Review Article

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Variations in herpes zoster manifestation

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Herpes zoster (HZ) is a neurocutaneous disorder due to endogenous reactivation of the varicella-zoster virus (VZV). The typical clinical manifestation is an acute segmental eruption of herpetiform umbilicated vesicles associated with malaise, pain, dysaesthesia, allodynia and probably fever. This review focuses on other possible clinical manifestations of the disease to sensitize physicians not to overlook HZ since only an early antiviral treatment can reduce the risk of post-zosteric neuralgia.

Key words Clinical findings - herpes zoster - varicella-zoster virus

Introduction

Herpes zoster (HZ) is a viral disease caused by endogenous reactivation of an infection by the varicella-zoster virus (VZV). Clinically, the disease is characterized by an acute segmental (dermatomal) eruption of herpetiform vesicles on the skin and/or mucosa[1]. Epidemiologic data from Europe and the US suggest a yearly incidence rate of 4 to 5 per 1000 person-years. Incidence increases with age. HZ is more common among females in all age groups[2,3]. In Germany, HZ morbidity has been reported to be 0.29 for females and 0.10 for males per 100,000 patient-years[4]. Patients at risk for HZ are those with one of the following underlying disorders and treatments: autoimmune diseases, asthma, diabetes, treatment with biologics or immunosuppressants, cancer or HIV/AIDS[1].

Clinical presentation

The prodromal phase of about one to five days is characterized by malaise, fever and pain. The classical clinical presentation of herpetiform umbilicated vesiculation within a dermatoma allows a visual diagnosis without the need for extensive diagnostic procedures. Later on, crusts develop that disappear within one or two weeks without leaving scars (Fig. 1).

The classical feature, however, may not always be present making diagnosis more challenging. A typical prodromal stage of HZ ophthalmicus is Hutchinson's sign: vesicles develop on the tip of the nose or on the side of the nose due to the involvement of the nasociliary branch of the trigeminal nerve, which innervates both the cornea and the nose. Hutchinson's sign is more common among patients with immunosuppression or immunodeficiency[5].

Herpes zoster with extended prodrome

HZ prodrome extending five days and up to 18 days have been reported. Extended prodrome is not necessarily associated with immunosuppression or immunodeficiencies[6].

Herpes zoster not respecting dermatoma borders

Some aberrant vesicles are not uncommon. However, HZ not respecting the borders of a dermatoma may be due to viraemic spread indicating a more severe subtype. HZ duplex is crossing the midline of the body. This subtype is seen more often in Asia than in Europe[7]. An association to immunologic aberrations is present in <50 per cent of patients[7]. Multi-segmental HZ and generalized HZ represent a continuum of more severe manifestations (Fig. 2A, B)[1].

Herpes zoster leaving scars

If the inflammation is very strong, protracted scars may develop. This can be seen in haemorrhagic and necrotic HZ (Figs 3 & 4). Healing is delayed and bacterial superimposed infection is an additional risk (Fig. 5). Necrosis can also develop after unremarkable HZ due to delayed nervous and vascular compromise. This subtype is most commonly seen in the head-and-neck region[1]. The development of keloids after HZ has been reported in a pregnant woman[8].

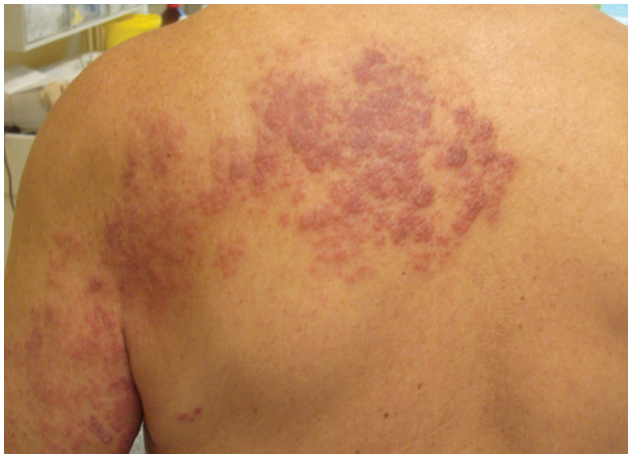

Fig. 1. Classical presentation of herpes zoster thoracicus.

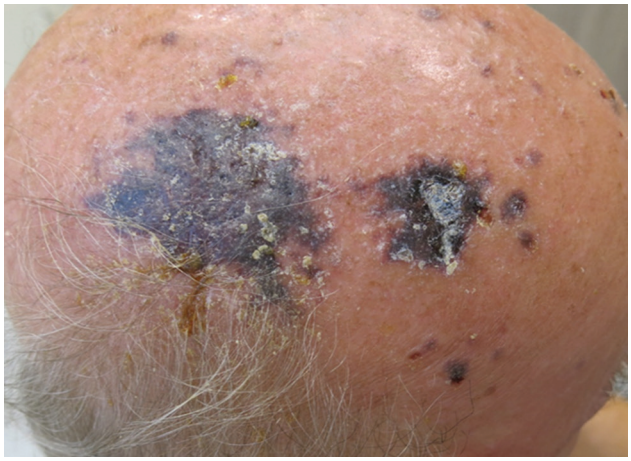

Fig. 3. Haemorrhagic-necrotizing herpes zoster ophthalmicus.

Herpes zoster with vascular manifestations

VZV vasculopathy covers a broad range of vascular manifestations in both immunocompetent and immunocompromised patients. Ischaemic stroke and intracerebral aneurysms may develop after VZV infection of cerebral arteries[9]. In patients ≥65 yr of age, HZ increases the risk of myocardial infarction 1.7-fold and of ischaemic stroke 2.4-fold during the first week of disease[10].

Leucocytoclastic VZV vasculitis can be a consequence of HZ[11]. VZV can even trigger the onset of temporal arteriitis[12]. Erythema multiforme (EM)-linked lesions have been observed in HZ patients[13]. HZ has been reported to increase the risk of peripheral arterial disease by 13 per cent[14].

Herpes zoster associated with neurologic impairment

An overview of specific neurological consequences of HZ is summarized in the Table. The central nervous

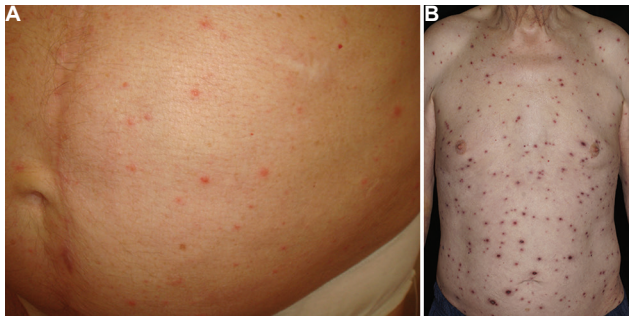

Fig. 2. Generalized herpes zoster. (**A**) Milder form, (**B**) more severe manifestation with haemorrhagic lesions.

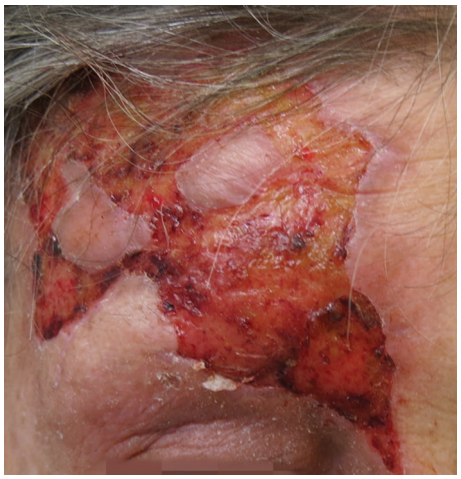

Fig. 4. Extensive necrosis after complete remission of herpes zoster ophthalmicus.

Table. Subtypes of herpes zoster associated with specific neurological consequences

Subtype	Affected nerve	Findings	Complications
Zoster ophthalmicus	First trigeminal nerve branch	Keratitis, blepharitis, keratoconjunctivitis	Uveitis anterior, orbital phlegmon, retinal necrosis, superior orbital fissure syndrome, blindness
Zoster oticus	Vestibulocochlear and facial nerve	Pain localized to the ear may also be affected	Bell's palsy
Ramsay-hunt syndrome	Vestibulocochlear and facial nerve	Vesiculation in auditory canal, buccal mucosa, cheeks	Tinnitus, hearing loss, laryngitis, failure of lid closure

Source: Ref 1

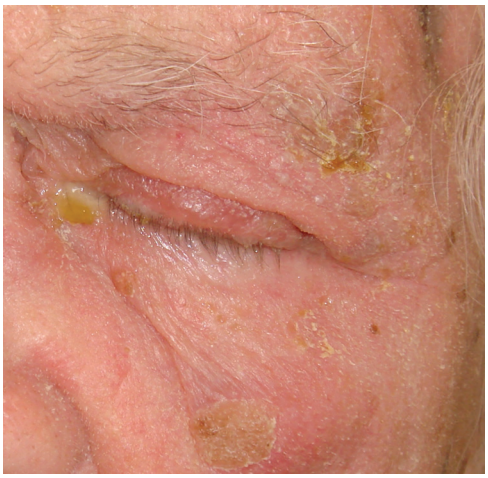

Fig. 5. Herpes zoster ophthalmicus with ocular involvement and superimposed bacterial infection.

system can be affected by HZV. Such patients suffer from headache, neck stiffness, behavioural abnormalities and somnolence. Typical manifestations are encephalitis and meningitis in addition to VZV vasculopathy. The diagnosis is hampered in particular in elderly patients with multiple comorbidities. Cerebrospinal fluid analysis is not always helpful since pleocytosis can be found even in uncomplicated HZ, but increased virus load is characteristic[15].

A study conducted in Taiwan investigated HZ in 10,296 elderly people (≥65 yr of age). Data were compared with 39,405 randomly selected individuals aged ≥65 yr without a diagnosis of HZ. The HZ group showed a hazard rate of 1.17 for the development of Parkinson's disease[16]. This is important to recognize early symptoms of Parkinson's disease among elderly people affected by HZ.

Wolf's isotopic response

Even after clinical remission, former HZ lesions represent a *locus minoris resistentiae*, on which other disorders may develop. The phenomenon has been called Wolf's isotopic response. The phenotypical variety is extraordinarily large. Such postherpetic disorders with Wolf's response include granuloma annulare, lupus erythematosus, morphoea, lichen planus, molluscum contagiosum or B-cell chronic lymphocytic leukaemia[17]. In such cases, histologic investigations are indispensable.

Pathergic phenomenon

Pathergy describes a skin condition, in which a minor trauma leads to the development of ulcerations or other skin lesions that may be resistant to healing. Pathergy can also lead to ulcerations at the site of surgical incisions. Pyoderma gangrenosum of the scalp has been observed as a pathergic response to HZ[18].

Herpes zoster as a marker for occult cancer

In a systematic review and meta-analysis[19] of 46 eligible studies, the pooled relative risk for any cancer was 1.42 and 1.83 at one year after zoster. The highest estimates were noted for haematological malignancies (Fig. 6). A study from Taiwan investigated the hazard rates for cancer after HZ infection in elderly people. Within the first two years after HZ, the risk of subsequent cancer was significantly increased, particularly lung cancer[20]. On the other hand, metastases may resemble HZ. This has been reported for metastatic melanoma[21], lung cancer[22], rectal adenocarcinoma[23], breast cancer[24] and nasopharyngeal cancer[25] among others.

Erythema multiforme (EM) after herpes zoster (HZ)

EM is commonly associated with herpes simplex virus infections. It is considered as a hypersensitivity reaction with polymorphous eruptions of macules, papules and targetoid lesions symmetrically distributed.

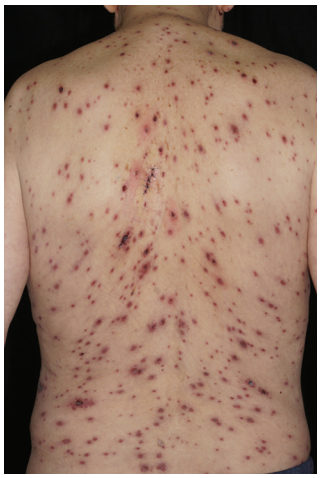

Fig. 6. Necrotic disseminated herpes zoster in occult chronic lymphatic leukaemia.

In contrast, EM has rarely been observed after HZ. Weisman *et al*[26] reported on four patients with HZ with marked increase in VZV antibodies and development of bullous EM about 10-14 days after resolution of HZ. Another patient was reported from Kyoto, Japan, who developed EM after HZ treated successfully with aciclovir[27].

Conclusions

HZ is a common disease caused by VZV. Although easily recognized by clinical features in the majority of cases, the clinical presentation is variable. The suspicion of HZ in such cases is of particular importance since early treatment is warranted *i.e.* within 72 h after onset of vesicular eruption[28].

***Conflicts of Interest*:** None.

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