

UC Davis

Dermatology Online Journal

Title

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

Permalink

<https://escholarship.org/uc/item/3wm6k85h>

Journal

Dermatology Online Journal, 21(3)

Authors

Ellis, Dana Lee-Anne
Barsell, Alexandra
Riahi, Ryan R.
[et al.](#)

Publication Date

2015

DOI

10.5070/D3213022994

Supplemental Material

<https://escholarship.org/uc/item/3wm6k85h#supplemental>

Copyright Information

Copyright 2015 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Case presentation

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

Dana L. Ellis MD¹, Alexandra Barsell BS², Ryan R. Riahi MD³, Brittany O. Stumpf MD¹

Dermatology Online Journal 21 (3): 16

¹The Department of Dermatology, Tulane University Hospital, New Orleans, Louisiana

²George Washington University School of Medicine, Washington, DC

³The Department of Dermatology, Louisiana State University, New Orleans, Louisiana

Correspondence:

Dana L. Ellis, MD
1430 Tulane Ave. #8036
New Orleans, Louisiana 70112
337-661-9052 (telephone)
dana1ellis@gmail.com (email)

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

may occur in 10–40% of immunocompromised individuals [4,5]. Reactivation of VZV in a single dorsal root ganglion with subsequent spread to a distant ganglion or reactivation of VZV in two separate dorsal root ganglia have been postulated as the potential mechanisms of multi-dermatomal zoster [4,5,7-10].

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 1gram 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.



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.

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

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]

Patient / Reference	Age	Gender	Treatments for VZV Rash	Outcome	Time from onset VZV rash to development of VZV encephalitis (first signs of neurologic compromise) in days
1 [3]	90	W	IV acyclovir, PO prednisone (40-50mg)	IV acyclovir and glucocorticosteroids were continued for 12-14 days, in combination with anticonvulsive and neuroleptic drugs. Full recovery after 2-3 weeks with only minor sequelae including ipsilateral mydriasis and inadequate light reaction.	1
2 [3]	83	W	IV acyclovir, PO prednisone	Complete recovery with no neurologic sequelae.	3
3 [3]	82	W	IV acyclovir, PO prednisone	Complete recovery with no neurologic sequelae.	6
4 [3]	79	W	IV acyclovir, PO prednisone	Complete recovery with minor sequelae including slight anomia and attention deficit.	9
5 [6]	75	W	PO valacyclovir q8hrs	Full recovery without neurologic sequelae following several days of treatment with IV acyclovir.	3
6 [7]	79	M	unknown	Died on day 34 of hospital stay.	unknown
7 [7]	86	W	unknown	Died with acute coma 2 months after discharge.	unknown
8 [7]	77	W	unknown	Died of unrelated cancer 2 years after discharge.	unknown
9 [7]	82	M	unknown	Improved with treatment and then dies suddenly on day 18 of hospital stay.	unknown
10 [7]	75	M	unknown	Died on day 23 of hospital stay secondary to aspiration pneumonia.	unknown
11 [7]	84	W	unknown	Poor outcome, specifics unknown.	unknown

Legend: CR: Current Report; IV: intravenous; M: Male; PO: oral; W: Woman

The timeframe between the appearance of the zoster eruption and neurologic symptoms/diagnosis of VZV encephalitis can range from 1 to 9 days after the initiation of antiviral treatment [3]. There is no consistent or clear timeframe reported that relates the appearance of skin lesions to the onset of central nervous system symptoms, however it appears to be in a similar range to that of the initiation of antiviral therapy (1-10 days) [3]. Perhaps this is because most patients present to the physician shortly following the initial appearance of their skin eruption and are started on treatment immediately thereafter. Neurologic symptoms should prompt evaluation of the cerebral spinal fluid [19]. The acute form of VZV encephalitis must be separated from chronic encephalitis - almost exclusively seen in severely immunocompromised patients - that clinically presents weeks to months after the skin lesions have resolved [3].

The rash and symptoms of herpes zoster are usually enough to make an accurate clinical diagnosis, however zoster can be more difficult to diagnose in children, young adults, and people with compromised immune systems who will often have more atypical presentations. In all cases, and especially in atypical cases, laboratory testing may be useful. Direct fluorescent antibody staining of VZV-infected cells is rapid, specific, and sensitive. Polymerase chain reaction can be used on biopsy material and on eosinophilic nuclear inclusions, and is more sensitive than direct fluorescent antibody testing [28]. Tzanck smears are inexpensive and can be performed at bedside, although they do not distinguish between VZV and herpes simplex virus infections. If the diagnosis is unclear clinically between these two, another test is normally needed for confirmation [28].

Recent guidelines for the management of herpes zoster recommend the administration of antiviral therapy, preferably within 72 hours of lesion onset [1, 8, 14, 21, 27]. Oral antiviral agents should be used in the treatment of uncomplicated zoster [1, 21, 27]. Nonsteroidal anti-inflammatories and acetaminophen are generally recommended for any associated mild pain or discomfort. Opioids such as oxycodone and morphine can often be very effective in controlling moderate to severe pain. There is conflicting evidence for the use of gabapentin in managing zoster-related pain as one placebo-controlled study showed that gabapentin was effective while another randomized showed that it did not provide greater pain relief than placebo [25, 26]. However, various studies have proved its effectiveness in helping to prevent postherpetic neuralgia if initiated early in the course of the infection [25]. Tricyclic antidepressants have not been shown to be effective for treating zoster-related pain in randomized controlled trials but have been used successfully in the treatment of postherpetic neuralgia. Tricyclic antidepressants are recommended as an adjunct when opioid medications are not effectively controlling the pain [21, 27].

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 utmost 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

1. Bader MS. Herpes zoster: diagnostic, therapeutic, and preventative approaches. *Postgrad Med* 2013; 125(5):78-91. [PMID: 24113666]
2. Amlie-Lefond C, Jubelt B. Neurologic manifestations of varicella zoster virus infections. *Curr Neurol Neurosci Rep* 2009;9:430-4. [PMID: 19818229]
3. Braun-Falco M, Hoffman M. Herpes zoster with progression to acute varicella zoster virus- meningoencephalitis. *Int J Dermatol* 2009;48:834-9. [PMID: 19673047]
4. Burdett, C., Mendoza, N., Arora, A., Bartlett, B., Gewirtzman, A., Tremaine, A.M., Tyring, S. A rare case of disseminated shingles in an immunocompetent patient following a 7-day treatment with oral valacyclovir. *Journal of Clinical Virology*. 2008;43:233-235.
5. Arvin A. Varicella-zoster virus. *Microbiol Rev* 1996;9:361-381.
6. Cunha BA, Strollo S, Durie N, Ibrahim MS. Facial herpes zoster complicated by varicella zoster virus (VZV) encephalitis: the diagnostic significance of atypical lymphocytes in cerebrospinal fluid (CSF). *Heart Lung* 2011;40:164-7. [PMID: 21144586]
7. De Broucker T, Mailles A, Chabreir S, Morand P, Stahl JP. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. *Clin Microbiol Infect* 2012;18:808-19. [PMID: 22085160]
8. Gildeen D, Cohrs RJ, Mahalingham R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* 2009;8:731-40.
9. Gildeen D, Williams L, Cohrs RJ. Clinical features of Varicella Zoster Virus infection of the nervous system. *ACNR* 2002;2:7-10.
10. Gnann JW Jr. Varicella-zoster virus: atypical presentations and unusual complications. *J Infect Dis* 2002; 186: Suppl 1:S91-8. [PMID: 12353193]
11. Klein NC, McDermott B, Cunha BA. Varicella-zoster virus meningoencephalitis in an immunocompetent patient without a rash. *Scand J Infect Dis*. 2010;42:631-633. [PMID:20214542]
12. Tavazzi E, Minoli L, Ferrante P, Scagnelli P, Del Bue S, Romani A, Ravaglia S, Marchioni E. Varicella zoster virus meningo-encephalo-myelitis in an immunocompetent patient. *Neurol Sci*. 2008;29:279-83. [PMID: 18810606]
13. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. *Mayo Clin Proc*. 2011; 86:88-93.
14. Sampathkumar P, Drage LA, Martin DP. Herpes Zoster (Shingles) and Postherpetic Neuralgia. *Mayo Clin Proc* 2009;84: 274-80. [PMID: 19252116]
15. Shin J, Kim D, Whang K, Lee J, Park Y, Cho M, Lee SL, Lee SY. A case of zoster duplex bilateralis. *Annals of Dermatology* 2009;21:423-5. [PMID: 20523839]
16. Gildeen DH. Varicella zoster virus and central nervous system syndromes. *Herpes* 2004;11: S89A–S94A
17. Sánchez-Guerra M, Infante J, Pascual J, et al. Neurologic complications of herpes zoster. A retrospective study in 100 patients. *Neurologia* 2001;16:112–117. [PMID: 11333780]
18. Jemsek J, Greenberg SB, Taber L, Harvey D, Gershon A, Couch RB. Herpes zoster-associated encephalitis: clinicopathologic report of 12 cases and review of the literature. *Medicine (Baltimore)*1983;62:81-97. [PMID:6298562]
19. Cohen PR. Tests for detecting herpes simplex virus and varicella-zoster virus infections. *Dermatol Clin* 1994;12:51-68. [PMID:8143385]
20. Habif TP. *Clinical Dermatology*. 5th ed. St. Louis, MO: Elsevier Mosby; 2009: chap 12.
21. Cohen JI. Clinical Practice: Herpes Zoster. *N Engl J Med*. 2013;369:255-63. [PMID: 23863052]
22. Whitley RJ, Weiss H, Gnann JW Jr, et al. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. *Ann Intern Med*. 1996;125:376–83. [PMID:8702088]
23. Wood MJ, Johnson RW, McKendrick MW, Taylor J, Mandal BK, Crooks J. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med*. 1994; 330:896–900. [PMID: 8114860]
24. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2013, Issue 3. Art no: CD005582. [PMID: 23543541]
25. Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain* 2009; 142:209. [PMID: 19195785]

26. Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain*. 2001; 94:215–24. [PMID:11690735]
27. Gan EY. Management of herpes zoster and post-herpetic neuralgia. *Am J Clin Dermatol*. 2013;14:77-85. PMID: 23456596
28. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster <http://www.cdc.gov/Other/disclaimer.html>. *N Engl J Med*. 2002 Aug;347(5):340-6. [PMID: 12151472]