

Review Article

Herpes zoster: complications and management

Jayakar Thomas

Senior Consultant – Dermatology, Apollo Hospitals, Chennai
& Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India

Abstract Herpes zoster is a common viral infection caused by *varicella-zoster* virus. Clinically it is characterized by painful vesico-bullous eruption in a dermatomal distribution. Systemic involvement occasionally occurs, especially in immunosuppressed hosts. Post-herpetic neuralgia is the most dreadful complication. The present review addresses the complications and management of this common ailment in routine and under special circumstances.

Key words

Herpes zoster

Introduction

Herpes zoster (HZ) is a manifestation of the reactivation of varicella-zoster virus (VZV). Following initial infection, the virus remains latent in the dorsal sensory ganglia until it reactivates and replicates. It is characterized by the presence of dermatomal pain, and usually a papulovesicular rash also in a dermatomal distribution, although the rash is not always accompanied by pain and vice versa (*zoster sine herpette*). The rash typically resolves within 2-4 weeks, although this can take significantly longer in immunocompromised individuals. Virus replication and transmission in nerves and ganglia, together with the subsequent development of skin rash, contribute to the prodromal and acute-phase pain of HZ. Subsequent to this, there can be chronic pain. Thus, pain associated with HZ is typically compartmentalized into three phases – prodromal, eruptive or rash, and

post-herpetic neuralgia (PHN). Other complications of herpes zoster may be addressed as dermatological, neurological, ophthalmologic, etc and are discussed in the text to follow. Prevention and management of complications, particularly PHN are the main objectives of therapy. In addition, treatment of HZ aims to increase the rate of healing of skin lesions. The continued application of mathematical modeling and detection techniques, such as polymerase chain reaction, will increase understanding of the pathogenesis and risk factors involved and provide the potential to develop new treatment methodologies to manage zoster associated pain (ZAP).

Complications

Zoster-associated complications are varied and affect different systems in the body having a negative impact on the quality of the patient's life. Those more likely to be at high risk of developing complications include:

- At the extremes of age (although HZ is not very common in children)

Address for Correspondence

Dr. Jayakar Thomas
2, West Mada Church Road,
Royapuram, Chennai 600013,
India

- With untreated HZ
- Individuals with AIDS
- Patients with malignancies
- Bone marrow transplant recipients
- Solid organ transplant recipients
- Patients receiving high-dose corticosteroids
- Children with leukemia

These individuals have an increased probability of cutaneous and visceral dissemination, VZV pneumonia, encephalitis, and hepatitis.

Dermatological

Bacterial infections with staphylococcal and streptococcal organisms are by far the commonest local complications as evidenced by the appearance of pustules, hemorrhagic crusting and necrosis of involved skin. Eventual scarring occurs in almost all patients and tends to be permanent in around 75%, the incidence increasing proportionately with the age at which HZ occurs. The scars may be pitted or non-pitted, pigmented or depigmented, atrophic or hypertrophic, and anesthetic or hyperesthetic. A number of unrelated dermatological conditions such as sarcoid granuloma, reactive perforating collagenosis, pseudolymphoma, xanthoma, and epitheliomas have been described. However, koebnerization-associated dermatoses such as psoriasis, lichen planus and molluscum contagiosum are more common. An unusual presentation of HZ in the immunocompromized is atypical generalized zoster that begins with a limited area of involvement in the primary dermatome, quickly followed by generalized cutaneous dissemination. Atypical lesions can occur in individuals with HIV infection

and low CD4 cell counts. These are seen as hyperkeratotic papules, ecthymatous lesions, and large punched-out ulcers with a central black eschar and a peripheral rim of vesicles.^{1,2}

Neurological

Physicians should be aware of the existence of rare but serious neurological complications of HZ, such as delayed contralateral hemiparesis, chronic VZV encephalitis, myelitis, polyradiculitis, and numerous cranial and peripheral nerve palsies (including Bell's palsy and Ramsay Hunt syndrome).

Direct VZV invasion of the cerebral arteries along intracranial branches of the trigeminal nerve, resulting in inflammation of the internal carotid artery or one of its branches on the same side as the HZ rash, is thought to be the pathogenesis of delayed contralateral hemiparesis. The typical presentation is headache and hemiplegia occurring in a patient with a recent history of HZ ophthalmicus. Examination of cerebrospinal fluid (CSF) reveals mononuclear cell pleocytosis and increased protein. Arteriography is usually diagnostic and demonstrates inflammation, narrowing, and thrombosis of the proximal branches of the anterior or middle cerebral artery.^{3,4}

Chronic VZV encephalitis is seen almost exclusively in patients with conditions involving depressed cellular mediated responses. It occurs months after an episode of HZ, making diagnosis problematic. The clinical presentation comprises headache, fever, altered mental status, seizures, and focal neurological defects (including aphasia, hemiplegia, and reduced visual

fields). Magnetic resonance imaging reveals plaque-like lesions in the white matter with hemorrhagic infarcts of cortical and subcortical gray and white matter. VZV DNA has been amplified by polymerase chain reaction from the CSF of these patients. The clinical course is often deterioration and death in up to half of cases although anecdotal reports suggest benefit from high-dose aciclovir therapy.^{5,6}

Ophthalmologic

No case of herpes zoster ophthalmicus (HZO) can be managed without the specialist advice of an ophthalmologist. HZO is observed in around 20% of patients with HZ and up to 90% of these may experience ocular complications if left untreated. These complications include conjunctivitis, scleritis, and episcleritis, ocular motor palsies, epithelial keratitis, stromal infiltrates, anterior uveitis, and acute retinal necrosis (ARN). Since the advent of AIDS, a more aggressive form of ARN referred to as rapidly progressive herpetic retinal necrosis (RPHRN) has been identified. The signs and symptoms include pain, photophobia, iritis, vitritis, uveitis, vitreous precipitates, vascular sheathing, large white plaques in retinal periphery, and necrotizing spreading retinal lesions. About 80% of these cases progress to become bilateral in 5-20 days. Intravenous antiviral therapy with aciclovir, followed by oral famciclovir, or valaciclovir should be considered in these cases.^{7,8}

Abdominal herpes zoster

A serious manifestation of HZ in the immunocompromised individual is abdominal HZ. Patients present with severe, unexplained abdominal pain that may

precede the appearance of cutaneous rash by hours or days. The diagnosis of HZ is usually not considered until the typical skin vesicles begin to appear in a thoracic dermatome. Abdominal HZ is associated with a high mortality rate, even when appropriate antiviral therapy is administered. Autopsy studies have revealed a high frequency of abdominal visceral involvement in patients with abdominal HZ. Polymerase chain reaction detection of VZV in peripheral blood mononuclear cells and whole blood has been used in a few cases to make the diagnosis of visceral VZV before the appearance of the rash.^{9,10}

Zoster associated pain (ZAP)

The most debilitating symptom of HZ is the associated pain, which may be both acute and chronic in nature and can persist for months or even years. This has a major impact on the patient's quality of life and once established, can be difficult to manage effectively, making this the most compelling reason for early treatment of HZ. Analysis of several studies indicates that antiviral treatment initiated within 72 hours of rash onset increases the rate of rash healing and also speeds the resolution of ZAP in many patients. Although the pain experienced during the acute phase usually resolves as the rash heals, chronic pain can persist for prolonged periods. The term post-herpetic neuralgia (PHN) has been variously used to describe:

- Pain that persists or occurs after resolution of the cutaneous rash
- Pain persisting more than 30 days after rash onset
- Pain at 3-6 months after the acute episode.

The three main risk factors that predict PHN are:

- Advancing age
- Presence of a prodrome
- Acute pain severity

Other hypothetical factors predictive for PHN include viremia, rash severity, and adverse psychosocial factors. With lack of good prospective population-based studies the incidence of PHN is unclear. However retrospective population-based studies report that, in the absence of therapy, 65-75% of patients with HZ develop pain persisting for more than 4 weeks. Thus there is a continuum of pain – from the pain of the prodrome through to the persisting pain. This continuum is referred to as zoster associated pain (ZAP).^{11,12}

HZ and pregnancy

HZ during pregnancy does not increase the risk of severe ZAP. Therefore, there is no argument to support oral antiviral therapy in such a condition. Long-term safety data on aciclovir and the experience of genital herpes management with aciclovir during pregnancy might suggest that this drug has a good tolerability profile. Clinicians caring for women of childbearing age should be aware of the various aspects of HZ. Determining the VZV serological status as part of the antenatal laboratory work-up helps predetermine the likelihood of developing HZ.

Women with no history of varicella should undergo serological testing and susceptible women should be vaccinated. Vaccination will reduce the risk of severe maternal morbidity caused by varicella-related complications that can occur during

pregnancy and obviate the need for varicella-zoster immunoglobulin (VZIG) prophylaxis during pregnancy. Pregnant women with no history of varicella should not be vaccinated while pregnant but should undergo serological testing to determine susceptibility. Vaccination of susceptible women of childbearing age may potentially also prevent congenital varicella syndrome, neonatal varicella, or childhood HZ.¹³

Pediatric aspects

Herpes zoster occurs rarely in children. The main risk factors for childhood HZ are the occurrence of varicella during the first year of life, or maternal varicella infections during pregnancy (either chicken pox or herpes zoster). Other factors are subclinical, unrecognized, or paucilesional chicken pox. Prodromal, acute, and persistent pain is almost non-existent in childhood. The attending pediatrician, however, should be vigilant on potential development of encephalitis, hepatitis, and pneumonitis and more so in the immune challenged as in the case of children with leukemia.¹⁴

Management

A complete review of literature on management of HZ is not within the scope of this article. As such only the key points are discussed. Barriers to the treatment of HZ may include the following:

- Lack of clear initial symptoms due to the variable nature of prodromal pain
- Time taken to obtain a consultation once rash appears due to waiting lists and appointment systems, and patient's fear of illness- especially in the elderly

- Time between consultation and dispensing of prescription
- Lack of awareness by some physicians of the suffering experienced by patients with HZ
- Perception among some physicians that treatments are expensive

It is important that patients with HZ are encouraged to present to physicians as early as possible for prompt medical care. Both public and medical education efforts are required to achieve this.¹⁵ In many individuals, HZ comprises rash and pain of relatively short duration. However, in some individuals, especially the elderly, HZ is associated with complications and prolonged pain. The aims of treatment are to minimize the duration and severity of pain and to prevent the complications.

General measures include bed rest, antibiotics, analgesics, and topical astringents.

Antiviral therapy for immunocompetent adults over 50 years of age with HZ is a *specific measure* that is routinely recommended, particularly if it can be instituted within 72 hours of lesion onset. Because of their improved pharmacokinetic profiles and simpler dosing regimens, valaciclovir (1000 mg three times a day) or famciclovir (250 mg or 500 mg three times a day) have replaced aciclovir (800 mg five times a day) as the preferred oral treatment. However, intravenous aciclovir seems the only available option in the treatment of HZ in immunocompromised individuals and in those who suffer from major complications discussed earlier. There is some evidence that antiviral therapy should be considered for patients whose rash has been present

longer than 72 hours and in whom clinical examination reveals new vesicle formation (indicative of ongoing virus replication). Similarly, if risk factors for severe or protracted pain are present at presentation, antiviral therapy should be initiated irrespective of time since rash onset.¹⁶

Tricyclic antidepressants, such as amitriptyline (25 mg once daily; 10 mg in the frail and elderly, elevated every few days to a dose that is effective without severe side-effects), particularly if initiated early in the clinical course of HZ, can relieve the acute pain associated with the disease and have the potential to prevent the development of PHN. Sympathetic nerve blocks have been studied in several trials, most of which were uncontrolled and lacked comparative groups. Thus, it is difficult to draw any conclusions about the efficacy of this intervention in HZ.

In general patients with HZ should receive antiviral therapy to limit viral replication and, thereby, minimize the acute pain associated with HZ, help prevent PHN, prevent complications, and speed the resolution of rash.

Corticosteroids and HZ

It is recommended that physicians consider the use of oral steroids to reduce inflammation that may be contributing to ZAP. Some recommend corticosteroids for the treatment and prevention of ocular disease caused by HZ. The literature concerning the use of corticosteroids for HZ either provides conflicting results or includes recommendations based on clinical experience rather than clinical trials. With the concern over possible dissemination, adverse effects, and questionable efficacy, a careful examination of medical literature is

warranted to determine the place of corticosteroids in the management of HZ.¹⁷

Potential of vaccine to prevent HZ

The availability of a safe and effective varicella vaccine prevents the opportunity to determine whether it may also be effective for preventing HZ in the elderly. The initial suggestion that vaccination may reduce the likelihood of HZ was prompted by a study in children with leukemia who received VZV OKA vaccine. Among these, the incidence of HZ was lower than in children who had experienced natural VZV infection.¹⁸

Conclusion

Herpes zoster is a disease that can most often impair the quality of the patient's life. The pain associated with it is the most compelling cause for concern. HZ is a prototype of a disease which needs newer therapeutic approaches for which research in the following directions are recommended:

- Improved and predictive animal models are needed for the study of acute disease and of latent VZV infection and to assess the effect of potential new drugs for the treatment of varicella and HZ. It is recommended that the development of suitable small animal models for studying VZV infection be continued.
- Although VZV reactivates in the dorsal root ganglia, it is unclear whether or not there are potential sites of reactivation. It is important to ascertain whether virus can reactivate in other sites and whether this reactivation can boost the

immune response. Further investigation of the hypothesis that reactivation occurs in peripheral blood mononuclear cells is recommended, as this would offer the chance of regularly monitoring reactivation and of predicting the onset of HZ.

- Continued research is recommended to obtain a better understanding of VZV latency, and, in particular, knowledge of the viral antigens expressed during that period. This may allow the development of approaches to prevent the reactivation of the virus and thus the onset of herpes zoster.

References

1. Requena L, Kutzner H, Escalonilla P *et al*. Cutaneous reactions at sites of herpes zoster scars; an expanded spectrum. *Br J Dermatol* 1998; **138**: 161-8.
2. Nico BMS, Bergonse FN, Godoy BM. Molluscum contagiosum in herpes zoster scars. *Int J Dermatol* 2001; **40**: 521-4.
3. Gildeen DH, Kleinschmidt-DeMasters BK, LaGuardia JJ *et al*. Neurologic complications of the reactivation of varicella-zoster virus. *N Eng J Med* 2000; **342**: 635-45.
4. Melanson M, Chalk C, Georgevich L. Varicella-zoster virus DNA in CSF and arteries in delayed contralateral hemiplegia: evidence for viral invasion of cerebral arteries. *Neurology* 1996; **47**: 569-70.
5. Horten B, Price RW, Jiminez D. Multifocal varicella-zoster virus leukoencephalitis temporally remote from herpes zoster. *Ann Neurol* 1981; **9**: 251-66.
6. Gray F, Mohr M, Rozenberg F. Varicella-zoster virus encephalitis in acquired immunodeficiency syndrome: a report of four cases. *Neuropathol Appl Neurobiol* 1992; **18**: 502-14.

7. Marsh RJ, Cooper M. Ophthalmic herpes zoster. *Eye* 1993; **7**: 350-70.
8. Womack LW, Liesgang TJ. Complications of herpes zoster ophthalmicus. *Arch Ophthalmol*; 1983; **101**: 42-5.
9. Stemmer SM, Kinsman K, Telschow S *et al.* Fatal noncutaneous visceral infection with varicella-zoster virus in a patient with lymphoma after autologous bone marrow transplant. *Clin Infect Dis* 1993; **16**: 497- 9.
10. Rogers SY, Irving W, Harris AW *et al.* Visceral varicella zoster infection after bone marrow transplantation without skin involvement and the use of PCR for diagnosis. *Bone Marrow Transplant* 1995; **15**: 805-807.
11. Whitley RJ, Weiss HL, Soong SJ *et al.* Herpes zoster: risk categories for persistent pain. *J Infect Dis* 1999; **179**: 9-15.
12. Whitley RJ, Shukla S, Crooks RJ. The identification of risk factors associated with persistent pain following herpes zoster. *J Infect Dis* 1998; **178**: 571-5.
13. Enders G, Miller E, Craddock-Watson J, *et al.* Consequences of varicella and herpes zoster in pregnancy: a prospective study of 1739 cases. *Lancet* 1994; **343**: 1548-51.
14. Guess HA, Broughton DD, Melton LJ *et al.* Epidemiology of herpes zoster in children and adolescents: a population-based study. *Pediatrics* 1985; **76**: 512-7.
15. Smith KJ, Roberts MS. Cost effectiveness of newer antiviral agents for herpes zoster: is the evidence spotty? *J Infect Dis* 1998; **178** (Suppl 1): 585-590.
16. Nikkels AF, Fierard GE. Oral antivirals revisited in the treatment of herpes zoster. *Am J Clin Dermatol* 2002; **3**: 591-8.
17. Santee JA. Corticosteroids for herpes zoster. *Am J Clin Dermatol* 2002; **3**: 518-24.
18. Takahashi M. Current status and prospects of live varicella vaccine. *Vaccine* 1992; **10**: 1007-14.