Varicella-zoster virus (VZV) infection causes 2 distinct disease processes. Primary VZV infection results in varicella (chickenpox), a common generalized eruption, and subsequent reactivation of VZV classically results in herpes zoster (shingles), which presents as a unilateral, dermatomal eruption. Although a single VZV infection typically confers protection against its reactivation, recurrent varicella rarely is reported, particularly in immunocompetent patients. We present the case of a 52-year-old black woman with an intact immune system who demonstrated 3 VZV infections.


Case Report
A 52-year-old black woman presented to our dermatology clinic for evaluation of a generalized pruritic rash of 5 days' duration. The eruption had started on the trunk and subsequently spread to the face, legs, and arms, including the dorsal surfaces of the hands (Figure 1). The patient reported that she had developed a similar rash 4 years prior. She recalled no sick contacts but had occupational exposure to many people as a food service worker. Two days prior, the

Figure 1. Papules, vesicles, and crusts on the dorsal surfaces of both hands in a 52-year-old black woman.
referring physician had initiated treatment with oral acyclovir 400 mg every 6 hours. The patient was in otherwise good health and reported no fever, chills, diaphoresis, or fatigue. She did not recall any recent insect bites, and a review of systems was negative.

The patient’s medical history was remarkable for 2 cases of varicella: the first, which occurred at 5 years of age, was diagnosed by a pediatrician and manifested as diffuse papules, vesicles, and crusts with concurrent mild fever. The infection followed a typical clinical course and resolved without complications after 1 week. The second case of varicella was diagnosed clinically at our dermatology clinic approximately 4 years prior to the current presentation and manifested as widespread pruritic lesions that were too numerous to count. Given her history of varicella in childhood, a punch biopsy specimen was taken from a lesion on the left trunk and a dermatopathologist confirmed the diagnosis of a herpesvirus infection. The second infection also resolved without sequelae after 12 days. Her medical history was otherwise unremarkable, revealing no exceptional sinopulmonary or gastrointestinal infections. The patient was not currently taking any medications or supplements and reported no known drug allergies.

Physical examination at the current presentation revealed a well-nourished, afebrile woman with vesicles and papules on the hands, arms, and legs along with vesicular and crusted papules in various stages of healing distributed on the chest, abdomen, and back. Lesions on the legs and feet were present but scant. The eruption was not confined to a single dermatome. No lesions were noted on the palms, soles, or oral mucosa and no epitrochlear, axillary, or supraclavicular lymphadenopathy was noted.

Initial laboratory values were obtained. A complete blood count demonstrated a normal lymphocyte number of 5700 cells/μL (reference range, 4500–11,000 cells/μL) and mild anemia with a hemoglobin level of 10.3 g/dL (reference range, 14.0–17.5 g/dL). Monocytes were mildly elevated at 11% (reference range, 1%–9%). Serologic tests showed positive titers for varicella-zoster virus (VZV) IgM at 1.64 (negative, <0.91) and VZV IgG at 1.72 (negative, <0.91), indicating current and past VZV infection, respectively. Antibodies against herpes simplex virus (HSV) types 1 and 2 were negative for IgM and positive for IgG at >5.00 (negative, <0.90), indicating a remote HSV infection. Furthermore, results from a culture of a lesion on the left hand were negative for HSV.

After consultation with the Department of Infectious Diseases, further laboratory studies were performed. The absolute lymphocyte number was within normal range at 1600 cells/μL (reference range, 850–3900 cells/μL). Likewise, CD4+ T lymphocytes were normal at 618 cells/μL (reference range, 490–1740 cells/μL) or 39% of total lymphocytes (reference range, 30%–61%). Screening results were negative for human immunodeficiency virus types 1 and 2. Immunoglobulin subtype analysis revealed slightly elevated IgG at 1709 mg/dL (reference range, 723–1685 mg/dL), elevated IgA at 487 mg/dL (reference range, 65–382 mg/dL), and normal IgM at 238 mg/dL (reference range, 63–277 mg/dL).

Consistent with the clinical presentation and serologic studies, recurrent varicella was accepted as the most plausible diagnosis. Over the next 2 weeks, the eruption resolved with postinflammatory hyperpigmentation (Figure 2). The patient returned to work without further incident.

Comment
As denoted by its hyphenated name, VZV infection can cause 2 distinct disease processes. Varicella, the generalized initial exanthem known as chickenpox, appears predominantly in childhood. With resolution of this primary infection, the virus lies dormant in sensory ganglia, persisting in neurons. Stress, advanced age, and/or compromised immunity may reactivate latent VZV. This secondary expression is known as herpes zoster (shingles),

Figure 2. Lesions on the back that resolved after 2 weeks with postinflammatory hyperpigmentation.
a unilateral eruption of lesions localized to a single dermatome.

In most cases, morphology of the varicella eruption confirms the diagnosis. Lesions evolve through stages from macules and papules to vesicles and pustules and then to crusts. This evolution typically takes 24 to 48 hours. The varicella eruption contains an admixture of elements from each stage simultaneously. Crusts usually resolve over an average of 14 days. Serologically, IgM is measurable as

### Immunocompetent Patients with Recurrent Varicella Reported in the Literaturea

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>No. of Patients</th>
<th>Patient Population</th>
<th>No. of Episodes per Patient</th>
<th>Evidence of Prior VZV Infection</th>
<th>Notes</th>
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<td>Weller1 (1983)</td>
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<tr>
<td>Gershon et al8 (1984)</td>
<td>3</td>
<td>Adults (2), child (1)</td>
<td>2</td>
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<td>Study included 8 total patients but only 3 were immunocompetent</td>
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<tr>
<td>Gurevich et al13 (1990)</td>
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<td>Junker et al9 (1991)</td>
<td>14</td>
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<td>Junker and Tilley10 (1994)</td>
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<td>Martin et al16 (1994)</td>
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<td>Terada et al11 (1996)</td>
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<td>2</td>
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<td>Ku et al14 (2005)</td>
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<td>Patient was a nurse; reinfection after exposure to patient with VZV infection</td>
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<td>Johnson et al15 (2011)</td>
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<td>2</td>
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</tr>
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</table>

Abbreviation: VZV, varicella-zoster virus.

*aImmunocompetence was defined as no history of conditions associated with impaired immunity (eg, human immunodeficiency virus, AIDS, diabetes mellitus) or conditions requiring treatment with systemic immunosuppressive therapy.
early as 1 to 2 days after appearance of the eruption.\(^3,4\) Next to appear are IgG antibodies, which generally remain detectable for life. With more than 90% of the US population being seropositive for VZV,\(^5\) diagnosis and management of varicella and herpes zoster usually are straightforward; however, there have been unusual variations on this classic sequence of pathogenesis.

In disseminated zoster, the clinical presentation includes more than 20 lesions outside the dermatoome primarily affected.\(^6\) Another permutation of VZV infection is zoster sine herpete, which causes the characteristic dermatomal pain of herpes zoster but without the rash.\(^7\) Occasionally, 2 cases of chickenpox occur in the same person, usually indicating an underlying immune deficiency. Recurrent varicella in those with intact immunity is purportedly rare. A PubMed search of articles indexed for MEDLINE using the search terms recurrent varicella, chickenpox reinfection, and immunocompetent revealed 41 cases of recurrent varicella in immunocompetent patients in the English language literature occurring among children,\(^8-11\) adults,\(^8\) the elderly,\(^12\) health care workers,\(^13-15\) and pregnant women\(^6\) (Table).

Surveillance studies, however, have challenged the apparent rarity of recurrent varicella, asserting that varicella may recur more frequently than is generally recognized.\(^17,18\) Hall et al\(^17\) described 9947 cases of varicella, with nearly 6.9% reporting prior varicella infection. Another surveillance report by Marin et al\(^18\) evaluating data from 1047 adults with varicella noted that 21% of participants reported prior VZV infections. Both of these studies defined varicella by clinical parameters as a condition with acute onset of generalized maculopapulovesicular rash without other known cause. Although laboratory confirmation of VZV infection was not documented in either study, a history of varicella is considered a reliable indicator of immunity. In fact, studies show that a history of varicella is associated with serologic evidence of immunity 97% to 100% of the time.\(^19,20\)

Immunity against VZV in humans is not well understood. Although both humoral and cellular factors play a role, cell-mediated immunity may be more important in suppressing primary infection and defending against reinfection. Varicella is more likely to disseminate in lymphopenic patients,\(^21,22\) while its course is uninfluenced by hypogammaglobulinemia.\(^1,2,3\) One study of simian varicella virus, which demonstrates 75% genetic homology with VZV, noted that simian varicella virus–infected rhesus macaques without CD4\(^+\) T lymphocyte response experienced higher viral loads, prolonged viremia, and disseminated varicella.\(^24\) The loss of CD20\(^+\) B lymphocytes did not intensify the severity of varicella in the primate model. It is accepted, however, that waning humoral immunity and lower antibody levels correlate with varicella recurrence.\(^25\) Ethnicity may impact immunoglobulin persistence. One investigation postulated that individuals with darker skin types experience reduced viral shedding and therefore less antigenic boosting from secondary VZV infections, as they may less readily maintain protective levels of VZV-specific immunoglobulins.\(^25\) This phenomenon may have contributed to the 3 episodes of varicella in our patient.

Virulence factors that are intrinsic to VZV may also prompt reinfection. Although taxonomy is still in flux, 3 to 5 major genotypes of VZV have been recognized to date, categorized into European (Dumas), Japanese (Oka), and mosaic clades.\(^26-28\) In one study population, approximately 80% of the VZV strains isolated in the United States were of the European variety.\(^26\) It is unclear whether infection with one strain of VZV affords immunoprotection against the other strains. Interestingly, one report documented recurrent herpes zoster caused by 2 distinct VZV strains in the same individual.\(^29\) Since subtypes of VZV vary geographically, it is possible that increasing global travel may correlate with increased incidence and reporting of varicella reinfection, particularly in cosmopolitan centers. In patients with recurrent varicella, a careful investigation of their international travel history may be necessary.

REFERENCES