Varicella Zoster Virus Pneumonitis and Brainstem Encephalitis Without Skin Rash in an Immunocompetent Adult

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Varicella zoster virus (VZV) pneumonia and brainstem encephalitis developed in an immunocompetent adult without rash. Chest computed tomography exhibited nodularity; lung biopsy revealed multinucleated giant cells, Cowdry A inclusions, VZV antigen, and DNA. Varicella zoster virus central nervous system disease was verified by cerebrospinal fluid (CSF) anti-VZV IgG antibody with reduced serum/CSF ratios.

Keywords. absence of rash; brainstem encephalitis; pneumonitis; VZV.

Reactivation of varicella zoster virus (VZV) usually produces zoster (shingles), often followed by chronic pain (postherpetic neuralgia). Zoster may also be complicated by meningitis, encephalitis, cerebellitis, cranial nerve palsies, vasculopathy, myelopathy, and various inflammatory disorders of the eye [1], all of which may develop in the absence of rash. To our knowledge, there has been only a single report of VZV infection involving both the nervous system and viscera in the absence of rash [2].

In this study, we describe a remarkable case of pneumonitis and brainstem encephalitis produced by VZV without rash.

CASE REPORT

A 37-year-old healthy woman in Oman with no past history of varicella or recent zoster rash presented with a 5-day history of productive cough, progressive paraparesis, urinary incontinence, lingual dysarthria, dysphagia, hiccup, and intractable vomiting. She was intubated and mechanically ventilated for 25 days. Brain magnetic resonance imaging (MRI) revealed a nonenhancing lesion in the dorsal medulla (Figure 1A and B) without diffusion restriction that was most likely inflammatory; the thoracic spinal cord MRI was normal. Chest x-ray and computed tomography (CT) scanning revealed bilateral upper lung consolidation and multiple nodules (Figure 1D and G). Diagnostic bronchial washing and sputum culture did not provide microbiological evidence for bacterial pneumonia as the cause of her lung pathology. She was treated with intravenous methylprednisolone 1 g/day for 5 days for the inflammatory brain and lung lesions, along with intravenous meropenem, 1 g 3 times daily for 3 weeks, because her intubated airway was colonized by Pseudomonas aeruginosa. After extubation, she was transferred to Sultan Qaboos University Hospital in Muscat, Oman for further evaluation.

On admission, positive neurological signs included gaze-evoked torsional nystagmus, a weak gag reflex, and a hypotonic paraparesis, greater on the left with an extensor plantar response. Cerebrospinal fluid (CSF) contained 6 cells, all mononuclear; CSF protein and glucose were normal; CSF acid-fast staining and culture for Mycobacterium tuberculosi, test for cryptococcal antigen, polymerase chain reaction (PCR) for Epstein-Barr virus, cytomegalovirus, herpes simplex virus-1 and -2, varicella zoster virus (VZV), enterovirus, and mumps virus were all negative. Serum immunoglobulin (Ig)G, IgM, C3, and C4 complement were normal; infectious mononucleosis antibody was negative; α1-antitrypsin was 3.14 g/L (normal 0.88–1.74 g/L). The vasculitis panel including antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigens, antiphospholipid antibody, anti-cardiolipin, anti-β2 glycoprotein, and lupus anticoagulant were negative. Serum was negative for antibody to aquaporin 4 and human immunodeficiency virus-1 and -2. She was treated with intravenous Ig (75 gm over 5 days) and oral prednisolone (40 mg/day) for the initial 13 weeks, which was tapered in the next 8 weeks for the inflammatory lung and brainstem disease, after which she received inhalational fluticasone (250 µg/dose).
Figure 1. FLAIR brain magnetic resonance imaging shows hyperintense signal (arrows) in dorsal medulla on sagittal (A) and axial (B) views, with regression 10 months later (C). Initial coronal (D) and axial (G) chest computed tomography (CT) revealed multifocal air-space opacification with multiple nodules predominantly in upper lungs bilaterally, greater on the right (D). One month later, coronal (E) and axial (H) chest CT revealed more prominent multifocal small nodular opacities randomly in both lung fields, cavitating cystic lesions in the right upper zone and resolving upper lobe consolidation bilaterally. Five months after initial presentation, coronal (F) and axial (I) lung CT showed marked persistence of small cystic areas in the right upper lung, but nearly complete resolution of the fibrotic lesions and micronodular shadows.

Table 1. Timeline of Relevant Clinical Features, Laboratory Analysis, Imaging Studies, and Treatment

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0–1</th>
<th>1–3</th>
<th>3–4</th>
<th>4–5</th>
<th>5–6</th>
<th>10</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td>Pulmonary and neurological symptoms; intubation</td>
<td>Extubation, transfer to Muscat at 1 month</td>
<td>Improvement at 3 months</td>
<td>Continued improvement at 5 months</td>
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<td><strong>Laboratory results</strong></td>
<td>Bronchial washings and sputum cultures negative; intubated airway <em>Pseudomonas</em>+</td>
<td>CSF, vasculitis labs; lung and renal biopsy performed</td>
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<td><strong>Imaging</strong></td>
<td>Brain MRI brain lesion (Figure 1A and B); chest CT abnormal (Figure 1D and G)</td>
<td>Chest CT chest shows resolving consolidation at 1 month (Figure 1E and H)</td>
<td>Chest CT improvement at 5 months, (Figure 1F and I)</td>
<td>Brain MRI lesion resolved (Figure 1C)</td>
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<td><strong>Treatment</strong></td>
<td>Methylprednisolone, 5 days; meropenem, 3 weeks</td>
<td>IVIG, 5 days; prednisolone, daily</td>
<td>Prednisolone, daily</td>
<td>Prednisolone, taper</td>
<td>Acyclovir IV for 2 weeks; then valacyclovir PO for 1 month; fluticasone/salmeterol, 24 days</td>
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Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging.
plus salmeterol (50 µg/dose twice daily) along with oral moxifloxacin (400 mg/day) for 24 days (Table 1).

One month after the onset of her illness, there was marked resolution of the concomitant consolidation in the upper lobes (Figure 1E and H). Lung biopsy indicated bronchiolitis obliterans organizing pneumoni and interstitial pneumonitis and multinucleated giant cells containing intranuclear inclusions (Figure 2A, arrows) but did not give rise to any organisms. The patient developed anemia, but a bone marrow biopsy revealed no abnormal infiltrates, blasts, or granuloma. She received blood transfusions, inotropic support, and initial mechanical ventilation followed by noninvasive ventilatory support for 1 month during her critical illness. Renal biopsy for transient nephrotic range proteinuria showed only mild mesangial hypercellularity in the glomerulus. Liver function remained normal.

Three months after onset of symptoms, cough and sputum had almost disappeared and 1–2 L/min of oxygen maintained an oxygen saturation of 98%. Repeat chest CT at 5 months revealed resolution of the fibrotic and micronodular lesions with persistence of small cystic areas (Figure 1F and I). Her paraparesis, sphincter dysfunction, dysphagia, and gag reflex also improved. Results of earlier CSF examination revealed anti-VZV IgG but not anti-HSV antibody, with reduced serum/CSF ratios of anti-VZV IgG antibody indicative of intrathecal synthesis of anti-VZV IgG antibody. Immunohistochemistry revealed VZV antigen (Figure 2B–E) and PCR-amplified VZV DNA in lung tissue as described [3]. The abundance of CD4 and CD8 T cells, macrophages, and neutrophils had also decreased (Figure 2F–I). Although our patient was markedly improved, because VZV can persist for months to years, she was treated with intravenous acyclovir (10 mg/kg 3 times daily for 2 weeks), followed by oral valacyclovir (1 g 3 times daily for 1 month) (Table 1). Brain MRI at 10 months after her initial symptoms showed marked regression of the dorsal medullary lesion (Figure 1C). Magnetic resonance angiography revealed no beading or narrowing of intracranial vessels.

**DISCUSSION**

In this study, we describe an extraordinary case of VZV pneumonia and brainstem encephalitis that developed simultaneously in an immunocompetent adult in the absence of rash.

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**Figure 2.** Hematoxylin-eosin staining of lung biopsy revealed multinucleated giant cells containing intranuclear inclusions (A, arrows). Of 200 5-µm sections cut from the formalin-fixed, paraffin-embedded lung biopsy, immunostaining of every other section as described [3] with 2 different antibodies to varicella zoster virus (VZV) revealed VZV in multiple nonconsecutive sections. Note detection of VZV antigen after immunostaining with mouse anti-VZV immunoglobulin (Ig)E antibody (B, pink color), but not after staining the adjacent section with control mouse IgG1 antibody (C). Varicella zoster virus antigen was also demonstrated after immunostaining with rabbit anti-VZV IgG antibody (D, pink color), but not with rabbit anti-HSV IgG antibody (E) or normal rabbit serum (data not shown). Further analysis of immune cells present in sections adjacent to those containing VZV antigen showed T cells expressing CD4 (F) and CD8 (G), macrophages expressing CD68 (H), and neutrophils expressing CD15 (I). Magnification ×600.
Because primary VZV infection would be expected to produce widespread rash (varicella) and VZV reactivation without rash is well documented, we presume that this was VZV reactivation and not primary infection. Although no particular lung lesion is VZV-specific, chest CT scanning did show nodularity typically described in VZV pneumonitis [4–6], and histopathology of the lung biopsy revealed multinucleated giant cells and Cowdry A inclusions characteristic of human herpesvirus infection. Virological analysis detected VZV antigen and VZV DNA. Detection of anti-VZV IgG antibody in CSF with reduced serum/CSF ratios of anti-VZV IgG antibody, indicative of intrathecal synthesis of anti-VZV IgG antibody, provided virological verification that VZV caused central nervous system (CNS) disease. The value of detecting anti-VZV IgG to diagnose CNS disease produced by VZV has been widely demonstrated, not only in a patient with repeated episodes of CNS disease, including brainstem inflammation without rash [7], but also in multiple patients with VZV myelopathy [8] and VZV vasculopathy [9]. Although VZV reactivation is well known to produce multiple neurological and ocular disorders in the absence of rash [1], visceral VZV infection without rash appears to be less frequent. Yet, rare cases of VZV reactivation without rash have produced fatal massive hepatic necrosis [10], disseminated infection of lung, liver, kidney, and bone marrow [11], as well as infection of the peripheral and CNS, esophagus, kidney, adrenal gland, and lymph nodes [2]. Finally, although our patient improved before VZV infection was verified virologically and received antiviral treatment, earlier virological analysis might have obviated months of intensive care.

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