Disseminated cutaneous herpes zoster in an immunocompetent elderly patient

Eric Gomez,1 Ivan Chernev1,2
1Department of Medicine, Appalachian Regional Healthcare, Beckley, WV; 2West Virginia School of Osteopathic Medicine, Lewisburg, WV, USA

Abstract

Herpes zoster is a clinical syndrome which usually presents with a localized, vesicular rash in a dermatomal distribution. Cutaneous dissemination rarely occurs in immunocompetent patients, therefore little is known about the baseline demographic, clinical characteristics, management and outcome of these patients. Herein, we report a case of disseminated cutaneous herpes zoster in an immunocompetent patient along with a review and analysis of 28 cases previously reported in the literature.

Introduction

Varicella zoster virus (VZV) is an exclusively human double-stranded DNA virus of the Herpesviridae family. The primary VZV infection, called varicella or chickenpox, presents clinically as a disseminated vesicular rash, typically during childhood. After the initial infection, this virus enters a lifelong latent state within the sensory ganglia. Under unknown conditions, the VZV Reactivates and travels along the nerve axon to the skin to cause a localized vesicular rash in a dermatomal distribution, called herpes zoster (HZ) or shingles.1

Varicella zoster virus-specific cell-mediated immunity (CMI) is required to halt the virus reactivation. During young adulthood, VZV-specific CMI is robust which explains the infrequent occurrence of HZ in this age group.2 With aging, the VZV-specific CMI declines, especially after age of 60.3,4 This decline in CMI correlates with increased incidence of HZ in the elderly population.2 Humoral immunity does not appear to protect against reactivation of VZV as antibodies levels are preserved throughout all age groups. Also, patients with humoral immunity deficiency (i.e. B-cell deficiency) are not more prone to develop severe varicella infections.4 VZV antibodies are believed to be important in preventing the acquisition of a new infecting virus.5

Among immunocompetent patients, HZ is considered a self-limited, localized infection commonly complicated by post-herpetic neuralgia. In contrast, patients with T-cell deficiency, such as HIV patients and bone marrow transplant recipients, can present with severe cutaneous and visceral disseminated disease.6 Cutaneous dissemination of HZ among immunocompetent hosts has been previously reported in the literature mainly as a single case reports or small case series. However, little is known about the baseline demographic, clinical characteristics, management and outcome of these patients. Therefore, we present here another case of disseminated cutaneous HZ (DCHZ) in an immunocompetent patient and summarize the data on the existed published cases.

Case Report

A 95-year-old Caucasian woman developed a cluster of vesicular lesions over the left lower lip, which spread to involve the left malar region and earlobe with associated burning-like pain over the affected area. She was also noted to have vesicular lesions over the lower left labial and gingival mucosa. Initially, the patient was empirically started on amoxicillin 500 mg orally three times daily and acyclovir 800 mg orally five times daily for possible dental infection and HZ, respectively. A dentist ruled out odontogenic infection and amoxicillin was discontinued. However, while on day two of antiviral therapy, new vesicular lesions appeared throughout the trunk, upper and lower extremities. She was admitted to the hospital for further evaluation and treatment. Patient had a history of coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) with no recent use of steroids. On admission, the patient was found to have right lower lobe pneumonia on chest x-ray. Her initial white blood cell (WBC) count was 35,000 cell/□L and elevated procalcitonin to 0.75 ng/mL. Piperacillin-tazobactam 3,375 g intravenously every 6 hours and acyclovir 5 mg/kg intravenously every 8 hours were started. Her procalcitonin and WBC count normalized while on antibiotic treatment. Intravenous acyclovir was continued for 7 days and subsequently changed to oral formulation to complete 14 days of treatment. Chest, abdomen and pelvis computer tomography was negative for malignancies. Immunoglobulin levels and serum protein electrophoresis were within normal limits. After six months of follow-up, no malignancy has been identified.

Discussion and Conclusions

An electronic search on PubMed and Google using the terms zoster, cutaneous, dissemination and immunocompetent in different combinations was conducted. Only cases of immunocompetent adult patients (age 16 or older) with DCHZ were included. We considered the following conditions immunosuppressive: use of antineoplastic and immuno suppressive medications, cancer, HIV infection, immunologic disorders, and organ transplants.7 After performing additional literature review, milliary tuberculosis (TB) was also added to the immunosuppressive conditions, as it has been associated with T cell deficiency.8 DCHZ was defined as >20 skin lesions beyond the primary or adjacent dermatomes.9 Sixteen related publications were identified. After review, the subjects in one of the articles were excluded from the tabulation due to the limited individual information available for analysis.10 A total of 33 cases were reviewed of which six were excluded due to use of prednisolone (2 cases), history of rheumatoid arthritis (1 case), history of idiopathic thrombo cytopenic purpura (1 case) and milliary TB (2 cases). A total of 28 cases were included for tabulation (Table 1).11-24
The average age of the patients was 59 years (range 22-97) with 54% men vs 46% women. Forty-six percent of these patients had at least one comorbidity, of which hypertension and diabetes were the most common (Table 1). Initial presentation of the rash was localized to one or several dermatomes that most frequently involved cranial nerves (42%) followed by thoracic (27%), lumbosacral (19%) and cervical (15%) dermatomes. On average, cutaneous dissemination occurred five days (range 1-12 days) after the initial dermatomal skin rash. Extracutaneous manifestations were reported in twelve cases (43%), four of which had mucosal lesion (including one herpes ophthalmicus), two had central nervous system manifestations, two had cranial or peripheral nerve paresis, two had Ramsay-Hunt syndrome, one had herpes ophthalmicus and one had visceral involvement. In all cases with reported antiviral treatment (15 cases) intravenous antiviral acyclovir was prescribed except for three patients that were treated with oral acyclovir (2 cases) and oral valacyclovir (1 case). All patients with reported outcomes recovered without sequelae, except for four patients who developed segmental paresis (2 cases) and post-herpetic neuralgia (2 cases).

Although disseminated HZ occurs more often in immunocompromised patients, VZV viremia seems to occur in all patients with HZ irrespective of T-cell immune status or clinical evidence of dissemination. Kronenberg et al. were able to amplify VZV DNA from serum samples of all tested immunocompetent patients (n=10) with localized HZ. Based on this, the potential for developing disseminated disease exists in all patients with HZ, and those with more profound deficiency of the CMI seem to be at increased risk of developing disseminated clinical disease. In a study by Koc et al., cutaneous dissemination among bone marrow transplant patients was observed in 17% of HZ cases. Overall, cutaneous dissemination have been reported in 10 to 40% of

### Table 1. Characteristics of patient with disseminated cutaneous herpes zoster.

| Case (ref.) | Age (yrs) | Sex | Comorbidities | Dermatome | Non-cutaneous manifestations | Interval to dissemination (days) | Treatment | Outcome |
|------------|-----------|-----|---------------|-----------|-----------------------------|-------------------------------|-----------|---------|
| 1 (11)     | 22        | F   | ACTH injections | C2-C4     | Uvula lesions               | 2                             | NR        | Recovered |
| 2 (11)     | 63        | F   | ACTH injections | CN V1     | Ophthalmic zoster           | 5                             | NR        | Recovered |
| 3 (11)     | 37        | F   | None           | CN V1 and V2 | Palate lesions            | 5                             | NR        | Recovered |
| 4 (11)     | 58        | M   | None           | CN V1     | Lip and palate lesions, ophthalmic zoster | 6 | NR | Recovered |
| 5 (11)     | 72        | F   | None           | C1-C3     |                            | 4 | NR | Recovered |
| 6 (11)     | 54        | F   | None           | CN V1     |                            | 3 | NR | Recovered |
| 7 (12)     | 75        | F   | Rheumatic heart disease s/p mitral and tricuspid valve replacement | Left T10 |                            | 8 | IV acyclovir | recovered |
| 8 (13)     | 43        | M   | None           | Right T8  |                            | 2 | NR | NR |
| 9 (13)     | 50        | M   | None           | Right thigh |                            | 1 | NR | NR |
| 10 (14)    | 70        | F   | CVA, depression, malnutrition | Left CN V2 |                            | NR | Oral acyclovir | Recovered |
| 11 (14)    | 79        | M   | None           | Left L3   |                            | NR | Oral acyclovir | Recovered |
| 12 (15)    | 24        | M   | None           | Left T5   | Aseptic meningitis         | 3 | NR | Recovered |
| 13 (16)    | 37        | F   | None           | T2        | Aseptic meningitis         | NR | IV acyclovir | Recovered |
| 14 (17)    | 72        | F   | DM             | Right peroneal | Left facial and right peroneal nerve paresis | 12 | IV acyclovir then IV vidaravine | Right foot palsy at 6 months | Recovered |
| 15 (3)     | 39        | M   | None           | Right T6  |                            | 9 | Oral valacyclovir then IV acyclovir | Recovered |
| 16 (18)    | 75        | M   | DM, angina     | Left CN V and C2 | Ramsay-Hunt | 11 | IV acyclovir | Recovered |
| 17 (19)    | 97        | F   | HTN, CHF       | Right CN V3 |                            | 4 | Oral valacyclovir | NR |
| 18 (20)    | 82        | F   | DM, HTN        | Right L1-L2 | Right femoral-peroneal paresis | NR | Oral and IV acyclovir | Leg motor weakness at 6 months |
| 19 (21)    | 76        | M   | HTH, angina, prostate CA s/p resection* | Right S3-S4 and bladder atonies | Intestinal NR | IV acyclovir | Recovered |
| 20 (22)    | 29        | M   | None           | CN VII    | Ramsay-Hunt                | 6 | None | Recovered |
| 21 (22)    | 51        | M   | TB LAD         | NR        |                            | 7 | None | PHN |
| 22 (22)    | 25        | M   | None           | CN V      |                            | 7 | None | Recovered |
| 23 (22)    | 40        | F   | None           | NR        |                            | 5 | None | Recovered |
| 24 (23)    | 79        | M   | None           | Left T7-T8 |                            | NR | IV acyclovir | PHN |
| 25 (23)    | 80        | M   | DM, HTN        | Right C3-C4 |                            | NR | IV acyclovir | Recovered |
| 26 (23)    | 71        | M   | CAD, HTN, Dementia | Left T8 |                            | NR | IV acyclovir | Recovered |
| 27 (24)    | 69        | M   | None           | Right CN V1 |                            | NR | IV acyclovir | Recovered |
| 28 (our case) | 95 | F   | CAD, COPD     | Left CN V1, V2, V3 | Gingiva lesions | 4 | Oral and IV acyclovir | Recovered |

M, male; F, female; CN, cranial nerve; s/p, status post; ME, meningencephalitis; CVA, cerebrovascular accident; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; CA, carcinoma; PHN, post-herpetic neuralgia; COPD, chronic obstructive pulmonary disease; TB, tuberculosis; LAD, lymphadenopathy; NR, not reported. *Patient did not have any evidence of cancer recurrence.
all immunocompromised patients with HZ.1 The prevalence of DCHZ in immunocompetent patients has not been established. Furthermore, the exact mechanism by which some apparently immunocompetent patients will develop disseminated zoster is not clearly understood.

In almost all reported cases (89%) reviewed here, patients initially presented with a localized HZ involving one or several dermatomes followed by a secondary diffuse papulovesicular rash which helps distinguish disseminated HZ from primary varicella infection of adults. Initial cranial nerve involvement was most common, which may suggest that these patients are most prone to cutaneous dissemination. This is in contrast with study by Mittal et al. (not tabulated) where the majority of patients had initial thoracic segments involvement. Age-related decline of VZV CMI seems to be one of the most important risk factor for VZV reactivation and subsequent HZ.1 This correlates with the average age of the patients (65 years) reviewed here. However, other factors might be involved in the cutaneous dissemination of HZ, as 25% of the reported cases were younger than 40 years.

In a recent study, the following chronic conditions were associated with an increase risk of HZ: allergic rhinitis, COPD, CAD, cerebrovascular accident, depression, diabetes, hyperlipidemia, hypothyroidism and osteoarthritis.7 In our review, nine patients (32%) had at least one of these chronic conditions. Of them, only diabetes had been directly linked to VZV-CMI deficiency. Okamoto et al. demonstrated that VZV-CMI was significantly lower than healthy volunteers.20 These findings corroborate other clinical studies, showing an increased risk of HZ in patients with diabetes.21,22 We identified four patients with diabetes (Table 1) plus three other patients (not tabulated) with DCHZ.10 In these cases cutaneous dissemination might be due to an underlying VZV-CMI deficiency. Except for diabetes, the other above mentioned conditions have not been directly linked to CMI deficiency and their role as risk factor for HZ need to be further investigated. In patients with COPD, treatment of acute exacerbations entails systemic steroid which could attenuate the CMI, however it is not clear if previous remote steroid treatment may affect VZV-specific immunity. Our patient had a history of COPD but there was no history of steroid use for at least eight months, and therefore no immunosuppressive condition was identified.

As the cutaneous dissemination of HZ is thought to be via viremia, patients are often treated with intravenous antivirals to prevent cutaneous and visceral dissemination. In our review, three patients presented with central nervous system or visceral disease complications which reaffirm the need of aggressive treatment at diagnosis. Intravenous acyclovir was the most common antimicrobial therapy instituted and just a few cases received oral antiviral therapy only.

There are several limitations in the cases reviewed here. Several of these reports were published several decades ago when diagnostics tests were limited or certain immunosuppressive conditions were not yet fully recognized such as human immunodeficiency virus infection (specially in the young patients). Moreover, follow-up information was lacking in many of these cases which makes it difficult to exclude underlying malignancy or immunocompromized states that can initially present with cutaneous dissemination of herpes zoster but their own diagnosis can be delayed. Two patients were also receiving adrenocorticotropic hormone injections for unknown reasons, leaving the possibility of an unidentified abnormality of the immune system.

Overall, cutaneous dissemination of HZ in the patients reviewed was associated with low morbidity and mortality. This could be a result of appropriate antiviral therapy or to a sufficient VZV-CMI to overcome the infection.

In conclusion, DCHZ can occur in any immunocompetent host, although it is more predominant in older patients. Despite cutaneous dissemination, overall mortality and morbidity is low. Chronic comorbidities may play additional role and further research is needed to identify the exact mechanisms by which they affect VZV CMI.

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