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Herpes zoster as a cause of atypical chronic ulcerations associated with tofacitinib

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Abstract

Tofacitinib is a targeted inhibitor of janus kinase (JAK), currently approved for the treatment of rheumatoid arthritis. We present a patient on treatment with tofacitinib who had an episode of classic dermatomal herpes zoster followed months later by atypical chronic cutaneous ulcers also caused by herpes zoster.

Keywords: herpes zoster, varicella zoster virus, tofacitinib, ulceration

Introduction

Tofacitinib is a JAK inhibitor that impairs gene transcription mediated via STAT leading to inhibition of cytokine activation, a major culprit in autoimmune diseases. It is approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis and is under investigation for the treatment of other cutaneous diseases, such psoriasis, alopecia areata, atopic dermatitis, and vitiligo, as well as non-dermatologic conditions, such as inflammatory bowel disease and hypereosinophilic syndrome [1, 2]. As the use of tofacitinib increases, it is important to recognize the adverse effects of this therapy in patients.

Case Synopsis

We present a 52-year-old woman with seronegative rheumatoid arthritis. Initial regimens included methotrexate, etanercept, leflunomide, and prednisone. Subsequently, she was treated with tofacitinib 5mg twice daily and prednisone 60 mg daily. After two years on tofacitinib therapy, she developed classic dermatomal herpes zoster (HZ) across her left upper thigh and was treated with valacyclovir with good response. Five months after her initial presentation of HZ, she developed tender, pruritic papules just above the left ankle, some of which ulcerated. After nearly four months of chronic ulcerations, she presented to our dermatology clinic for evaluation. On examination, she had two well-demarcated ulcers with peripheral erythema and eschars on the lower leg. The clinical differential diagnosis included pyoderma gangrenosum, deep fungal infection, venous stasis ulcer, and vasculitis. A punch biopsy of a lesion at the ulcer edge demonstrated varicella zoster infection, confirmed by immunohistochemistry and polymerase chain reaction. Microbial cultures grew out yeast; viral culture was negative. Tofacitinib was discontinued and the patient remained on methotrexate and prednisone. The patient was treated with a two-week course of valcyclovir, but the ulcers worsened over the next two months. Examination at this time revealed ulcers in the same region, but now in association with surrounding erythematous papules and small flaccid bullae (**Figure 1**A, B). The clinical diagnosis was recurrent/persistent herpes zoster. A punch biopsy at an ulcer edge revealed large, multinucleated keratinocytes in the surface and follicular epidermis with nuclear molding and margination of the chromatin (**Figure 2**A). Immunostain for varicella zoster virus was positive in the atypical keratinocytes (**Figure 2**B). The patient's ulcers improved after a second course of valacyclovir of 7 weeks duration.

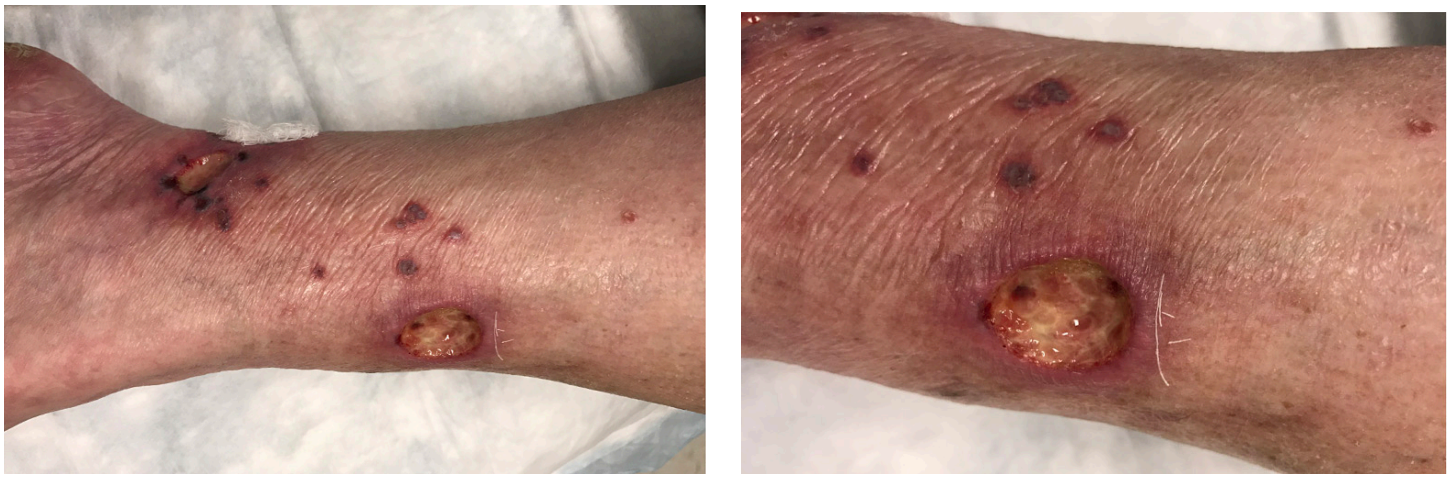

Figure 1. *Clinical examination revealed well-demarcated ulcers with peripheral erythema on the lower leg with surrounding erythematous papules and small flaccid bullae.*

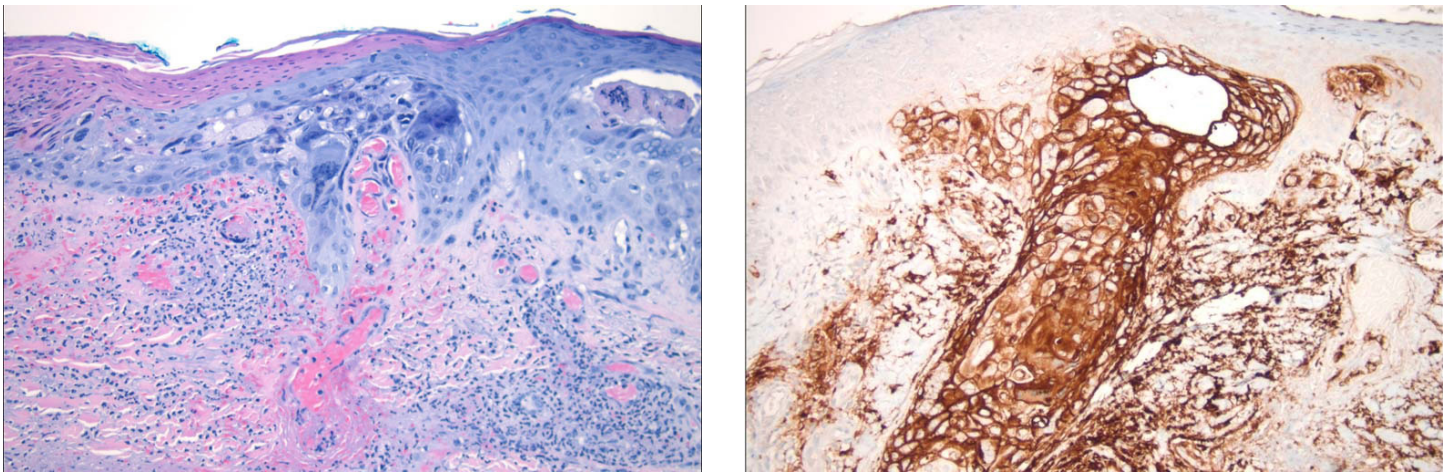

Figure 2. *A skin punch biopsy at the edge of an ulcer revealed large, multinucleated keratinocytes with molding and margination of the chromatin, involving the surface epidermis and the follicular epidermis (A) H&E, 10%). (B) Immunohistochemistry for varicella zoster virus was positive in the atypical keratinocytes, 20%.*

Case Discussion

In an open label study of Japanese patients with rheumatoid arthritis treated with tofacitinib, VZV was the most common adverse event leading to permanent discontinuation; with a 19.3% incidence of VZV (94/486 subjects). Fourteen cases were reported as serious, including one case of disseminated VZV, but no oral or ophthalmic events [3]. The incidence rate of herpes zoster in patients on treatment with tofacitinib is 4.4/100 patient-years (PY), with increases in Asian populations (7.7/100 PY), particularly in Japan and Korea (9.2/100 PY), [4]. Other cutaneous side effects of tofacitinib that are reported in trials include allergic contact dermatitis and erythema, which are associated with topical preparations [5].

We present the first report in the American literature, to our knowledge, of varicella zoster virus triggering classic dermatomal herpes zoster followed by atypical chronic ulcers in a rheumatoid arthritis patient treated with tofacitinib. Although similar lesions owing to herpes simplex virus are well-described in immunocompromised patients [6], this appearance is unusual for VZV. A potential contributing factor to the delay in response to treatment may have been an altered immune response while receiving tofacitinib during the preceding episode of dermatomal HZ in the same leg. The correct diagnosis of the subsequent chronic lesions was established by a combination of tissue biopsy for histopathology and immunohistochemistry, microbial cultures, and PCR studies. The possibility of the patient's concurrent immunosuppressants as the cause of increased risk for HZ was considered. Although some disease-modifying antirheumatic drugs (DMARD), such as TNF inhibitors, have reported associations with HZ,

the relationship between most DMARDs and the risk of HZ has not been well established [7]. One caveat is that oral corticosteroids have been consistently demonstrated to increase risk for HZ, albeit at low relative risk of 1.6 to 2.4-fold [8]. Overall, whereas studies have shown that DMARD and prednisone may increase the rate of HZ above age-matched controls, the use of tofacitinib has been associated with a further clinically and statistically meaningful increase, with nearly one-fifth of patients in large clinical trials suffering from HZ [3, 6]. Furthermore, the patient's lesions improved with treatment following the discontinuation of tofacitinib, while remaining on prednisone and methotrexate.

Conclusion

Based on our observation and other literature reports, we conclude that VZV in patients on tofacitinib may have an atypical presentation, and thus, work up for cutaneous ulcerations in patients on tofacitinib should include VZV in addition to other herpes viruses (e.g., HSV, CMV and EBV), fungal, and mycobacterial infections.

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