A Fatal Case of Atypical Disseminated Herpes Zoster in a Patient with Meningoencephalitis and Seizures Associated with Steroid Immunosuppression

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Conflict of interest: None declared

Patient: Male, 69
Final Diagnosis: Disseminated herpes zoster
Symptoms: Rash • seizures
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Diagnostic/therapeutic accidents
Background: Herpes zoster is caused by the reactivation of the varicella zoster virus (VZV) and usually presents with vesicular skin lesions with a dermatomal distribution. Disseminated herpes zoster (DHZ) infection is characterized by non-dermatomal skin eruptions, often with involvement of other organs, and occurs in immunocompromised patients.

Case Report: A 69-year-old man who was treated with prednisolone for amiodarone-associated interstitial lung disease, presented with seizures and altered consciousness. He had an erythematous rash with raised vesicles involving the skin of the genital region, left thigh, and abdomen. Following a diagnosis of DHZ with herpes zoster meningencephalitis, he was treated with intravenous acyclovir. However, his level of consciousness did not improve, and he died of respiratory failure due to aspiration pneumonia.

Conclusions: A diagnosis of DHZ should be considered in immunosuppressed patients treated with steroids who present with seizures. A detailed search for skin eruptions should be conducted to enable early diagnosis and treatment.

MeSH Keywords: Acyclovir • Encephalitis, Varicella Zoster • Fatal Outcome • Herpes Zoster • Seizures • Steroids

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/910521
Background

Herpes zoster is caused by the reactivation of the varicella zoster virus (VZV) and usually presents with vesicular skin lesions with a dermatomal distribution. Disseminated herpes zoster (DHZ) infection is characterized by non-dermatomal skin eruptions and can occur in immunocompromised patients.

In immunocompromised patients who develop DHZ, associated complications can include pneumonia, hepatitis, encephalitis, or involvement of other organs [1]. DHZ can also occur without the presence of a skin rash [2]. DHZ may result in death because of delayed diagnosis in immunocompromised patients, including patients with bone marrow transplantation and acquired immunodeficiency syndrome (AIDS) [3]. Although cutaneous dissemination of VZV (shingles) is not usually life-threatening [4], cutaneous and visceral dissemination of VZV is associated with increased morbidity and mortality [3]. However, there have been few previously reported cases of patient mortality due to DHZ in patients with a history of steroid treatment [5,6]. This report presents a fatal case of DHZ in a patient on steroid therapy, who presented with seizures and disseminated skin lesions.

Case Report

In August 2016, a 69-year-old man with chronic kidney disease and type 2 diabetes mellitus was admitted to our hospital with a diagnosis of amiodarone-induced interstitial pneumonia. He had been treated with amiodarone for paroxysmal atrial fibrillation. When amiodarone was discontinued, he was treated with high-dose intravenous methylprednisolone (1,000 mg daily) for three days, followed by prednisolone (60 mg daily). In his past medical history there was also a history of herpes encephalitis.

On day 40 after the initiation of steroid treatment, when the dose of prednisolone had been decreased to 40 mg daily, he developed seizures and a change in his level of consciousness. The seizures spontaneously ceased after a few minutes. However, he remained in a semi-comatose state. His vital signs included the following: a Glasgow Coma Scale score of 11/15 (E3, V3, M5); blood pressure, 137/59 mmHg; pulse rate, 116 beats/min; peripheral capillary oxygen saturation, 96% in room air; and body temperature, 37.4°C. He had no other neurological signs, such as neck or limb stiffness and no paralysis of the extremities. His main symptoms were seizures and impaired levels of consciousness. Laboratory findings included a creatinine concentration of 1.20 mg/dl and hemoglobin A1c (HbA1c) level of 9.3%, with no increased levels of inflammatory markers, no electrolyte abnormalities, and no hypoglycemia (Table 1).

In this patient, we initially suspected a diagnosis of symptomatic epilepsy caused by a history of herpes encephalitis, and head imaging with computed tomography (CT), which showed an area of low density in the left temporal lobe (Figure 1A). Therefore, he was placed under observation, without drug treatment, including the use of antiepileptic drugs. A day after the seizures

Table 1. Laboratory data after seizures.

| Complete blood count | Blood chemistry |
|----------------------|-----------------|
| WBC 10,900/μl        | AST 65 U/l      |
| RBC 3.99×10⁶/μl      | ALT 89 U/l      |
| HGB 14.9 g/dl        | LDH 574 U/l     |
| PLT 14.9×10⁴/μl      | ALP 281 U/l     |
| CRP 0.17 mg/dl       | γ-GTP 66 U/l    |
| TP 5.2 g/dl          | T-BIL 1.2 mg/dl |
| GGT 13 U/l           | UN 28.6 mg/dl   |
| Glucose 106 mg/dl    | CRE 1.2 mg/dl   |
|                      | Na 143 mmol/l   |
|                      | K 3.3 mmol/l    |
|                      | Cl 95 mmol/l    |
|                      | HbA1c 9.3 %     |
began, while changing his protective underwear (adult diaper), a nurse detected an erythematous rash with raised vesicles on the genital region along the right side, in the distribution of the third to fourth sacral dermatomes (S3–S4) (Figure 2A). Although the patient was aware of the skin rash and had mild pain in the same area one week before the seizures occurred, he did not report it to the clinicians because he was embarrassed. Similar rashes were found on his left thigh and abdomen, and examination of his entire body showed that these lesions did not follow the distribution of the dermatomes, but were more widespread (Figure 2B, 2C).

Therefore, a provisional diagnosis of disseminated herpes zoster (DHZ) was made. Analysis of cerebrospinal fluid (CSF) showed a white blood cell (WBC) count of 287/μl (proportion of segmented neutrophils, 80%), a CSF protein level of 481 mg/dl, and a CSF glucose level of 69 mg/dl (blood glucose value, 129 mg/dl). Bacterial cultures of the CSF and herpes simplex virus (HSV) polymerase chain reaction (PCR) were negative. Positive serum levels of varicella zoster virus (VZV) IgM and IgG and intrathecal IgG were detected. However, the antibody titer of HSV in the CSF showed negative findings. Based on these findings, a diagnosis of DHZ-induced meningoencephalitis was considered to be the most likely cause of the patient’s seizures and impaired levels of consciousness.

Treatment immediately began with intravenous acyclovir, before confirmation of the diagnosis of DHZ (Figure 3). Although his consciousness level improved slightly after treatment began, his impaired levels of consciousness persisted for 14 days (Figure 3). Neurotoxicity due to acyclovir was considered as a potential cause, because of the clinical course of his cerebral symptoms. Acyclovir was discontinued after 14 days.

Seven days after discontinuation of acyclovir treatment, his level of consciousness deteriorated. At this time, analysis of the CSF analysis showed a white blood cell count of 741 per μl (mononuclear cells, 94%), and a CSF protein level of 213 mg/dl. Also, a head CT showed bilateral low-density areas around the frontal lobes, which were suspected to be due to hematoma or cerebral edema (Figure 1B). A prolonged clinical course of meningoencephalitis due to DHZ was suspected, and treatment with acyclovir was resumed. However, his level of consciousness did not improve, and the patient died of respiratory failure due to aspiration pneumonia.

**Discussion**

The present case demonstrated several important clinical findings that might provide lessons regarding the importance of...
Figure 2. Disseminated erythematous rashes involving the skin of the genital areas, buttocks, left thigh, and abdomen. 
(A) An erythematous rash with raised vesicles involving the genital regions and involving the right third to fourth sacral (S3–S4) dermatomes. (B) An erythematous rash with raised vesicles is shown to involve the skin of the buttocks. (C) An erythematous rash with raised vesicles is shown to involve the skin of the left thigh and abdomen, which did not follow the distribution of a dermatome.

Figure 3. The clinical course of the patient.
CRP – C-reactive protein; CSF – cerebrospinal fluid; VZV – varicella zoster virus; HSV – herpes simplex virus; mono – monocyte; seg – segmented neutrophil; WBC – white blood cell.

| Day  | Conscious disturbance | Blood examination | Treatment |
|------|----------------------|-------------------|-----------|
| -52  |                      |                   |           |
| 40   |                      |                   |           |
| 39   |                      |                   |           |
| 38   |                      |                   |           |
| 37   |                      |                   |           |
| 36   |                      |                   |           |

Admitted
Seizure

| Body | White blood cell (×10³) | Seg (%) | Mono (%) | Protein (mg/dl) |
|------|-------------------------|---------|----------|-----------------|
| Crash | 10900                  | 7600    | 8400     | 10200           |
|       | 10000                  | 7000    | 8200     | 10000           |
|       | 10000                  | 7000    | 8200     | 10000           |
|       | 10000                  | 7000    | 8200     | 10000           |
|       | 10000                  | 7000    | 8200     | 10000           |

| CSF | Pressure (cm H₂O) | White blood cell (×10³) | Seg (%) | Mono (%) | Protein (mg/dl) |
|-----|------------------|-------------------------|---------|----------|-----------------|
|     |                  |                         |         |          | 10000           |
| Day 2 | 72                | 287                     | 80      | 20       | 10000           |
| Day 6 | 76                | 287                     | 80      | 20       | 10000           |
| Day 15| 78                | 287                     | 80      | 20       | 10000           |
| Day 24| 80                | 287                     | 80      | 20       | 10000           |

| Blood | VZV-IgM (+) | VZV-IgG (+) |
|-------|------------|------------|
|       | CSF: HSV-DNA (-) |

Prednisolone 40 mg/day

Aciclovir
Sulbactam/Ampicillin
Tazobactam/Piperacillin

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early diagnosis of disseminated herpes zoster (DHZ). First, the diagnosis of DHZ may be delayed if skin eruptions occur in a location that makes detection difficult, such as the genitals or pudendum. Second, as this case has demonstrated, DHZ can present with seizures due to meningoencephalitis as an initial symptom in immunosuppressed patients. Third, patients undergoing steroid therapy can be affected by DHZ, which may be accompanied by meningoencephalitis that is refractory to antiviral drugs and can be fatal.

In immunosuppressed patients presenting with seizures, DHZ should be considered in the differential diagnosis. As previously reported, there are varied neurologic complications that occur with herpes zoster infection, including Bell’s palsy, Ramsay Hunt syndrome, transverse myelitis, transient ischemic attacks (TIAs), and stroke [1]. Also, varicella zoster virus (VZV) is the third most common cause of viral meningitis, with 44% of VZV-associated meningitis cases presenting without skin rash [2]. In the present case, the skin rash occurred in the genital area of the patient, one week before the seizures began, which made the skin lesions difficult to detect. Also, in this case, we initially suspected symptomatic epilepsy caused by a past history of herpes encephalitis, which may have delayed the diagnosis of DHZ on this most recent presentation. To avoid delay in diagnosis, DHZ should be considered in immunosuppressed patients presenting with seizures, and a thorough physical examination of the skin, including the genital area, should be conducted to detect associated skin rashes.

In patients receiving steroid therapy, DHZ can be accompanied by meningoencephalitis that is refractory to antiviral drugs and can be fatal. Diseases that cause immunosuppression, including human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), and human T-cell leukemia virus type 1 (HTLV-1), are risk factors for DHZ [7,8]. The risk of opportunistic infection is 1.6 times higher in patients receiving prednisolone (%10 mg/day), 1.8 times higher in patients with diabetes mellitus, and patients taking steroids have a high risk of DHZ [9]. If DHZ is accompanied by disseminated intravascular coagulation (DIC), meningoencephalitis, and pneumonia, the mortality rate in cases with these comorbidities has been reported to be approximately 55% [10]. DHZ-induced meningoencephalitis has been previously reported in severely immunosuppressed patients [7,8]. In the present case, 40 mg oral prednisolone was administered daily following steroid pulse therapy, and the patient had a history of diabetes and chronic renal failure. A combination of these factors could have resulted in severe immunosuppression, resulting in accelerated progression of DHZ and death, despite acyclovir treatment.

Combining molecular testing for HSV and VZV infection, including polymerase chain reaction (PCR) with antibody tests is useful for the diagnosis and exclusion of virus-induced neurologic disease. Although this patient had a history of herpes encephalitis, we diagnosed DHZ meningoencephalitis based on HSV PCR of the cerebrospinal fluid (CSF), and serum VZV antibody tests. However, in this patient, the presence of VZV IgG could have represented persistent titers from the previous disease, with a false positive VZV IgM, or reactivation of VZV IgM due to a systemic illness not due to DHZ. Therefore, caution should be undertaken when interpreting the results of routine antibody tests, which may show false-positive reactions or reactions due to prior infection. Also, the use of molecular diagnostic methods when examining the CSF, including PCR for the diagnosis of active HSV and VZV are useful for the confirmation or exclusion of a diagnosis of DHZ meningoencephalitis. The combination of serological and CSF studies using VZV PCR has previously been recommended for the identification of cases of VZV infection of the central nervous system infections in patients who present without a skin rash [11]. However, VZV PCR testing is not covered by health insurance for tests involving serum, skin vesicles, and CSF in Japan. Although HSV meningoencephalitis is not uncommon and treatment with acyclovir is effective, meningoencephalitis caused by DHZ occurs less frequently [12,13]. Therefore, in the present case, HSV PCR was performed for the analysis of the CSF and VZV PCR was not performed. Although a positive serum IgM and intrathecal IgG was consistent with the diagnosis of DHZ, VZV PCR of the CSF should be performed to obtain a definite diagnosis.

Conclusions

In conclusion, a case of disseminated herpes zoster (DHZ) has been presented associated with fatal meningoencephalitis. In immunosuppressed patients who present with seizures and impaired levels of consciousness, including patients who are treated with steroids, DHZ should be included in the differential diagnosis, and a thorough clinical examination should include examination for skin eruptions, for the early diagnosis and treatment of DHZ.

Conflict of interest

None.
References:

1. Cohen JI: Herpes zoster. N Engl J Med, 2013; 369: 1766–67
2. Becerra JC, Sieber R, Martinetti G et al: Infection of the central nervous system caused by varicella zoster virus reactivation: A retrospective case series study. Int J Infect Dis, 2013; 17: e529–34
3. Koc Y, Miller KB, Schenkein DP et al: Varicella zoster virus infections following allogeneic bone marrow transplantation: Frequency, risk factors, and clinical outcome. Biol Blood Marrow Transplant, 2000; 6: 44–49
4. Gomez E, Cherniev I: Disseminated cutaneous herpes zoster in an immunocompetent elderly patient. Infect Dis Rep, 2014; 6: 5513
5. Nagel MA, Lenggenhager D, White T et al: Disseminated VZV infection and asymptomatic VZV vasculopathy after steroid abuse. J Clin Virol, 2015; 66: 72–75
6. Nomdedéu J, Nomdedéu J, Martino R et al: Ogilvie’s syndrome from disseminated varicella-zoster infection and infarcted celiac ganglia. J Clin Gastroenterol, 1995; 20: 157–59
7. Mabuchi T, Yamaoka H, Kato M et al: Case of disseminated vesicles of herpes zoster developing one day before the onset of local eruption in a hospitalized immunocompromised patient. Tokai J Exp Clin Med, 2013; 38: 52–54
8. Fujii N, Itoh Y, Tomoda H: Disseminated herpes zoster with multifocal neurologic involvement in an HTLV-1 carrier. Intern Med, 1993; 32: 854–56
9. Greenberg JD, Reed C, Kremer JM et al: Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis, 2010; 69: 380–86
10. Schiller GI, Nimer SD, Gajewski JL, Golde DW: Abdominal presentation of varicella-zoster infection in recipients of allogeneic bone marrow transplantation. Bone Marrow Transplant, 1991; 7: 489–91
11. DeBlasi RL, Kleinschmidt-DeMasters BK, Weinberg A, Tyler KL: Use of PCR for the diagnosis of herpesvirus infections of the central nervous system. J Clin Virol, 2002; 25(Suppl. 1): S5–11
12. Kamei S, Takasu T: Nationwide survey of the annual prevalence of viral and other neurological infections in Japanese inpatients. Intern Med, 2000; 39: 894–900
13. Wada-Isoe K, Kusumi M, Kai T et al: Epidemiological study of acute encephalitis in Tottori Prefecture, Japan. Eur J Neurol, 2008; 15: 1075–79

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