

A Unique Case Report on Hypersensitivity Vasculitis as an Allergic Reaction to the Herpes Zoster Vaccine

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Vikram Puram, BS¹ , Danielle Lyon, BS¹, and Nedaa Skeik, MD¹

Abstract

Hypersensitivity vasculitis (HV) or leukocytoclastic vasculitis is a rare small-vessel vasculitis that may occur as a manifestation of the body's extreme allergic reaction to a drug, infection, or other foreign substance. Characterized by the presence of inflammatory neutrophils in vessel walls, HV results in inflammation and damage to blood vessels, primarily in the skin. Histologically, when neutrophils undergo leukocytoclasia and release nuclear debris into the vasculature, vascular damage manifests as palpable purpura. The incidence of HV is unknown and its relationship and interaction with certain vaccinations is rare and poorly understood. Affected patients with HV generally have a good prognosis; however, fatality may occur if organs such as the central nervous system, heart, lungs, or kidneys are involved. We report a unique case of a 60-year-old man who presented with a serious case of HV after receiving the herpes zoster vaccine. A thorough literature review yielded only one similar case of vascular reaction to the varicella vaccine that was reported in the *Annals of Internal Medicine* in 1997; however, no other reported cases with regard to the herpes zoster vaccine have been found. Our case presents a rare glimpse into HV that may result from varicella vaccine administration.

Keywords

hypersensitivity vasculitis, leukocytoclastic vasculitis, rash, herpes zoster vaccination

Case Report

A 60-year-old white man with a history of hypertension, obesity, obstructive sleep apnea, and hyperlipidemia presented with a 2-week history of generalized red/purple skin, itchy rash, and swelling of the tongue and mouth. The rash initially involved the arms and legs, then progressed into the torso and was associated with a severe burning sensation and swelling. The patient had received the herpes zoster vaccination (Merck & Co, Kenilworth, New Jersey) 6 weeks prior to symptom onset. He denied any history or symptoms of autoimmune, blood, connective tissue, or rheumatological disorders. He also denied any recent medication changes (vitamin D₃, multivitamin), travel, or contact with sicknesses.

Physical examination revealed a right arm blood pressure of 117/79 mm Hg, pulse of 87 per minute, oral temperature of 98.2°F, and body mass index of 55.55 kg/m². Physical examination also revealed diffuse petechial rash involving the 4 extremities and the torso (Figure 1A) along with angioedema. Later on, he developed a full-thickness left mid leg ulcer due to a delicate skin breakdown with underlying edema. The rest of the physical examination was unremarkable. In view of the rapid rash progression and angioedema, he was admitted for further management.

The patient's laboratory test results were unremarkable for complete blood count (CBC) and complete metabolic profile (CMP). Further blood work revealed elevated C-reactive

protein (CRP) of 7.46 mg/dL and normal erythrocyte sedimentation rate (ESR) of 10 mm/h. He had negative antinuclear antibodies, cryoglobulin, and HIV testing. The patient had no clinic evidence of antiphospholipid syndrome, coagulopathy-, or antineutrophil cytoplasmic antibodies (ANCA)-related vasculitis, so these laboratory tests were not performed. Furthermore, the biopsy was pathognomonic for leukocytoclasia with no pathologic evidence of ANCA-related vasculitis. Additionally, no drugs had been used at the time, eliminating the possibility of drug-associated immune complex vasculitis. Left calf skin biopsy revealed mixed inflammatory infiltrate within and surrounding dermal vessels accompanied by leukocytoclasia, fibrinoid change within vessel walls, and erythrocyte extravasation confirming the diagnosis of leukocytoclastic vasculitis (Figure 2A and B).

The patient was managed with methylprednisolone 40 mg intravenously every 8 hours that was changed to a prednisone taper down dosage starting with 40 mg daily. He also received

¹Department of Vascular Medicine, Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN, USA

Corresponding Author:

Nedaa Skeik, Department of Vascular Medicine, Minneapolis Heart Institute, 800 East 28th Street, H2100, Minneapolis, MN 55407, USA.
Email: nedaa.skeik@allina.com

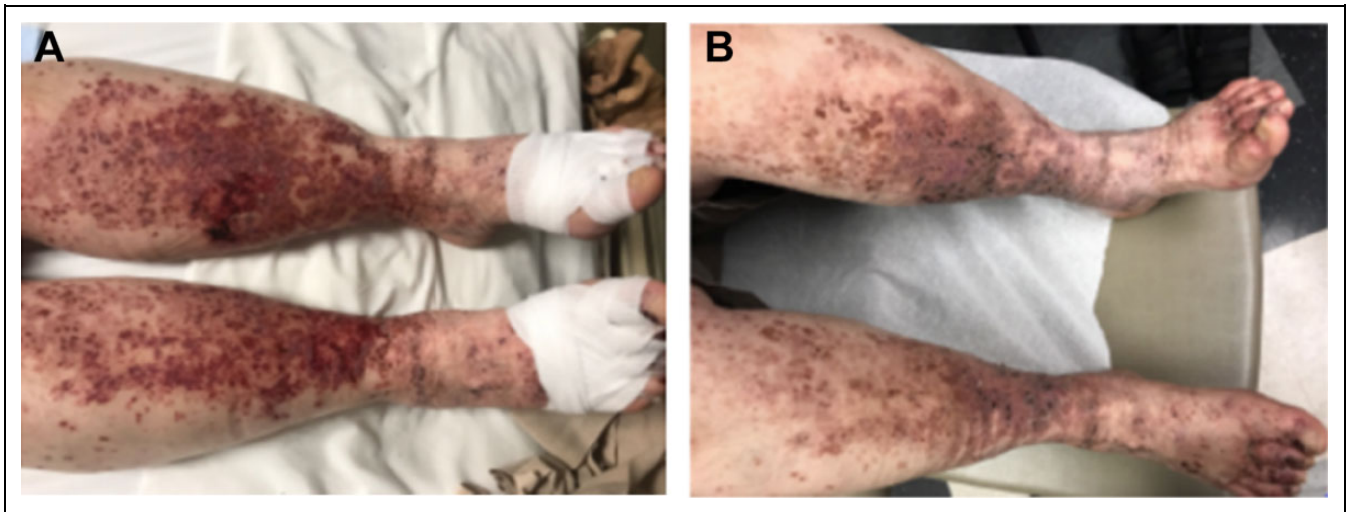


Figure 1. Hypersensitivity vasculitis at initial presentation onset (A) and 2 weeks posttreatment (B) reveals significant purpuric rash improvement.

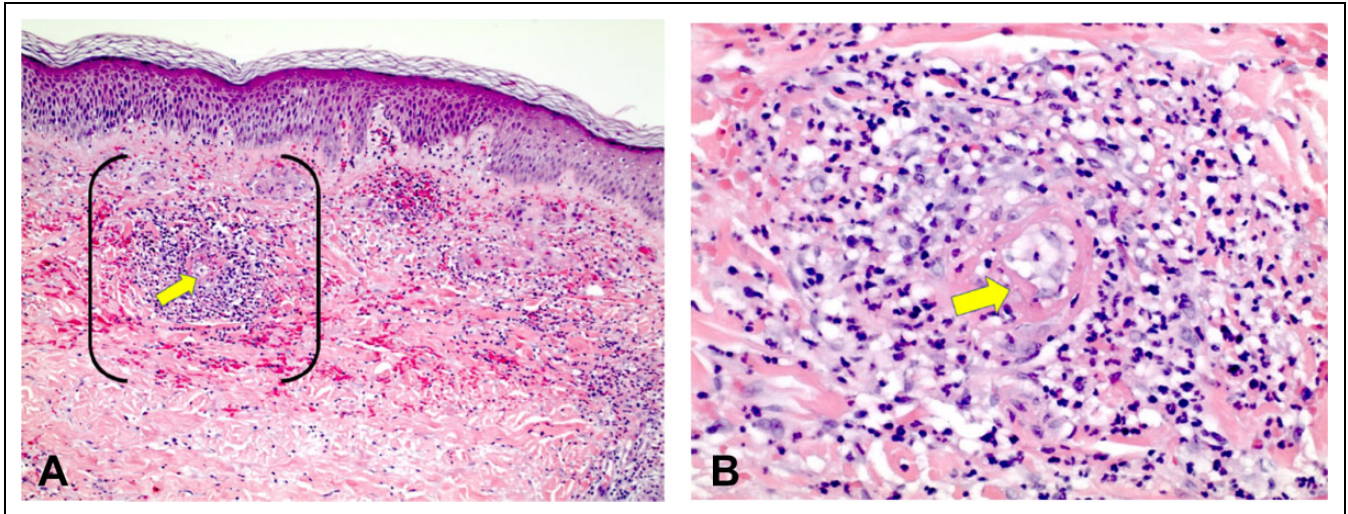


Figure 2. A, Leukocytoclastic vasculitis involves small vessels in the upper to mid dermis (arrow indicates an involved vessel, with black brackets around the inflammation and extravasated erythrocytes). The inflammation is composed predominately of neutrophils with some admixed eosinophils and lymphocytes. The inflammatory cells can be seen infiltrating the vessel wall, with subsequent fibrinoid change and erythrocyte extravasation (hematoxylin and eosin, $\times 20$). B, Arrow indicates fibrinoid necrosis of the vessel wall. The vessel is surrounded by a brisk neutrophil-predominant inflammatory infiltrate. Extravasated erythrocytes can also be seen (hematoxylin and eosin, $\times 40$).

topical 0.05% clobetasol cream twice daily, diphenhydramine 25 mg every 8 hours, and trimethoprim–sulfamethoxazole (160-800 mg tablet) twice daily for superimposed bacterial cellulitis caused by *Escherichia coli* and methicillin-sensitive *Staphylococcus aureus* proven by skin culture from the left leg ulcer. His symptoms improved significantly and the rash continued to fade and finally healed with hyperpigmentation at 6-month follow-up visit (Figure 1B).

Discussion

Vasculitis refers to a group of disorders involving inflammation of the blood vessels. Based on the vessel size involved, vasculitis

can be categorized into small (eg, leukocytoclastic vasculitis), medium (eg, polyarteritis nodosa), and large (eg, giant cell and Takayasu arteritis).¹ Hypersensitivity vasculitis also referred to as leukocytoclastic vasculitis (based on the histologic findings) targets and damages small vessels in the skin.^{1,2} Although the case presented in this report involves HV confined to the skin, which is generally self-limited and has a better prognosis, the disease has the potential to affect many different organs and increase morbidity and mortality. Hypersensitivity vasculitis may be short term or may have a chronic course.³ Among the 30 million cases per year that affect men and women equally, it has been noticed that a wide variety of factors such as infections and medications may lead to its development.⁴⁻⁶

Table 1. Some of the Known Autoimmune Disorders, Infectious Diseases, and Malignancies for Hypersensitivity Vasculitis.

Key Etiologies for Leukocytoclastic Vasculitis		
Autoimmune Disorders	Infectious Diseases	Malignancies
Lupus	Hepatitis B	Tumor necrosis factor inhibitors
Rheumatoid arthritis	Hepatitis C	Propylthiouracil
Sjögren syndrome	Erythrovirus B19	Cocaine/Levamisole
Polyarteritis nodosa	Endocarditis	Minocycline
Psoriatic arthritis	Cytomegalovirus	Rituximab
Crohn disease	Varicella-zoster	Montelukast
Behçet syndrome	HIV	Statins
Juvenile rheumatoid arthritis	Syphilis, brucellosis	Penicillin
	Human T-cell lymphotropic virus	Hydralazine
		Allopurinol
		Thiazides
		Quinolones
		Warfarin
		Hodgkin disease

The disease's etiology is not always known and its onset as a result of vaccination is rare, though some of the known etiologies include drug reactions, response to infection, and autoimmune disorders (Table 1).⁷⁻¹² Some vaccinations have rarely been reported as the underlying etiology. There are reported cases of HV following human papillomavirus, influenza, and hepatitis B vaccinations.¹³ Additionally, the measles, mumps, and rubella vaccine has reportedly caused HV in some infants.¹⁴ The exact mechanism behind this immune-mediated vasculitis is thought to be type III allergic reaction or serum sickness disease.¹⁵ Many of these documented cases do not claim a direct causal relationship between the vaccine and the outcome, rather, it is only a close temporal association that prompts the presumption that symptoms may be potentially caused by the vaccine.¹⁶ Although these immunizations have been reported to be associated, our case of herpes zoster vaccination-related HV is very rare.^{7,8} The rarity of the case is due to the length of time between vaccination and presentation. Hypersensitivity vasculitis usually presents within 1 to 3 weeks but may occur several months later especially if it is related to type III allergic reaction.¹⁷ Our patient presented 6 weeks post-vaccination making this case rare.

Based on our literature search, we were only able to find 1 case report of a 26-year-old man who had a similar adverse reaction 2 weeks postinoculation with the varicella virus vaccine. Their patient responded well to rapidly tapering oral prednisone.¹⁸

Although HV can be classified by the etiologies mentioned, many cases have no identifiable cause and its relation to vaccine inoculation has yet to be established.¹⁹ Patients who develop vasculitis secondary to medication or infection often

experience a single, limited episode; however, those with HV due to relapsing or chronic disease are at much higher risk for a longer duration ranging from days to decades.²⁰

In terms of diagnosis, since HV is often secondary to medication use or infection, it is extremely important to inquire about new medications, symptoms of infection, recent illness, sick contact, and recent vaccination. In fact, HV is often difficult to distinguish from other forms of vasculitis unless other manifestations are present.²¹ In the presence of systemic vasculitis involving multiple organs, imaging studies may be useful to provide further information about the disease involvement and activity.²² A lack of evidence suggesting systemic manifestation is instrumental in a diagnosis of localized cutaneous vasculitis.²³

Given that drug-induced vasculitis most often occurs 7 to 10 days after the introduction of the inciting medication and within 4 weeks of a vaccine allergy, gathering detailed information about the timing of the symptom development and the exact date of vaccination can be helpful in determining the temporal relationship between the disease and its etiology.²⁴

Painful and palpable lower extremity erythematous rash may feature many dermatologic or systemic disorders including purpura, hemorrhagic bullae, subcutaneous nodules, livedo reticularis, livedo racemosa, or urticaria.^{4,6,25} Proper diagnosis requires detailed medical history, thorough physical examinations, and appropriate workup including CBC, CMP, ESR, CRP, and other laboratory work relevant to the patient presentation and history.²³ Since palpable purpura and petechial lesions may also occur in other conditions, biopsy results afford a confirmation.²¹ The histological diagnostic criteria for HV involve processes that result in damage to vessel walls including angiocentric and/or angioinvasive infiltrates and fibrinoid necrosis. Other histopathological findings such as nuclear debris, necrosis of eccrine glands, endothelial cell damage, cutaneous ulceration, or extravasated erythrocytes might suggest but are not purely diagnostic for HV.²⁶

Optimal management has not yet been established for patients with HV; however, systemic immunomodulatory therapies remain widely used.²⁷ Its clinical presentation along with its categorization as an acute (short-term) or long-lasting disease influences the approach to treatment. Systemic glucocorticoids, such as oral prednisone used on our patient, typically serve as first-line therapy.²⁸ Second-line therapy is initiated in the event of a relapse. This includes use of colchicine, dapsone, or aggressive immunosuppressive therapy.²⁹

The insufficient understanding of HV and its onset as an allergic reaction may have an adverse impact on quality of life. Clinical awareness of this case, including its presentation, diagnosis, and prognosis, is important and we believe that there is need for further research to address the pathogenesis and management of HV and its relation to certain vaccinations. In our patient, the presentation of a purpuric rash, characteristic pathological findings, denial of relevant risk factors, and unremarkable laboratory test results confirmed the diagnosis of HV. The temporal correlation between symptom onset and the patient's inoculation with the herpes zoster vaccine led to the

conclusion that the two are related. Based on our literature research, this case of herpes zoster vaccination-related HV is the second to be reported (to our knowledge). It raises the importance of elucidating the underlying mechanisms linking HV and this common vaccination as well as the need for greater understanding of the subject as a means of identifying contraindications of herpes zoster vaccine inoculation.

Authors' Note

Informed consent has been obtained from the patient (or patient's guardian) for publication of the case report and accompanying images. Pathologist for photography credit: Andrea Conway, MD.

Declaration of Conflicting Interests

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ORCID iD

Vikram Puram, BS  <http://orcid.org/0000-0002-0764-6053>

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