Post–Varicella-Zoster Virus Granulomatous Dermatitis: A Report of 2 Cases

Natalie A. Wright, MD; Carlos A. Torres-Cabala, MD; Jonathan L. Curry, MD; Jonathan E. Cutlan, MD; Sharon R. Hymes, MD

Practice Points

- Granulomatous dermatitis, as well as other entities, can occur in sites of prior varicella-zoster virus infection.
- Granulomatous dermatitis symptoms present within days to years after varicella-zoster virus infection and resolve normally within 6 weeks; however, symptoms persisted for 10 weeks in one of our patients.
- Antiviral medications do not improve the clinical symptoms of postzoster granulomatous dermatitis.

Granulomatous dermatitis (GD) is known to occur following varicella-zoster virus (VZV) infection. Lesions may appear at varying times after the acute eruption in both immunosuppressed and immunocompetent hosts. The etiology of GD is unclear, and findings of VZV in the lesions often are inconsistent. We describe 2 immunocompromised patients who presented with GD following VZV infection; their lesions were examined for the presence of VZV. We also review the literature on postzoster GD.

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Many cutaneous reactions have been reported to develop in resolved varicella-zoster virus (VZV) lesions, including granuloma annulare, sarcoidal granuloma, tuberculoid granuloma, lymphoma, leukemia, pseudolymphoma, granulomatous vasculitis, psoriasis, granulomatous folliculitis, lichen sclerosus, cutaneous Rosai-Dorfman disease, lichen planus, dermatophyte infections, squamous and basal cell carcinomas, Kaposi sarcoma, lichen planus–like graft-versus-host disease, contact dermatitis, morphea, and angiosarcoma. Granuloma annulare is the most frequently described of these cutaneous reactions, but other granulomatous reactions have been noted. Granulomatous dermatitis (GD) is known to occur in postzoster scars but has been infrequently reported in the medical literature.[1-8] The etiology of GD is unclear and is further complicated by inconsistent findings of VZV in the lesions.

We describe 2 immunocompromised patients with postzoster GD who underwent histopathologic analysis and were examined for the presence of VZV protein via immunohistochemistry. This entity is important to recognize, especially in immunosuppressed patients who may be treated with a variety of antiviral agents to clear what appears to be a resistant infection.

Case Reports

Patient 1—A 68-year-old man with a history of acute myelogenous leukemia and allogeneic stem cell transplant presented with red papules on the back and upper and lower extremities. Two weeks prior to presentation, the patient was hospitalized for disseminated vesicular VZV infection confirmed by both

Dr. Wright is from the Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas. Drs. Torres-Cabala, Curry, Cutlan, and Hymes are from the The University of Texas MD Anderson Cancer Center, Houston. Drs. Torres-Cabala, Curry, and Cutlan are from the Department of Pathology, and Dr. Hymes is from the Division of Internal Medicine and the Department of Dermatology.
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Correspondence: Sharon R. Hymes, MD, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Unit Number 1452, Houston, TX 77030 (srhymes@mdanderson.org).

biopsy and direct immunofluorescence. The disseminated herpes zoster occurred after prophylactic doses of valacyclovir were stopped. He was treated with acyclovir, according to guidelines for VZV infection, and intravenous immunoglobulin. Ten days after initial hospitalization he was discharged on valacyclovir and his vesicles were resolving.

Nine days after discharge, the patient noticed an increasing number of papules but no vesicles. An increased dose of valacyclovir did not improve the eruption. Physical examination at that time revealed widespread 3- to 5-mm erythematous papules on the back, chest, shoulders, arms, and legs (Figure 1).

Histology showed a collection of epithelioid histiocytes forming small discohesive granulomas with a mixed inflammatory infiltrate (Figure 2). Gram, Fite, and Gomori methenamine-silver staining was negative for bacteria, acid-fast bacilli, and fungi, respectively. Varicella-zoster virus immunohistochemical studies were negative.

Antiviral coverage was decreased to prophylactic levels and the lesions resolved over a period of 8 weeks.

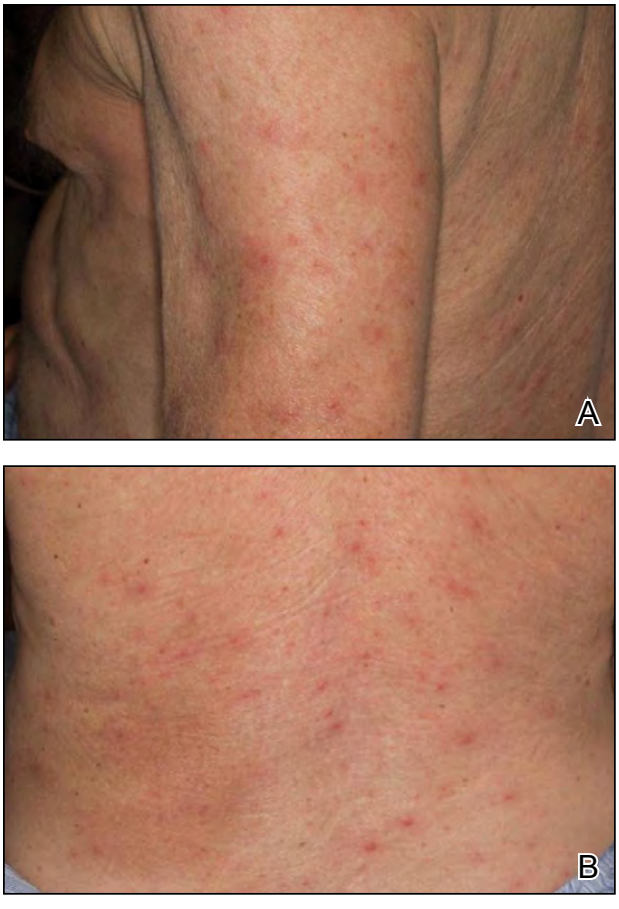

Figure 1. Scattered 3- to 5-mm erythematous papules on the left arm (A) and back (B).

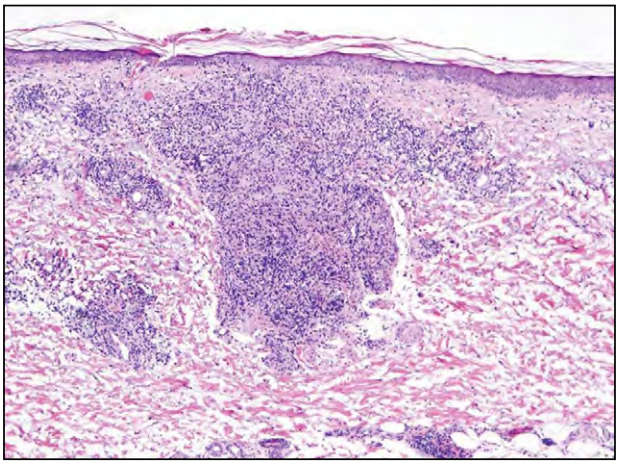

Figure 2. Collection of epithelioid histiocytes forming small discohesive granulomas with a mixed inflammatory infiltrate (H&E, original magnification ×4).

Patient 2—A 62-year-old woman with a history of breast cancer and chronic lymphocytic leukemia most recently treated with rituximab presented with VZV infection and Ramsay Hunt syndrome. Six weeks prior to presentation, the patient began to have facial pain, vesicles distributed along the V2 and V3 branches of the trigeminal nerve, and oral mucosal ulcers that were treated with hydrocodone-acetaminophen, cephalexin, and valacyclovir 1 g 3 times daily for 2 to 3 weeks. The patient was subsequently hospitalized for worsening pain and intravenous acyclovir was administered. She was discharged on a regimen of valacyclovir.

The patient reported resolution of the vesicular lesions but 4 weeks later she started to develop a papular eruption in the involved area. Physical examination showed drooping of the left side of the face, erythematous papules and plaques distributed along the V2 and V3 branches of the trigeminal nerve, and erythema and scaling of the left ear (Figure 3). She was hospitalized and treated with foscarnet for possible acyclovir-resistant VZV infection.

Histology showed a collection of epithelioid histiocytes with scattered multinucleated giant cells forming small discohesive granulomas with a mixed inflammatory infiltrate (Figure 4). Gram, Fite, and Gomori methenamine-silver staining was negative for bacteria, acid-fast bacilli, and fungi, respectively. Immunohistochemical studies were negative for VZV and herpes simplex virus. A $CD3^+$ inflammatory infiltrate in the dermis with rare $CD20^+$ T cells ruled out chronic lymphocytic leukemia in the skin.

The patient was started on prednisone 20 mg prior to discharge and continued on foscarnet for

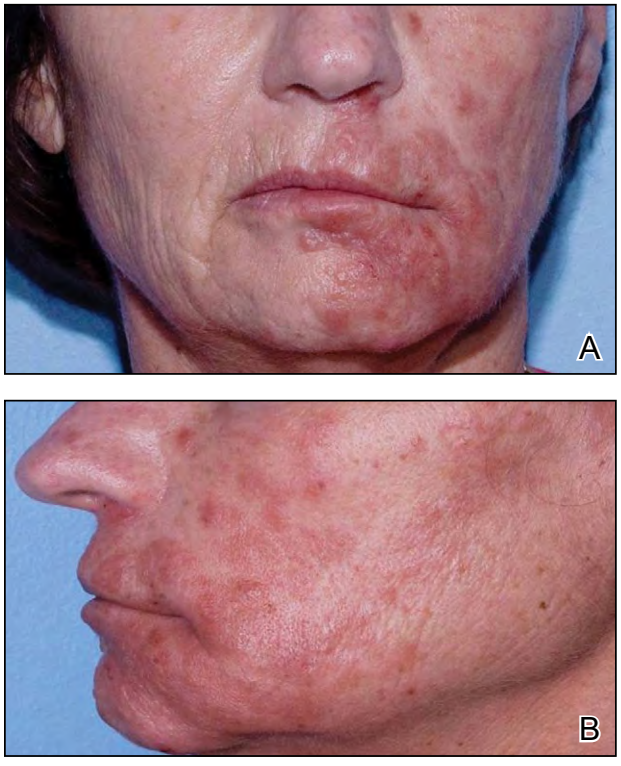

Figure 3. Drooping of the left side of the face and distribution of erythematous papules and plaques along the V2 and V3 branches of the trigeminal nerve (A and B).

14 days with marked improvement of skin lesions over 10 weeks.

Comment

Granulomatous dermatitis is a known reaction that can follow VZV infection,[1-8] usually presenting as papules and plaques in a zosteriform distribution at the sites of prior infection. This dermatitis may appear immediately in resolving VZV vesicular lesions or up to 4 years after the acute eruption in both immunosuppressed and immunocompetent hosts.[1,4,9,10] The diagnosis is primarily clinical and confirmed by histopathologic analysis. Limited or no improvement has been reported with antiviral agents, and the eruption tends to spontaneously remit without treatment within days to 6 weeks.[11,12] A review of reported cases of postzoster GD are presented in the Table.

Postzoster GD represents an isotopic response or the appearance of a new unrelated disease at the site of a previously healed disease, usually caused by a herpesvirus.[13] The pathogenesis of this phenomenon occurring in prior VZV scars has yet to be elucidated. Viral, immunologic, vascular, and neural origins all have been considered.[14] Some researchers postulate that the herpesvirus, although not directly responsible for the second disease, is accountable for altering cutaneous nerve fibers and allowing an immune response to occur; in fact, a type III or type IV delayed hypersensitivity reaction[6,9,15] or Koebner phenomenon has been thought to be a possible source.[9,13,15]

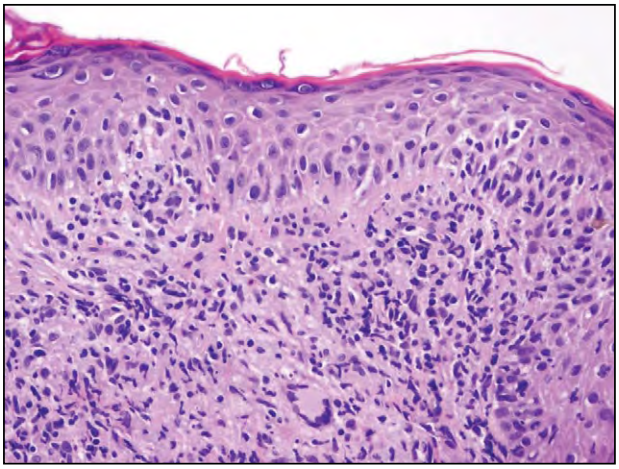

Figure 4. Histology showed a collection of epithelioid histiocytes with scattered multinucleated giant cells forming small discohesive granulomas with a mixed inflammatory infiltrate (H&E, original magnification ×20).

Testing for the presence of VZV DNA via the polymerase chain reaction technique has yielded inconsistent results. Polymerase chain reaction has been used to positively identify VZV DNA in lesions occurring less than 5 weeks from a VZV outbreak but not in lesions arising thereafter.[2-4,11,12] The lack of VZV DNA in all but the earliest of lesions lends itself to the idea that VZV antigens are not the source of the reaction; instead, an incomplete viral genome, viral glycoproteins, or tissue antigens altered by the virus could be responsible.[6,16] The fact that GD fails to respond to antiviral treatment supports the hypothesis that delayed hypersensitivity to an incomplete viral genome or antigen altered by VZV is responsible.

Patient 1 was notable for the widespread development of GD in the resolving disseminated VZV lesions. One case of herpes zoster occurring in more than 5 contiguous dermatomes with subsequent development of GD has been reported[8]; however, generalized GD, as seen in our patient, is rare. Both of our patients were immunocompromised. Patient 2 had a prolonged 10-week course of GD, which usually begins to resolve within days to weeks but has been described to persist for up to 45 days.[4] The patient was treated with foscarnet for a possible drug-resistant VZV infection, but no substantial improvement was appreciated until after the addition of oral corticosteroids. The failure of both of our patients to respond to multiple courses of antiviral agents

Reported Cases of Postzoster GD

Reference (Year)	Patient No.	Gender	Age, y	Interval Prior to GD	Characteristics of New Lesions	History of Immunocompetence	Presence of VZV DNA	Method of VZV Detection
Current report	1	M	68	9 d	3- to 5-mm erythematous papules	Acute myelogenous leukemia, allogeneic stem cell transplant	No	Anti-VZV monoclonal antibody
	2	F	62	4 wk	Erythematous papules and plaques	Chronic lymphocytic leukemia, breast cancer	No	Anti-VZV monoclonal antibody
Gesierich et al[2] (2004)	3	M	74	Unknown	Red-brown papules	Chronic lymphocytic leukemia	Yes	PCR
Gutzmer et al[3] (2001)	4	Unknown	54	2 wk	Red papules	T-cell non-Hodgkin lymphoma	Yes	PCR
Vu et al[8] (1999)	5	M	69	3 mo	Plaques and papules in a noncontiguous zosteriform distribution	End-stage renal disease, history of cadaveric renal transplant	No	Viral culture
Serfling et al[4] (1993)	6	F	74	4 y	Pink indurated papules	None	No	PCR
	7	F	82	1 mo	Firm nodules	None	No	PCR
	8	F	67	4 mo	Pink-purple papules	None	No	PCR
	9	M	73	<1 mo	Erythema and lichenoid papules	None	Yes	PCR
Pujol et al[5] (1990)	10	M	68	3 wk	Grouped lichenoid brownish papules	Chronic lymphocytic leukemia	No	Immunofluorescence and electron microscopy
Winkelmann et al[7] (1992)	11, 12, 13	Unknown	Unknown	Unknown	Erythematous to plum-colored papular and nodular dermal lesions and plaques	None noted	Untested	N/A

Abbreviations: GD, granulomatous dermatitis; VZV, varicella-zoster virus; M, male; F, female; PCR, polymerase chain reaction; N/A, not applicable.

supports the idea that a delayed hypersensitivity reaction to an incomplete viral genome or antigen altered by VZV is responsible, not VZV itself. The GD showed no evidence of VZV by immunohistochemistry, and the role of the VZV infection in postzoster GD remains to be determined.

Conclusion

Even though GD represents a known entity, clinicians must be aware of the possible lack of efficacy in antiviral use in its resolution in post-VZV cases of the disease.

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