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Peer reviewed
Case presentation

Varicella zoster virus encephalitis in a patient with disseminated herpes zoster: report and review of the literature

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Abstract

Herpes zoster infection occurs owing to reactivation of varicella zoster virus and classically manifests as a vesicular eruption involving a single dermatome. Disseminated herpes zoster - defined as having greater than twenty vesicles outside the primary or adjacent dermatome - is uncommon and typically occurs in immunocompromised individuals. Central nervous system complications during or following a zoster outbreak are exceedingly rare. Encephalitis is reported to affect only 0.1-0.2% of patients and occurs more often in disseminated cases and in outbreaks involving those dermatomes in close proximity to the central nervous system. We present an elderly woman with disseminated herpes zoster and altered mental status who was subsequently diagnosed with varicella zoster virus encephalitis and describe the characteristics of patients with disseminated zoster who developed varicella zoster virus encephalitis.

Keywords: acyclovir; chickenpox; disseminated; dissemination; encephalitis, glucocorticoids; herpes; human herpes virus; meningoencephalitis; reactivation; steroids; varicella; virus; zoster

Introduction

Varicella zoster virus (VZV) is a double stranded DNA virus and the etiology of both varicella (chickenpox) and herpes zoster [1-5]. After primary exposure, VZV remains latent in the dorsal root ganglia; reactivation due to waning immunity gives rise to herpes zoster [1]. Zoster typically presents with a prodrome of intense pain, pruritus, or tingling with subsequent development of a painful eruption of grouped vesicles [1-10].

Herpes zoster infection classically manifests as a vesicular eruption involving a single dermatome. Disseminated herpes zoster infection is defined as the involvement of greater than two noncontiguous dermatomes or the presence of at least twenty lesions occurring outside of the primary affected dermatome [1-5]. Although rare in immunocompetent hosts, disseminated herpes zoster
Disseminated cutaneous zoster may have visceral involvement and can affect the central nervous system, liver, or lungs [4,5,9]. Central nervous system complications during or following a zoster outbreak are exceedingly rare. Indeed, encephalitis, the most serious complication of VZV, is reported to affect only 0.1-0.2% of patients and occurs more often in disseminated cases and in outbreaks involving dermatomes in close proximity to the central nervous system [2]. We present an elderly woman with disseminated herpes zoster and altered mental status that was subsequently diagnosed with VZV encephalitis. We also describe the characteristics of patient’s with disseminated VZV who developed encephalitis.

Case synopsis

An 85-year-old woman with history of Alzheimer’s dementia and recent history of urinary tract infection was diagnosed with herpes zoster involving the right upper extremity by Tzank smear by an outside emergency room. The patient was started on cephalexin for the urinary tract infection and valacyclovir 1 gram three times daily with prednisone 60 milligrams daily for the VZV outbreak. Three days later, the patient was referred to our dermatology clinic by her nurse practitioner for worsening rash and altered mental status.

At the time of exam, the patient was accompanied by her niece and nursing home attendant. The patient appeared lethargic and was difficult to arouse. On examination, there were scattered erythematous papules and dusky vesicles on background of erythema primarily over the right upper arm (Figure 1a) with involvement on the back, chest (Figure 1b), face, flank (Figure 1c), and neck. The affected dermatomes over the right arm included C4, C5, and C6. Tzank smear from vesicles on the right arm, and upper back demonstrated multinucleate giant cells. Owing to worsening somnolence and apparent mental status changes, the patient was referred to our hospital emergency room for evaluation of her altered mental status and admission to the hospital for intravenous acyclovir.

Upon arrival to the emergency department, the patient was hemodynamically stable. A head computerized tomography scan showed no acute process and chest x-ray showed increased vascular congestion and interstitial edema. Complete blood count and comprehensive metabolic panel were within normal limits, except for a microcytic anemia and slightly increased creatinine at 1.2 mg/dL. The patient was admitted to the intensive care unit and started on intravenous acyclovir for the disseminated zoster. A lumbar puncture, including viral cerebral spinal fluid studies, was performed; cerebral spinal fluid VZV polymerase chain reaction was positive, indicating VZV encephalitis.

The patient was continued on intravenous acyclovir at a dose of 10 milligrams per kilogram every 8 hours for a total of 21 days to treat the viral encephalitis. The patient had improvement in her mental status and complete resolution of her skin lesions. The patient was discharged back to her nursing facility at her baseline without any sequela.

Discussion

Figure 1 (a, b, c). Scattered erythematous papules and dusky vesicles on background of erythema primarily over the right upper arm (a) with involvement on the back, chest (b), face, flank (c) and neck.
Herpes zoster occurs as the reactivation of the VZV following primary varicella infection (chickenpox) [1-15]. The virus enters a latent state within the dorsal root ganglion; during reactivation, the virus replicates and causes inflammation and necrosis of neuronal and non-neuronal cells. Neuronal damage has been implicated as the source of the prodromal pain experienced by many patients [14]. The virus travels to the skin via the axons of the spinal sensory nerves, resulting in the dermatomally-distributed vesicular eruption [15]. Factors causing reactivation of VZV are not completely understood, but it is suspected to occur as a result of decreased cell-mediated immunity.

Central nervous system complications can develop if the virus spreads to the arteries of the brain and spinal cord [6-18]. Central nervous system manifestations of VZV can include acute cerebellar ataxia, encephalitis, unifocal vasculopathy, meningitis, myelitis, and facial nerve palsies [16,17]. Symptoms of VZV encephalitis include altered sensorium, fever, headache, lethargy, and mental status changes. These symptoms may present from two weeks prior to six months after the development of the rash [4]. VZV encephalitis has also been noted to occur in the absence of a clinically detectable skin eruption (zoster sine herpete) [2,7-12].

The incidence of encephalitis following VZV reactivation is highest when the involved dermatomes lie in close proximity to the central nervous system, particularly those in the head and neck region [6-18]. Cunha and co-authors presented a woman with unilateral facial herpes zoster and subsequent VZV encephalitis [6]. Braun-Falco and coauthors followed 38 patients hospitalized for reactivated VZV; 4 of these patients subsequently developed meningoencephalitis [3]. Three of the affected patients had VZV involvement of the trigeminal a cervical nerves and one patient had disseminated disease [3]. Similar to these patients, our patient had progressive development of disseminated lesions involving cranial and cervical dermatomes prior to development of encephalitis.

Similar cases of disseminated zoster progressing to VZV encephalitis are summarized (Table 1) [3,6,7]. A PubMed search using keywords disseminated, dissemination, encephalitis, human herpes virus, meningoencephalitis, reactivation, varicella, virus, and zoster was performed. To the best of our knowledge, there have been 11 previously reported cases of disseminated zoster leading to VZV encephalitis. The average age of all these individuals was 81 years (range 75-90 years). Nine of these patients were women (75%) with an average age of 82 years; men (3 patients, 25%) were of an average age of 78 years at the time of diagnosis.

### Table 1. Characteristics of patients with disseminated varicella zoster who developed encephalitis[^3,6,7]

<table>
<thead>
<tr>
<th>Patient / Reference</th>
<th>Age</th>
<th>Gender</th>
<th>Treatments for VZV Rash</th>
<th>Outcome</th>
<th>Time from onset VZV rash to development of VZV encephalitis (first signs of neurologic compromise) in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [3]</td>
<td>90</td>
<td>W</td>
<td>IV acyclovir, PO prednisone (40-50mg)</td>
<td>IV acyclovir and glucocorticosteroids were continued for 12-14 days, in combination with anticonvulsives and neurologic drugs. Full recovery after 2-3 weeks with only minor sequelae including ipsilateral mydriasis and inadequate light reaction.</td>
<td>1</td>
</tr>
<tr>
<td>2 [3]</td>
<td>83</td>
<td>W</td>
<td>IV acyclovir, PO prednisone</td>
<td>Complete recovery with no neurologic sequelae.</td>
<td>3</td>
</tr>
<tr>
<td>3 [3]</td>
<td>82</td>
<td>W</td>
<td>IV acyclovir, PO prednisone</td>
<td>Complete recovery with no neurologic sequelae.</td>
<td>6</td>
</tr>
<tr>
<td>4 [3]</td>
<td>79</td>
<td>W</td>
<td>IV acyclovir, PO prednisone</td>
<td>Complete recovery with minor sequelae including slight anemia and attention deficit.</td>
<td>9</td>
</tr>
<tr>
<td>5 [6]</td>
<td>75</td>
<td>W</td>
<td>PO valacyclovir q8hrs</td>
<td>Full recovery without neurologic sequelae following several days of treatment with IV acyclovir.</td>
<td>3</td>
</tr>
<tr>
<td>6 [7]</td>
<td>79</td>
<td>M</td>
<td>unknown</td>
<td>Died on day 34 of hospital stay.</td>
<td>unknown</td>
</tr>
<tr>
<td>7 [7]</td>
<td>86</td>
<td>W</td>
<td>unknown</td>
<td>Died with acute coma 2 months after discharge.</td>
<td>unknown</td>
</tr>
<tr>
<td>8 [7]</td>
<td>77</td>
<td>W</td>
<td>unknown</td>
<td>Died of unrelated cancer 2 years after discharge.</td>
<td>unknown</td>
</tr>
<tr>
<td>9 [7]</td>
<td>82</td>
<td>M</td>
<td>unknown</td>
<td>Improved with treatment and then dies suddenly on day 18 of hospital stay.</td>
<td>unknown</td>
</tr>
<tr>
<td>10 [7]</td>
<td>75</td>
<td>M</td>
<td>unknown</td>
<td>Died on day 23 of hospital stay secondary to aspiration pneumonia.</td>
<td>unknown</td>
</tr>
<tr>
<td>11 [7]</td>
<td>84</td>
<td>W</td>
<td>unknown</td>
<td>Poor outcome, specifics unknown.</td>
<td>unknown</td>
</tr>
</tbody>
</table>
and elderly immunocompetent patients, as in our above case [1,13]. The mortality of herpes zoster-associated encephalitis ranges from 10% to 20% [20]. Early diagnosis of more serious central nervous system and peripheral nervous system complications of VZV reactivation is important, as aggressive treatment with intravenous acyclovir with the concomitant administration of corticosteroids alone, resulting in encephalitis. There is no clinical data suggesting an increased risk of viral encephalitis with steroid use, when given along with an antiviral. There are also no documented cases or studies, in which herpes zoster was treated with corticosteroids alone, resulting in encephalitis.

Systemic corticosteroids have been demonstrated to be ineffective in preventing postherpetic neuralgia. However they have been shown to decrease acute pain, resolve edema, and shorten the time period until recovery in acute herpes zoster [1, 3, 21-24]. Meta-analysis of several randomized controlled studies demonstrated that short courses of corticosteroids do not result in significantly more adverse effects in patients with acute zoster [24]. Thus, 10-14 days of antiviral therapy with the concomitant administration of corticosteroids (at tapering doses over a 3-week period) is recommended for patients 50 years of age and older, with moderate to severe pain at presentation and with no contraindications for their use [21-24, 27]. Patients with disseminated zoster and/or ocular or visceral involvement (including the central nervous system) require hospitalization and should be immediately treated with intravenous acyclovir and supportive care.

Systemic steroids can dampen the immune response to viral (and other) infections, thus corticosteroids should never be given without the simultaneous administration of antiviral therapy [21]. The majority of patients as described in Table 1 were treated with both antiviral and steroid medications for their zoster outbreaks. In all cases, this treatment was initiated prior to the development of encephalitis. There is no clinical data suggesting an increased risk of viral encephalitis with steroid use, when given along with an antiviral. There are also no documented cases or studies, in which herpes zoster was treated with corticosteroids alone, resulting in encephalitis.

Recent findings suggest that VZV encephalitis is more accurately a vasculopathy that affects large and small cerebral arteries [3,8]. Long-term sequelae of VZV encephalitis, including seizure disorders and neuropsychological sequelae, are reported in 10–50% of survivors. Although predominantly seen in immunocompromised patients, VZV encephalitis can also manifest in young and elderly immunocompetent patients, as in our above case [1,13]. The mortality of herpes zoster-associated encephalitis ranges from 10% to 20% [20]. Early diagnosis of more serious central nervous system and peripheral nervous system complications of VZV reactivation is important, as aggressive treatment with intravenous acyclovir with the concomitant administration of corticosteroids in some cases can provide substantial clinical benefit.

**Conclusion**
Increasing age is associated with increased incidence and severity of herpes zoster, increased incidence and intensity of postherpetic neuralgia, and a higher rate of overall complications. The inclusion of VZV encephalitis in the differential of altered mental status in a patient with herpes zoster lesions should be considered, especially if the patient is immunocompromised, has disseminated zoster, or has involvement of the cranial and/or cervical dermatomes. Early diagnosis is of upmost importance as aggressive treatment with intravenous acyclovir can help prevent long-term sequelae and decrease mortality. We have characterized the patients with disseminated zoster who subsequently developed VZV encephalitis. An index of suspicion and prompt evaluation to prevent central nervous system complications should be performed for any patient with herpes zoster who presents with altered mental status.

References

