Varicella zoster virus presenting as lower extremity ulcers and an atypical myeloid infiltrate

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Key words: atypical myeloid infiltrate; herpes zoster; immunosuppression; leg ulcers; methotrexate; varicella zoster virus.

INTRODUCTION

The cutaneous manifestations of varicella zoster virus (VZV) include diverse clinicopathologic presentations, particularly in immunocompromised patients. The potential of VZV to mimic various cutaneous disorders is well recognized, yet, a PubMed search of the English language literature using the terms varicella zoster virus, VZV, herpesviridae, histopathology, myeloid infiltrate, myeloproliferative, myelodysplasia, leukemia cutis, and myeloid leukemia revealed no prior reports of VZV presenting as an atypical myeloid infiltrate mimicking leukemia cutis. We describe a patient with VZV presenting with atypical clinical and histopathologic features suggesting a leukemic infiltrate. Evaluation revealed no occult myeloproliferative disorder.

Abbreviation used:

VZV: varicella zoster virus

CASE REPORT

A 75-year-old man with a 35-year history of Crohn's disease treated with methotrexate presented with a few months of progressive ulcerations of the lower portion of the left extremity and new ipsilateral palpable purpura. His past medical history was significant for left foot osteomyelitis resulting in toe amputations and macrocytic anemia of unknown etiology, with normal vitamin B_{12} and folate levels. A recent empiric systemic prednisone taper (from 80 to 40 mg by mouth daily) resulted in no improvement over the past few weeks, and the patient reported evolution of the palpable purpura of the lower portion of the left extremity. Physical examination revealed large ovoid ulcers with eschars of the posterolateral aspect of the left leg and dorsal aspect of the foot and palpable purpura extending proximally to the knee. Concurrent cribriform ulcerations coalesced over the left ankle and dorsal aspect of the foot (Fig 1).

A skin biopsy near the edge of an ovoid ulcer of the left leg revealed a perivascular and interstitial mixed infiltrate predominantly composed of cells with pleomorphic nuclei, prominent nucleoli, and ample granular cytoplasm with overlying focal vacuolar changes and mild papillary dermal edema. Immunohistochemical stains demonstrated lysozyme and myeloperoxidase reactivity in the cells of interest, suggesting an atypical myeloid infiltrate (Fig 2).

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Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;7:68-70.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.11.003

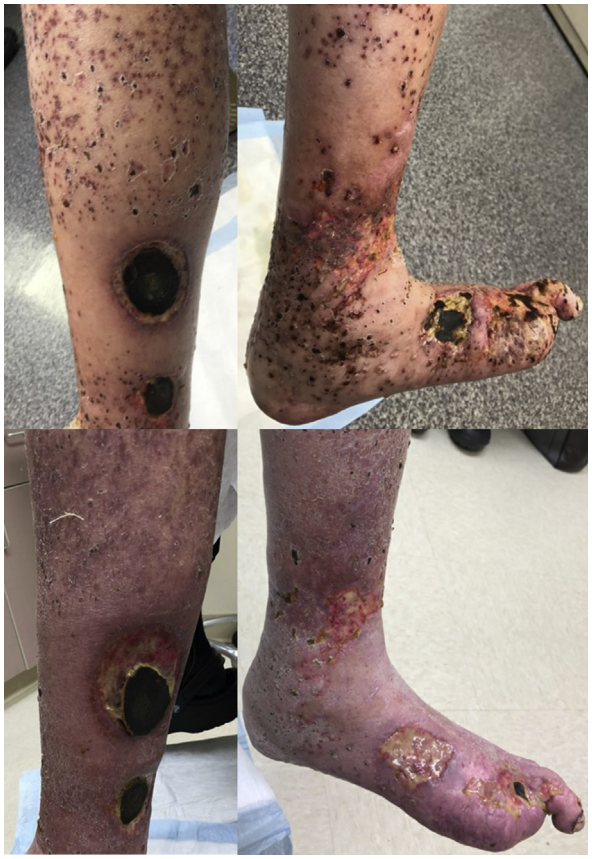

Fig 1. Disseminated cutaneous VZV. Posterolateral aspect of the left leg and dorsal aspect of the foot: ovoid ulcers with eschar, cribriform ulcers, and purpuric papules (*top panel*); re-epithelialization after 4 weeks of oral administration of valacyclovir (*bottom panel*). *VZV*, Varicella zoster virus.

Peripheral blood studies showed relative leukocytosis (white blood cells 10.9 × $10^3/\mu$L, patient baseline 7 × $10^3/\mu$L to 8 × $10^3/\mu$L) with neutrophilia (absolute neutrophils 8300/mm^3). Bone marrow biopsy, flow cytometry, and fluorescence in situ hybridization analysis results were negative. Subsequent skin biopsy of a purpuric papule demonstrated ballooning degeneration of keratinocytes forming an intraepidermal vesicle with adjacent basal vacuolar changes; immunohistochemistry and polymerase chain reaction confirmed VZV and ruled out herpes simplex virus and cytomegalovirus (Fig 2). Previously observed findings of an atypical myeloid infiltrate were not present. Oral administration of valacyclovir (1 g 3 times daily) resulted in a marked cutaneous improvement after 4 weeks (Fig 1), with resolution of the peripheral neutrophilia; the therapy was continued for a full 6 weeks.

DISCUSSION

Atypical clinicopathologic presentations of cutaneous VZV have been described in immunocompromised patients, including large leg ulcerations and lymphoid atypia during treatment with methotrexate and prednisone[1]; however, a search of the English language literature revealed no prior reports of an atypical myeloid infiltrate.

Cutaneous infiltrates associated with herpesviridae infection are typically lymphocytic in nature, mimicking inflammatory and neoplastic disorders, including erythema multiforme, lupus erythematosus, lymphomatoid papulosis, B-cell lymphoma, and lymphocytic leukemia cutis.[2] Admixed neutrophils have been reported in a case of VZV histopathologically masquerading as linear IgA bullous dermatosis, with positive direct immunofluorescence results.[3] In addition to mimicking neoplasms, cutaneous VZV may serve as the initial locale of hematologic malignancies.[4] As VZV may demonstrate either histopathologic mimicry or Wolf's isotopic response, a complete workup may include bone marrow analysis.

The rare potential of aleukemic myeloid leukemia to manifest with isolated skin involvement preceding a systemic presentation was considered,[5] but continued follow-up 7 months after the initial cutaneous presentation has shown no evidence of a myeloproliferative disorder. Additionally, in the setting of Crohn's disease treated with methotrexate, the possibility of an iatrogenic myelodysplastic syndrome or myeloid leukemia must be addressed, but again, the patient's negative bone marrow analysis result and rapidly resolving cutaneous findings after systemic antiviral therapy strongly support a reactive myeloid infiltrate. Furthermore, diagnosis of an autoimmune disease has been reported to precede the development of a myeloid neoplasm by a median period of 8 years,[6] and this patient had a more than a 3-decade history of Crohn's disease. Finally, compared with other immunomodulatory agents, the association of methotrexate therapy with the development of a myeloid neoplasm may not be statistically significant.[6] This case emphasizes the necessity for careful clinicopathologic correlation to navigate the varied presentations of VZV and broadens the reported histopathologic findings to include an atypical myeloid infiltrate mimicking leukemia cutis in a dually immunosuppressed patient.

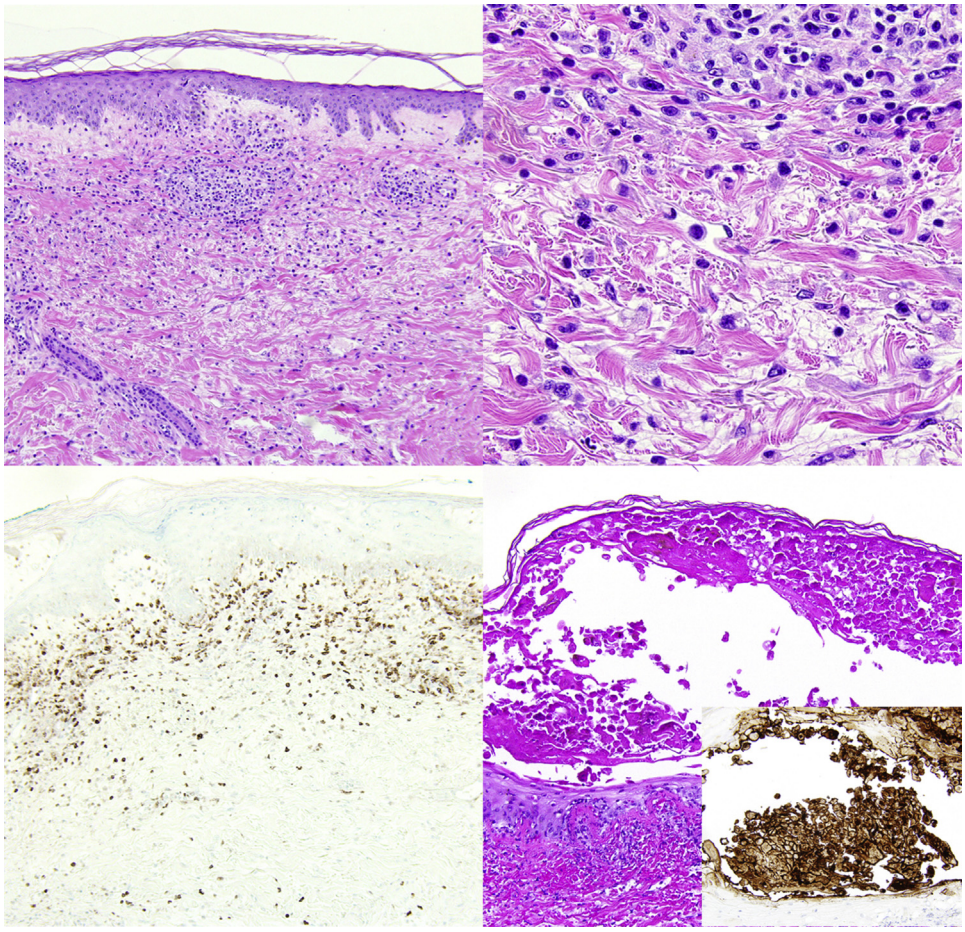

Fig 2. Atypical myeloid infiltrate associated with disseminated cutaneous VZV. Initial biopsy demonstrating an atypical myeloid infiltrate with abundant granular cytoplasm, pleomorphic nuclei, and prominent nucleoli. (*Top panel*: hematoxylin-eosin stain; original magnifications: *left* ×100, *right* ×400. *Lower left panel*: lysozyme stain; original magnification: ×200) The *lower right panel* shows a second biopsy revealing an intraepidermal vesicle with ballooning degeneration (hematoxylin-eosin stain; original magnification: ×100) and VZV stain positivity. (*Inset*, original magnification: ×100.) *VZV*, Varicella zoster virus.

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