Case Report

Symmetric herpes zoster: atypical herpes zoster presentation in renal transplant patient

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Abstract
Herpes zoster (HZ) is not uncommon viral disease which develops in 20% of immunocompetent individuals and 50% of immunocompromised patients. This disease has significant morbidity and can be fatal. Thus early identification and management of this viral illness is critical to diminish the serious sequels. HZ can have unusual presentations in immunocompromised patients as in our patient who developed asymptomatic, symmetric erosive eruption in multiple dermatomes. Unusual presentation of herpes zoster can interfere with early recognition of this disease and subsequently with initial management leading to severe complications. This report highlights the typical and atypical manifestations, complications as well as the management of HZ.

Key words
Herpes zoster, atypical presentation.

Introduction
Herpes zoster (HZ) is a viral disease, commonly known as shingles and characterized by a painful unilateral vesicular rash in a restricted dermatomal distribution. It is caused by reactivation of varicella-zoster virus (VZV) which is also the etiological agent of varicella (chickenpox). VZV is double-stranded DNA virus related to the family of Herpesviridae. Humans are the only known reservoir for VZV. The virus is very contagious and it can be easily transmitted among people through airborne droplets or indirectly by contact with clothing or other items contaminated with virus.

The initial infection with VZV causes the acute illness chickenpox which is characterized by diffuse vesicular eruption and generally occurs in children and young adults. Following the clinical resolution of chickenpox, VZV remains latent within the sensory dorsal root ganglia. Reactivation of this neurotropic virus leads to herpes zoster and it develops in approximately 20% of healthy adults and 50% of immunocompromised persons. Early initiation of antiviral treatment is crucial as it can reduce or eliminate serious complications. In this report, a case of atypical herpes zoster, as well as, comprehensive review of this common disease is presented.

Case Report
A 47-year-old Pakistani male was admitted in Mafraq hospital on June 2014 due to pneumonia. He was a known case of renal transplantation since 2008 following chronic renal failure due to diabetic nephropathy on subsequent long-term immunosuppression. His immunosuppressive
medications included everolimus, prednisolone, mycophenolate mofetil. Levofloxacin was prescribed for the management of pneumonia. Moreover, patient developed acute rejection of renal transplant, which necessitated the escalation of immunosuppressive medication dosage. During hospitalization and one month following admission he developed asymptomatic symmetric circinate confluent vegetating erosive eruption with groups of blisters over buttocks following S1-S4 dermatomes. He did not complained of oral mucosal involvement. Previous medical history included varicella in his childhood, as well as, insulin-dependent diabetes mellitus, diabetic nephropathy and hypertension.

Skin biopsy was done to aid the diagnosis of atypical herpes zoster and to rule out pemphigus vegetans, pemphigus foliaceus and contact dermatitis. The histological examination revealed intraepidermal blisters associated with edema and multinucleated epithelial cells with inclusion bodies. The dermis showed fibrinopurulent exudate. A diagnosis of atypical herpes zoster was established and the patient was treated initially with intravenous acyclovir 5 mg/kg q24 for 4 days followed by oral acyclovir 200mg twice a day for 3 days. Consequently the skin eruptions crusted and resolved.

**Discussion**

Herpes zoster (HZ) is not an uncommon complication of solid organ transplantation. The incidence of HZ following organ transplantation is 8.6% and it is 7.4% following renal transplantation. HZ can be serious disease with significant morbidity. It can be associated with neurological complications such as encephalitis. Dissemination and visceral involvement can be life threatening. Thus early recognition and management of this condition is essential to prevent the complications. However, atypical presentation of HZ can be challenging. Therefore great awareness of this condition is essential to assist early diagnosis and management. This review will illustrate the manifestations, complications of HZ as well as the diagnostic tools and antiviral therapy in details.

**Epidemiology**

Each year about 1 million cases appear in the United States, with an incidence of 3.2 cases per 1000 person-years. In Europe the incidence varies by country from 2.0 to 4.6/1 000 person-years with no remarkable geographic tendency. It has been observed that age-specific HZ incidence is: approximately 1/1000 children<10 years, about 2/1000 adults aged <40 years, and nearby 1-4/1000 adults aged 40-50 years. After the age of 50 years the incidence increased rapidly to about 7-8/1000, up to 10/1000 after 80 years of age. Moreover, it has been noticed in 21 studies that the incidence rates were higher among women than men, and this difference increased with age. 

![Figure 1](image_url)
Increasing age is the main risk factor for the development of herpes zoster. The disease usually appears between 50 and 79 years of age and around 60 percent of cases develop in women. Other risk factors that enhance the reactivation of VZV are HIV infection, neoplastic disease, organ transplantation, use of immunosuppressive drugs, and other conditions that suppress the cell-mediated immunity.1-7

Pathogenesis
The usual route of transmission of primary varicella is airborne droplets, although VZV can be acquired by direct contact with vesicular fluid. Varicella is highly infectious as 80-90% of susceptible household contacts evolve clinical infection. The infected individuals are infectious until all of the vesicles have crusted.

After an inoculation of VZV through airborne droplets, the primary VZV infection begins with replication in epithelial cells of the upper respiratory mucosa. Following that generalized vesicular eruption that is typical of varicella appears after an incubation period of 10-21 days. This pattern probably reflects viral dissemination to the tonsils and other regional lymphoid tissues, from where infected T cells can transport the virus via hematogenous route to the skin. Subsequently VZV reaches the sensory ganglia by retrograde axonal transfer from cutaneous replication sites or by T cell viremia, and consequently initiates latent phase of infection.1-3,8-9

Reactivation of VZV may occur spontaneously or may be induced by stress, fever, and radiotherapy, tissue damage due to trauma or immunosuppression. Following the reactivation, VZV migrates to the skin through anterograde axonal transport leading to HZ, which manifests as a vesicular eruption in the dermatome that is innervated by the affected ganglion.

During a HZ infection, the virus replicates further in the affected dorsal ganglion causing a ganglionitis resulting in a severe neuralgia that intensifies as virus extends through the sensory nerve. Both varicella and zoster skin eruptions contain high concentrations of VZV and are highly contagious. Thus individuals with varicella or zoster can cause varicella if the susceptible person has direct contact with vesicular fluid, however, they cannot directly cause shingles, because HZ is caused by the reactivation of latent VZV.5-9

Manifestations
HZ often begins with prodromal symptoms including malaise, headache, photophobia, and abnormal skin sensations which range from pruritus and burning to hyperesthesia and severe pain. These symptoms may develop one to five days before the appearance of the rash which starts as erythematous papules then rapidly evolve into grouped vesicles or bullae on an erythematous base. Within three to four days, these vesicular lesions turn to more pustular or occasionally hemorrhagic eruption. Rarely, the pain is not followed by the maculopapular eruption of HZ, and this clinical presentation is known as zoster sine herpete.1-5

The cutaneous eruption of HZ typically appears in a single sensory dermatome but can occasionally affect two or three adjacent dermatomes and rarely can it cross the midline.

When VZV invades the first branch of trigeminal nerve, it results in the development of zoster ophthalmicus. Which present as blepharitis, conjunctivitis, scleritis, or episcleritis. Although intracranial thrombotic cerebrovasculopathy is rare complication, it may occur. Other sequelae include corneal ulceration and blindness; therefore patients with this condition should be referred to an
ophthalmologist for adequate evaluation and treatment.\textsuperscript{10,11}

Ramsay-Hunt syndrome is serious otologic manifestation of VZV reactivation. It occurs when VZV affects the geniculate ganglion of the facial nerve. It typically presents with triad of ipsilateral facial palsy and pain in the ear and face with vesicles in the external ear canal. Auditory and vestibular disturbances can occur with this manifestation.\textsuperscript{13}

In immunocompromised patients, HZ may be quite severe and can have unusual clinical presentations, such as persistent crusted verrucous lesions and postherpetic hyperhidrosis in HIV infected patients. Disseminated cutaneous disease occurs in approximately 10% of immunocompromised persons and it is characterized by appearance of more than 20 vesicles apart from the area of primary or adjacent dermatomes or visceral involvement. Involvement of more than one dermatome is called zoster multiplex which is also common in immunocompromised patients.\textsuperscript{4,5,10-12}

**Diagnosis**

HZ is usually diagnosed clinically, based upon both history and distinctive presentation of the cutaneous eruption. However, cases of zoster sine herpete or atypical zoster presentation are difficult to diagnose and require laboratory confirmation. Tzanck smear and recognition of the characteristic multinucleated epithelial giant cells by light microscopy can aid the diagnosis VZV reactivation but cannot differentiate it from those due to herpes simplex virus infection.\textsuperscript{13-15}

On the other hand direct immunofluorescent antigen (DFA) test assists the distinction. Also lesional biopsy will demonstrate histopathologic features for both HSV and VZV but immunohistochemical staining is required to differentiate between the two viral infections. Fluid obtained from vesicles may be evaluated with polymerase chain reaction testing, which is highly sensitive diagnostic tool. Viral culture is an additional laboratory test; it is very specific test but not very sensitive.\textsuperscript{13-15}

**Complications**

The incidence and intensity of HZ sequelae increase as age increases and cell-mediated immunity compromises. The most common cutaneous complication of VZV is bacterial superinfection, most often by *Staphylococcus aureus* or *Streptococcus pyogenes*. Moreover, cutaneous scarring is not a rare complication.\textsuperscript{13}

Postherpetic neuralgia (PHN) is a common neurological complication of VZV infection, and is more common in patients who have acute pain during the initial VZV reactivation. Both the severity and incidence of PHN increase with age, with 10-15% of all zoster patients developing this complication. PHN typically follows onset of zoster manifestation between 1 and 6 months. This pain can be intermittent or constant in duration. PHN can be variable in presentations; it can be throbbing, stabbing, aching, or burning in quality. The patient may have intense pain that may interfere with normal activities.\textsuperscript{15,16}

Furthermore, new skin disorders (infections or tumours) can develop at the site which was previously infected by VZV; this phenomenon is known as Wolf’s postherpetic isotopic response. Whereas sparing of that area by diffuse skin disorders or eruption refers to Wolf’s postherpetic isotopic nonresponse. The exact pathophysiology of these phenomena is not totally clear. Recent studies proposed that the viral damage to sensory nerve fibers, which release neuromediators, can cause immune dysregulation in the zoster infected dermatome either inadequately or extremely.\textsuperscript{17}
Other complications of zoster include herpes myelitis, meningoencephalitis, motor paralysis, pneumonitis, hepatitis and nephritis.\(^1\)\(^3\)

**Management of acute herpes zoster**

The first-line treatment for HZ is antiviral therapy. Three antiviral agents are approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute HZ; they are acyclovir, famciclovir, and valacyclovir. These agents accelerate the resolution of lesions, reduce the development of new lesions, decrease viral shedding, and reduce the intensity of acute pain. They have minimal adverse effects. The treatment should be initiated within 72 hours of rash onset and it is usually given for 7 days in the absence of complications of HZ. Intravenous acyclovir is recommended for immunocompromised patients and for those with severe neurologic complications. Foscarnet is another antiviral agent which is used in immunocompromised patients with acyclovir-resistant VZV.\(^1\)\(^9\)\(^{20}\)

Antiviral agents alone are usually insufficient to relieve the unbearable pain of acute HZ. Mild to moderate pain may be controlled with acetaminophen or nonsteroidal anti-inflammatory drugs. Opioids, such as oxycodone, are used for more severe pain associated with HZ. Anticonvulsant agents such as gabapentin and tricyclic antidepressants have been used for management of acute pain associated with HZ which is not responding to opioids.\(^1\)\(^9\)\(^{20}\)

**Prevention of herpes zoster**

A live attenuated herpes zoster vaccine (Zostavax®) is recommended by FDA to prevent HZ in persons \(\geq 50\) years of age, including patients who have a prior history of HZ except those shown in Box 1. The vaccine can be given also to patients \(\geq 50\) years who have received the varicella vaccine.\(^1\)\(^9\)\(^{20}\)\(^{21}\)

<table>
<thead>
<tr>
<th>Immune status of patient</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td><strong>Immunocompetent patient</strong></td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>800mg five times daily for 7 days</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500mg three times daily for 7 days</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1000mg three times daily for 7 days</td>
</tr>
<tr>
<td><strong>Immunocompromised patient</strong></td>
<td></td>
</tr>
<tr>
<td>Acyclovir (intravenous)</td>
<td>10mg/kg three times daily for 10 days</td>
</tr>
</tbody>
</table>

**Table 2** Contraindications for zoster vaccine (Zostavax®)

- Pregnancy
- Malignancies affecting the bone marrow or lymphatic system
- Chemotherapy or radiation therapy
- Solid organ transplantation
- Daily corticosteroid therapy with a dose \(\geq 20\) mg/day of prednisone (or equivalent) for \(\geq 14\) days
- Immunomodulatory therapy with rituximab or a tumor necrosis factor-alpha inhibitor
- HIV and a CD4 cell count \(< 200\) cells/\(\mu \text{L}\)

The efficacy of the vaccine in preventing HZ is 70% for persons 50 to 59 years of age, 64% for persons 60 to 69 years of age, and 38% for persons 70 years of age or older. However, it should be avoided in populations that are at high risk for developing disseminated varicella-zoster virus infection since it is a live attenuated vaccine.\(^2\)\(^0\)\(^{21}\)

**Conclusion**

The clinical manifestations of HZ are usually distinctive and characterized by painful vesicular rash appearing in a unilateral, dermatomal distribution. Disseminated lesions, visceral involvement or atypical clinical presentation may occur in immunocompromised host. The most common complication of HZ is postherpetic neuralgia. Other complications include herpes zoster ophthalmicus or oticus, acute retinal necrosis, aseptic meningitis, and encephalitis. HZ is usually diagnosed clinically; however, in
atypical presentation additional diagnostic techniques are required to confirm the diagnosis such as viral culture, direct fluorescent antibody testing, and the polymerase chain reaction assay. This disease can be treated with one of the three FDA approved antiviral agents which are acyclovir, famciclovir, and valacyclovir. The aim of antiviral therapy is the rapid resolution of cutaneous lesions and acute neuritis.

References