CASE REPORT

Disseminated herpes zoster causing acute respiratory distress syndrome in an immunocompetent patient

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SUMMARY

Disseminated cutaneous varicella herpes zoster with visceral involvement is rare and seen almost exclusively in immunocompromised patients. We describe an unusual case of fulminant herpes zoster (HZ) in a healthy, immunocompetent 37-year-old woman. She initially presented to an urgent care centre with a classic HZ rash localised to her neck, and upper respiratory symptoms and was treated with prednisone and cephalexin. Within 1 week, the rash became diffuse and her clinical status rapidly deteriorated with development of severe acute respiratory distress syndrome. Varicella zoster infection was confirmed via skin biopsy, bronchial viral PCR and serology for varicella antibodies. She was successfully treated with intravenous acyclovir and aggressive supportive care. Though physicians readily recognise typical zoster infection, this case reminds clinicians that HZ infection can be fulminant and potentially life-threatening in younger, immunocompetent individuals. Early recognition and antiviral therapy is important to reduce morbidity and mortality.

BACKGROUND

Primary varicella zoster viral (VZV) infection, or 'chickenpox', is a highly contagious disease that usually occurs as a generalised vesicular rash in young unvaccinated children and non-immune adults. Primary VZV infection conveys immunity against repeat clinical manifestations of primary varicella; however, following infection resolution (and postvaccination with varicella vaccine), VZV lies dormant in sensory root ganglia. This allows for reactivation of disease as herpes zoster (HZ) later in life. Reactivation pathogenesis is not completely understood but is related to relative immunodeficiency, including advanced age with resultant decline in cellular immunity, pathogenic or iatrogenic immunosuppression, and primary infection prior to 18 months of age.¹ Reactivation is also associated with stress and trauma.²

HZ is a common problem. The Centre for Disease Control (CDC) estimates that '1 out of 3 people in the United States' will develop HZ during their lifetime, with an estimated 1 million cases annually.³ Approximately 50% of individuals 85 years or older will be affected.⁴ Most clinicians recognise the classic dermatomal rash of HZ and are aware of the more frequent complications including postherpetic neuralgia (PHN) and ophthalmologic disease. However, HZ can present atypically with cutaneous dissemination and visceral involvement, particularly

in immunocompromised individuals. This case serves to remind physicians that severe disseminated HZ infection can affect healthy immunocompetent young individuals. It remains important that physicians familiarise themselves with this atypical clinical presentation in order to initiate rapid treatment to decrease potential mortality and morbidity.

CASE PRESENTATION

A 37-year-old woman with history of tobacco abuse presented to an urgent care centre with a new linear, vesicular, erythematous rash of her neck and mild upper respiratory symptoms. She was otherwise healthy and on no medications. The treating physician described her rash as grouped vesicular lesions limited to a cervical dermatome consistent with HZ. However, both she and her mother stated that she never had chickenpox and had not received varicella vaccination which was not available during her childhood years. All other childhood vaccinations were completed. The physician prescribed cephalexin and prednisone, but at 5 days, the rash rapidly progressed to her torso and extremities, and she developed significant fever, myalgia and dyspnoea, prompting admission to her local hospital. Chest radiography was initially unremarkable, and blood cultures, Epstein-Barr viral titers and rapid antigen testing for streptococcus were negative. Intravenous ceftriaxone and azithromycin were started and a dermatology consult was obtained. A punch biopsy of her vesicular rash demonstrated epidermal necrosis with multinucleated cells with ground glass nuclear inclusions, nuclear moulding and margination of chromatin, and lymphohistiocytic infiltrate with leukocytoclasia. Findings were consistent with VZV infection or disseminated herpes simplex virus. On day 2 of her hospitalisation, intravenous acyclovir therapy 10 mg/kg every 8 hours was started; however, her condition significantly deteriorated. She developed respiratory failure consistent with severe acute respiratory distress syndrome (ARDS) (PaO₂ 56, FiO₂ 0.65, ratio 88) requiring mechanical ventilation, and hypotension requiring vasopressor support. She was transferred to our hospital for further care on day 4.

On arrival, the patient was intubated, paralysed and on vasopressor therapy to maintain mean arterial pressure of 65 mm Hg and improve oxygenation (PaO₂ 77, FiO₂ 0.80, ratio 96). Her temperature was 99.1 F. A diffuse vesicular rash was noted on her face, trunk and extremities in various stages of healing, including unruptured

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Figure 1 Diffuse vesicular rash of the head, neck, thorax and extremities was noted on hospital day 4.

vesicles (figures 1 and 2). Tachycardia was noted, but cardiac sounds were otherwise normal. Pulmonary examination revealed diffuse decreased air movement with mild bilateral lower lung zone crackles. Her abdomen was soft and non-distended, without mass or organomegaly, and she had no focal neurological deficits or meningeal signs.

INVESTIGATIONS

Complete blood count and differential showed haemoglobin of 12.6 g/dL, white blood cell count of 11.6 with 65% neutrophils and platelet count of $65 \times 10^3 \mu\text{L}$. An International Normalized Ratio (INR) was 1.5, fibrinogen level was 185 and D-Dimer was 16.19. Serum electrolytes and renal studies were normal, aspartate aminotransferase was elevated to $107 \mu\text{L}$ (normal 10–40 μL), alanine aminotransferase was $57 \mu\text{L}$ (normal 7–56 μL) and alkaline phosphatase was $123 \mu\text{L}$ (normal 44 to 147 μL). Serum glucose was 117 mg/dL and a lactate level was 1.0. Repeat blood, respiratory and urine cultures showed no growth; however, chest radiography now showed ‘diffuse

Figure 3 Chest radiography on hospital day 2 was normal.

Figure 2 A diffuse vesicular rash was noted of the head, neck, thorax and extremities.

bilateral opacities which could be secondary to noncardiogenic oedema or extensive infiltrative process or a combination of both, new since the previous examination’, and consistent with ARDS (figures 3 and 4). Bronchoscopy and bronchoalveolar lavage were performed and positive PCR testing of the lavage contents confirmed VZV infection. Serum IgM and IgG viral titers were also positive for VZV (greater than 1: 165).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included primary VZV infection versus disseminated HZ or herpes simplex infection. Though differentiation between primary VZV and reactivation HZ can be quite difficult from a clinical standpoint, infectious disease consultants believed that positive IgG titers (drawn on hospital day 4) and initial presentation with a classic cervical dermatomal rash before becoming widespread at 5 days favoured disseminated HZ. Further, despite reporting a negative history of primary varicella or chickenpox infection, historical review revealed that the patient did indeed have a positive IgG VZV

Figure 4 Chest radiography demonstrates diffuse bilateral opacities consistent with acute respiratory distress syndrome.

titer in 7/2006 obtained during regular pregnancy evaluation, indicative of prior primary infection with wildtype VZV. Clinical presentation, PCR tests and documented VZV immunity prior to symptom onset all supported a final diagnosis of disseminated HZ with visceral involvement.

TREATMENT

Intravenous acyclovir 10 mg/kg every 8 hours was continued on admission to our hospital. Because she was critically ill with hypotension, thrombocytopenia and pneumonia requiring ventilator assistance, linezolid and cefepime were initiated for broad coverage of both gram-negative and gram-positive organisms, including methicillin resistant *Staphylococcus aureus* (MRSA) infection. However, when all bacterial cultures returned negative, and once viral serology and PCR testing confirmed VZV infection, these antibiotics were discontinued. The patient responded well to vasopressor support and mechanical ventilation, with significant clinical improvement by day 5 of acyclovir therapy. Corticosteroid therapy was not initiated because of excellent clinical response to antiviral therapy alone. She was successfully extubated and weaned from vasopressor therapy at 1 week, and transitioned to oral valacyclovir 1000 mg twice daily by day 10. Her thrombocytopenia resolved and liver enzymes normalised, and she was discharged to home with plans to complete 14 total days of antiviral therapy.

OUTCOME AND FOLLOW-UP

The patient was seen in follow-up 10 days after hospital discharge. She complained of mild generalised fatigue and rare dry cough, but was otherwise well.

DISCUSSION

Classic HZ disease typically presents later in life as a unilateral blistering rash which occurs along one to two dermatomes and is often accompanied by pain or paresthesias. Prodromal symptoms, including mild localised pain, paresthesias, headache, malaise and fever, often precede rash onset, which appears as grouped herpetiform vesicles on an erythematous base. In most people, the rash remains limited and crusts over in 7–10 days, with complete resolution in 2–4 weeks.^{5 6} However, complications causing acute and chronic morbidity can occur in 15%–40% of HZ-affected individuals,⁷ primarily restricted to immunocompromised individuals or elderly patients.⁶ Jackson *et al* reported that HZ-associated hospitalisations range from 10 per 100 000 in adults aged 60–69, and increase to 65 per 100 000 for those aged 80 or older.⁸

The most common complication of HZ is PHN, affecting 18%–20% of single occurrence reactivation in the general population and 33% of those aged 79 or older.⁹ Some authors suggest PHN can affect up to 70% of patients with HZ.¹⁰ Other well-reported complications include ophthalmologic involvement in 10%–20%, motor neuropathy in 1.6% and meningitis in 0.5%.^{11–13} HZ can also present with more extensive skin involvement. Multidermatomal zoster involves several adjacent dermatomes, while disseminated cutaneous herpes zoster (DCHZ) is defined as 20 or more vesicular lesions outside the primary and adjacent dermatomes.² HZ duplex unilateralis and bilateralis describe zoster skin lesions in distant or non-adjacent dermatomal regions, on either one or both sides of the body. DCHZ generally starts as a classic dermatomal rash before becoming more diffuse, within 5–7 days.¹⁴

A diffuse HZ rash, as seen in our patient, is extremely rare,² and distinguishing DCHZ from primary varicella infection is difficult, particularly when the patient denies prior history

of wildtype VZV infection, as in this case. Documentation of primary varicella infection by a medical provider has high positive predictive value for immunity to disease, but neither patient history nor parent recall are reliable for determining immunity. In one study, parent recall of varicella history was only 60% for children 5–9 years old.¹⁵ Studies evaluating the predictive value of a patient's reported history of VZV exposure find a negative predictive value of 0%; thus, a negative history of VZV exposure is a poor predictor of seronegativity.¹⁶ The majority of patients who report a negative history of prior wildtype VZV infection actually have immune status when tested for seropositivity.¹⁷ The CDC recommends use of the ELISA test, which is highly sensitive and specific, to document immune status in patients who report a negative history and for those with history of atypical varicella disease.¹⁸

The vast majority of DCHZ cases occur in immunocompromised individuals. Reported incidence rates vary between 6% and 37% for immunosuppressed patients who are not taking antiviral therapy.^{6 10} Malignancy, HIV infection, therapy with immunosuppressive medications and diabetes all increase risk.¹⁹ Though DCHZ has been reported in immunocompetent individuals, it is rare.²⁰ Two recent reviews identified only 30 cases of DCHZ in immunocompetent patients, the majority of whom were 65 years of age or older.^{21 22}

Generally, DCHZ remains limited to the skin, but extracutaneous or visceral disease can occur, with resultant pneumonia, encephalitis, meningitis, motor neuropathies and/or abdominal symptoms. The International Herpes Management Forum recommends that if central nervous system (CNS) involvement or VZV vasculopathy is suspected, cerebrospinal fluid should be tested with PCR for VZV DNA and for VZV-specific antibody.²³ Our patient's course was complicated by pneumonia and severe ARDS, proven by PCR for VZV in bronchial sampling.

Pneumonia is the most frequent severe complication of primary VZV infection,²⁴ but it is a rare complication in patients with HZ. Between 1902 and 1965, only 21 cases of HZ with pulmonary involvement were identified, with radiographic findings in only seven cases and histological documentation of disease in only two patients, both of whom were immunocompromised with lymphoma.²⁵ In systematic reviews reporting DCHZ in immunocompetent patients, pneumonia was reported in only one of 30 documented cases.^{21 22} Thus, our case of disseminated HZ with visceral involvement in an immunocompetent young adult is extremely unusual.

Interestingly, smoking is a known risk factor for development of pneumonia with primary VZV infection.^{26 27} Whether or not our patient's smoking history contributed to her complications of pneumonia and ARDS secondary to disseminated HZ is not known. One study that evaluated risks associated with development of HZ found no relationship to self-reported smoking.²⁸ It is important to note that investigators have amplified VZV DNA from the serum of immunocompetent patients, with no evidence of impaired T-cell immunity, who present with classic HZ but have no clinical evidence of disseminated disease.²⁹ Thus, all patients with HZ have a potential risk to develop visceral complications.

Fortunately, rapid diagnosis and initiation of acyclovir reportedly prevent organ system involvement and shorten the disease course in patients with DCHZ, and improve outcomes with disease resolution and limited chronic sequelae.³⁰ The majority of previously reported cases of DCHZ were treated with intravenous acyclovir.^{21 22} The role of corticosteroids is less clear. Adding corticosteroids to antiviral therapy may decrease neuropathic sequelae (particularly pain), even though clinical trials supporting this practice have shown variable results.^{10 31} Concomitant corticosteroid

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