab. Stable remission was finally achieved with tofacitinib (10 mg twice a day for 8 weeks, followed by a maintenance dose of 5 mg twice a day) initiated 10 months prior to presentation. Clinical examination showed extensive erythematous papules and pustules on the face with minor extension to the ears, neck, and upper trunk. There were no comedones. Her body temperature was 39.2°C. Laboratory investigations, including antinuclear antibodies (ANA), were unremarkable. Microbiologic swabs were negative for bacteria, fungi, and herpes simplex virus. Histopathologic findings of a 4-mm punch biopsy of facial skin revealed spongiosis with intraepidermal microabscesses, dense neutrophilic infiltrates around the hair follicles, and abundant *Demodex folliculorum* (Fig 2, *B*). A total of 4 mites were found in the biopsy specimen (representing a skin surface area of 0.1256 cm^2), corresponding to around 32 mites/cm^2. Considering this dense *Demodex* infestation, which was well above the threshold of 5 mites/cm^2 used as a diagnostic criterion for demodicosis, the diagnosis of

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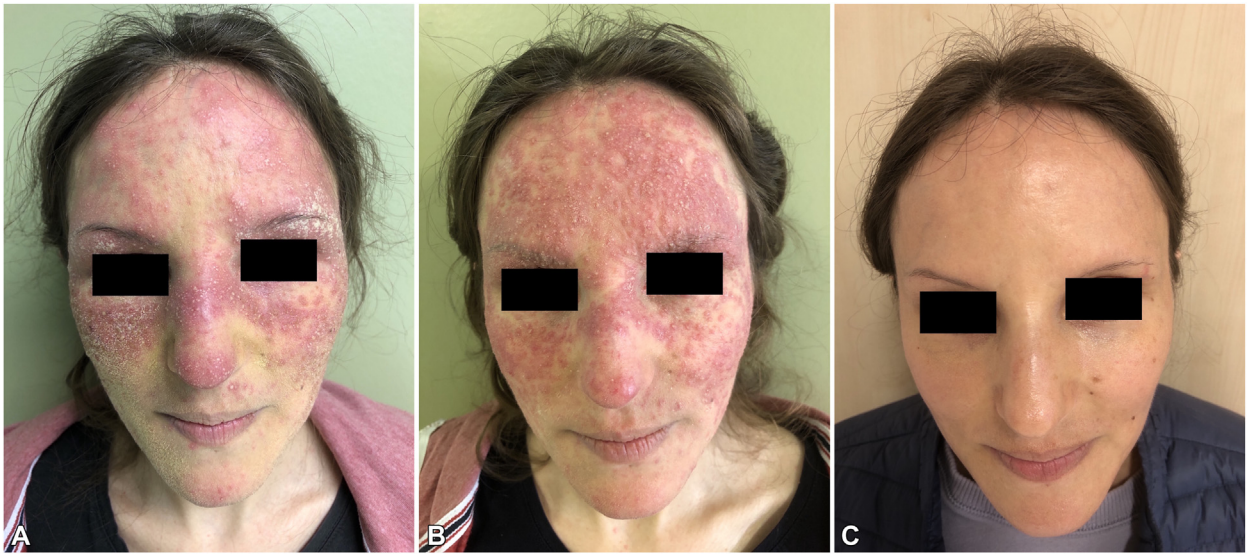

Fig 1. Clinical presentation. **A,** initial presentation with extensive papulopustular eruptions on the face. **B,** 2 weeks after initiation of lymecycline. **C,** 12 weeks after lymecycline was stopped.

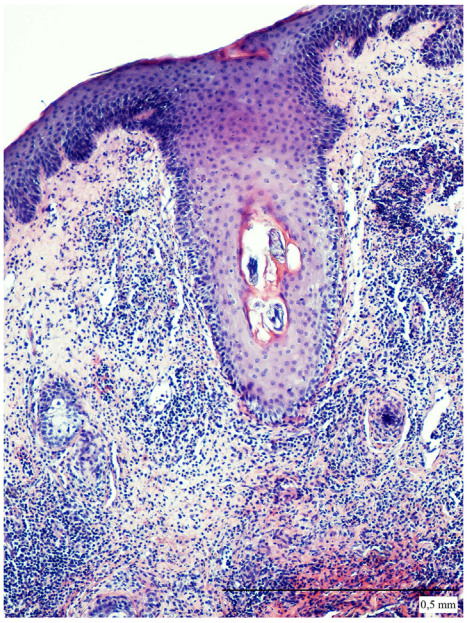

Fig 2. Histopathology showing spongiosis, intraepidermal microabscesses, and dense neutrophilic infiltrates around the hair follicles with abundant *Demodex folliculorum*.

tofacitinib-related *Demodex folliculitis* was made.[5] Metronidazole gel was stopped and oral lymecycline (300 mg once daily) was initiated. Fever resolved, but the skin response was still poor after 2 weeks of lymecycline (Fig 1, *B*). Topical ivermectin once daily was added, followed by a single dose of oral ivermectin (200 μg/kg body weight) 4 weeks later. Shortly thereafter, with continued lymecycline and topical ivermectin, folliculitis improved slowly and eventually resolved completely (Fig 1, *C*). Lymecycline was stopped 16 weeks after initiation, and topical ivermectin was maintained. Throughout this period, tofacitinib was continued to ensure disease control of colitis. After 5 months, with ongoing tofacitinib and topical ivermectin, the patient is still in complete remission for both conditions.

DISCUSSION

Few reports on JAKi-related acneiform or rosacea-like dermatitis and folliculitis have been published so far. It is not even clear yet whether these reactions represent a single entity, whether their reported different clinical pictures are pathophysiologically separate, and how they are causally related to exposure to JAKi.[4,6]

A meta-analysis of 14 studies including a total of 275 patients treated with tofacitinib for alopecia areata showed that "acne" and "folliculitis" were among the most commonly reported adverse events, observed in 13.2% and 4.5% of patients, respectively.[4] Furthermore, acneiform lesions have been reported with the use of the JAK-1 inhibitor upadacitinib in 9.8% (mainly occurring within the first 3 months of therapy) and with the JAK-1/JAK-2 inhibitor baricitinib in 4% of atopic dermatitis patients.[3,7] These observations seem particularly paradoxical as some studies suggest that the activation of the JAK-signal transducer and activator of transcription pathway plays a role in the pathogenesis of acne, rosacea, and *Demodex folliculitis*

(demodicosis).[8,9] A small retrospective case series even reported on a beneficial effect of tofacitinib in rosacea.[10]

Because of the lack of evidence, there is no guideline on the management of JAKi-associated acneiform eruptions. Therefore, the therapeutic approach is mainly based on their analogy with acne, rosacea, and other drug-induced acneiform rashes and on the individual clinical presentation. Thus, topical (eg, retinoids, benzoyl peroxide, and azelaic acid) and systemic therapies (eg, tetracyclines) represent possible treatment options.[3,9] As shown, ivermectin (topical and/or systemic) can be effective when *Demodex folliculitis* is suspected. Oral isotretinoin might be considered for granulomatous rosacea-like and nodulocystic acneiform lesions but has been related to inflammatory bowel disease and should be avoided in these patients.[6] The discontinuation of JAKi should be considered as the preferable option in severe cases when other effective therapies are available. Recently, Neumann et al[6] reported about a patient with UC who developed a granulomatous rosacea-like dermatitis related to tofacitinib. In this case, after lack of improvement with doxycycline, JAKi was switched to ustekinumab with final resolution of the rash.

Based on our case, no causal relationship between tofacitinib and the subsequently emerged skin eruption can be implied, yet the Naranjo Adverse Drug Reaction Probability Score of 3 indicates a possible tofacitinib-related adverse drug reaction. However, this case demonstrates that even with a fulminant course, at least when *Demodex* is prevalent and discontinuation of JAKi is a poor choice, tofacitinib-associated acneiform dermatitis in UC can be successfully managed with a combination of lymecycline and systemic and topical ivermectin while continuing the JAKi. Furthermore, it raises the questions of what role *Demodex folliculorum* might play in the pathogenesis of JAKi-associated acneiform eruptions and what influence mite-directed therapies might have in its management.

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Conflict of interest

None disclosed.

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