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Herpes zoster ophthalmicus

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Abstract Herpes zoster ophthalmicus (HZO) occurs when latent varicella zoster virus reactivates in the ophthalmic division of the fifth cranial nerve (CNV1). HZO commonly affects older and immunocompromised patients. This disease is considered an ophthalmic emergency due to the wide range of associated ocular symptoms, including severe chronic pain and vision loss. HZO is typically a clinical diagnosis due to its classic presentation of a unilateral vesicular eruption in the dermatomes corresponding to CNV1. Timely treatment is imperative to minimize ocular morbidity in HZO, given that ocular involvement is present in 50% of affected patients.

Introduction

Herpes zoster (HZ) results from the reactivation of latent varicella zoster virus (VZV), typically decades after primary infection.[1] VZV remains dormant in the dorsal root ganglia and, upon reactivation, travels anterograde to the skin along the affected afferent nerves to manifest a painful, unilateral, vesicular eruption in a dermatomal distribution.[1] Herpes zoster ophthalmicus (HZO) occurs when HZ is reactivated in the ophthalmic division of the trigeminal nerve (ophthalmic nerve, CNV1) and accounts for 10% to 20% of HZ cases overall.[1] Cutaneous manifestations are frequently the first sign of infection, and diagnosis can be made clinically.[2] When HZ is complicated by ophthalmic nerve involvement, there is a risk for partial or complete blindness.[3] Early and accurate diagnosis and treatment are critical in preventing the vision-threatening ocular and periocular complications of HZO.[3]

Epidemiology

There are an estimated 1 million new cases of HZ in the United States each year, and HZO accounts for about 10% to 20% of all HZ cases.[1,3]

Anyone who has been infected with wild-type VZV can develop HZ.[4] More than 90% of unvaccinated people become infected with VZV before adolescence and thus are susceptible to HZ.[5] The reactivation of HZ from its latent state may be induced when cell-mediated immunity is compromised due to the use of immunosuppressants, HIV infection, bone marrow or organ transplant, or chemotherapy.[6]

Age is one of the most significant risk factors for HZ. Sixty-eight percent of cases occur after the age of 50, with a mean age of 59.4 years.[7] This age-related increase in incidence reflects a decline in VZV-specific cell-mediated immunity.[8] The trigeminal nerve is involved more frequently in geriatric patients with HZ than in patients of other age groups.[9] Women have a higher risk of HZO than men, and the prevalence of HZO is higher in White Americans than in Black Americans.[10]

The risk of postherpetic neuralgia (PHN) and other complications, including loss of vision following HZO, increases with age. One study found that patients older than 50 years

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of age had a 14.7-fold higher prevalence of PHN 30 days after developing HZ and a 27.4-fold higher prevalence 60 days after developing zoster.[11] The risk factors and epidemiology of HZO closely mirror those of HZ.[10]

Pathophysiology

Varicella zoster virus is a double-stranded DNA virus spread primarily through respiratory droplets that invade the host's upper respiratory tract.[12] After primary infection, which occurs about one week following invasion, the virus becomes latent in cranial nerve or dorsal root sensory ganglia.[12] HZ occurs when the immune system fails to suppress viral replication, leading to reactivation in an anterograde fashion toward the skin. This reactivation leads to cutaneous manifestations in the dermatome associated with the affected cranial or spinal nerve.[12] When the sensory ganglion of CNV1 is implicated in HZ pathogenesis, HZO ensues.[12] CNV1 divides into the frontal, nasociliary, and lacrimal branches, with the frontal branch being the most commonly affected in HZO.[1,13] The frontal branch innervates the skin of the upper eyelid and forehead.[1] The nasociliary branch innervates the conjunctiva, sclera, iris, cornea, and choroid, as well as the skin of the nasal tip.[1,14]

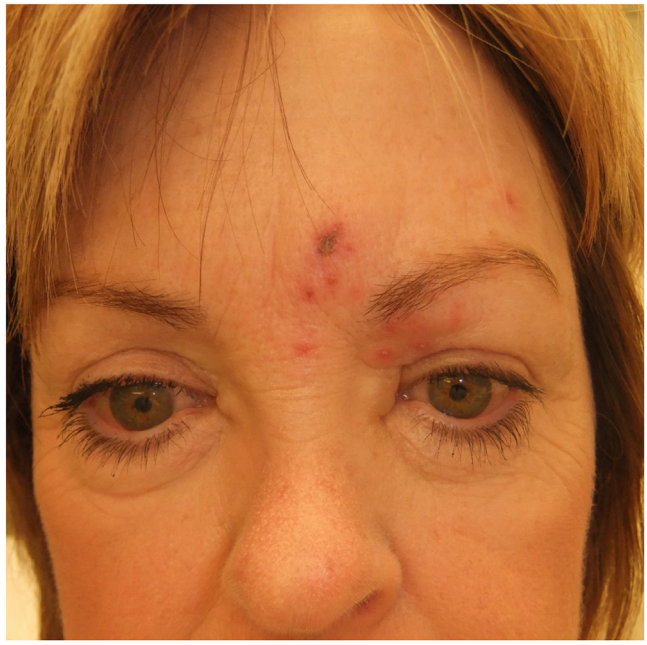

Fig. 1 Herpes zoster ophthalmicus. Vesicles and erosions on the forehead and upper eyelid skin with sharp demarcation at the midline. This distribution reflects involvement of the frontal nerve of the ophthalmic branch (V1) of the fifth cranial (trigeminal) nerve.

Clinical presentation and diagnosis

HZO manifests in three phases: the pre-eruptive phase, acute eruptive phase, and chronic phase. The pre-eruptive phase consists of a prodrome with headache, fever, and ocular pain.[15] Prodromal pain presents as a unilateral "burning" or "shooting" pain in the V1 dermatome.[15] Pain and fever can last up to ten days before the onset of the second, or acute eruptive, phase.[15] The acute phase is characterized by patchy erythema in a V1 distribution associated with regional lymphadenopathy.[15] Grouped papules and clear vesicles then develop on the erythematous base, which spare the midline in immunocompetent patients.[15] Lesions present on the scalp, forehead, and eyelids[16] (Figure 1). The vesicles eventually become cloudy, rupture, crust over, and involute.[15] Involvement of the nasal tip is known as Hutchinson sign and reflects involvement of the nasociliary branch of CNV1[1,14] (Figure 2). It is critical to evaluate for Hutchinson sign because it indicates a 3.35-fold increased risk of ocular inflammation and 4.02-fold increased risk of corneal denervation,[17] but the absence of Hutchinson sign does not preclude ocular involvement.[17] One-third of patients with HZO without Hutchinson sign will still develop ocular complications.[3]

If ocular involvement is suspected, an ophthalmologist should evaluate the patient to mitigate the risk of visual morbidity.[18] HZO results in ocular involvement in approximately half of cases.[1,6] When the eye is involved, HZO is an ophthalmic emergency.[1,6]

Ocular manifestations of HZ can result from two main sources: direct infection by the virus or a secondary inflammatory response to the viral antigen. VZV can infect every layer of the eye including: the conjunctiva (conjunctivitis), cornea (keratitis), sclera (scleritis), trabecular meshwork (trabeculitis resulting in glaucoma), iris (iritis), uveal tract (anterior and posterior uveitis), retina (retinitis), and optic nerve (optic neuritis). Thus, patients with HZO need to be closely followed by an ophthalmologist as some of these complications can manifest months after the cutaneous findings.

Herpes zoster ophthalmicus keratitis can be further separated into epithelial keratitis, which usually presents as a pseudodendritic, stromal keratitis that can result in inflammation. This inflammation produces corneal scarring and endotheliitis, which causes diffuse corneal swelling.[19] Unfortunately, all of these usually result in a dramatic loss in vision. A common sequela of HZO corneal infection is neurotrophic keratopathy in which a loss of corneal sensation can result in ulceration, thinning, and corneal perforation[20] (Figure 3). Other findings commonly associated with HZO keratitis include dense corneal neovascularization and lipid keratopathy. A certain subset of patients can develop an ischemic occlusive vasculitis resulting in elevated intraocular pressures, significant anterior chamber inflammation, and transillumination defects.[21] Iris atrophy may be a prominent sign of HZO iritis. Contiguous posterior dissemination may result in vitritis, retinitis, and optic neuropathy. Cranial neuropathy

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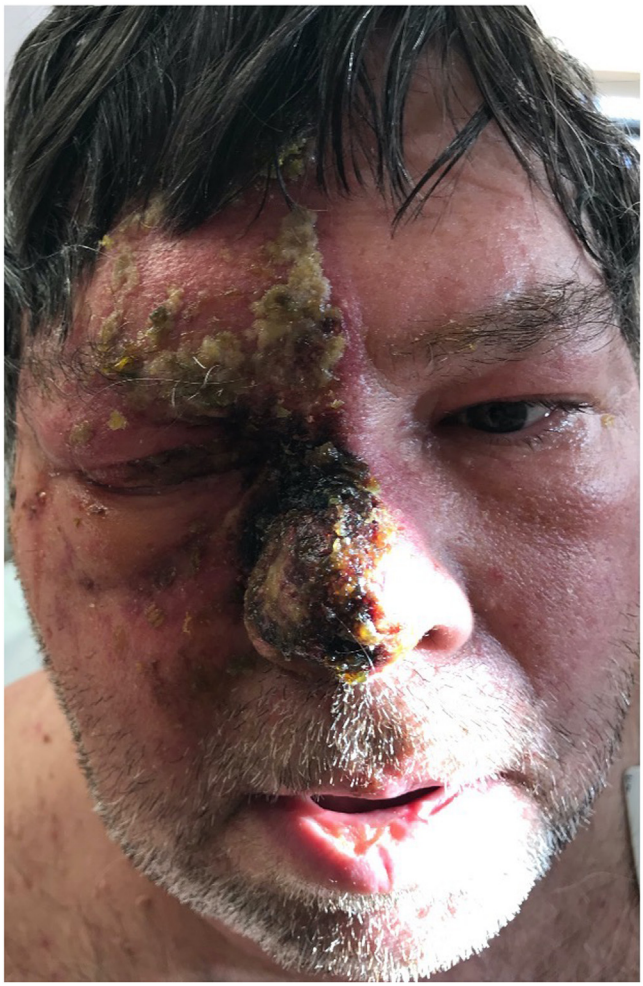

Fig. 2 Multidermatomal herpes zoster, including herpes zoster ophthalmicus with ocular involvement. Crusted erosions, necrosis, and erythema distributed over the forehead, upper and lower eyelids, nose, and cheek, with sharp demarcation at the midline. Distribution on the nasal tip reflects involvement of the nasociliary nerve of the ophthalmic branch (V1) of the fifth cranial (trigeminal) nerve. Distribution on the lower eyelid, cheek, and nasal ala reflects involvement of the adjacent V2 dermatome.

and cavernous sinus thrombosis are rare manifestations that can be observed in severely immunosuppressed patients.

The chronic phase is the third and final phase of HZO and results in persistent, recurring pain confined to the V1 dermatome, also known as PHN.[15] PHN occurs in 9% to 45% of all cases and can be severe and incapacitating and can persist for years, especially in older patients.[15,22,23] PHN is more frequently experienced when upper-body dermatomes are involved, particularly in cases of HZO.[15,23]

The diagnosis of HZO is typically clinical. Pertinent history that should be elucidated includes prior varicella infection, vaccination status, and immunocompetency. Immunocompromised patients are more prone to severe outcomes.[24] Diagnostic confirmation is unnecessary when patients present with a unilateral, painful eruption involving the

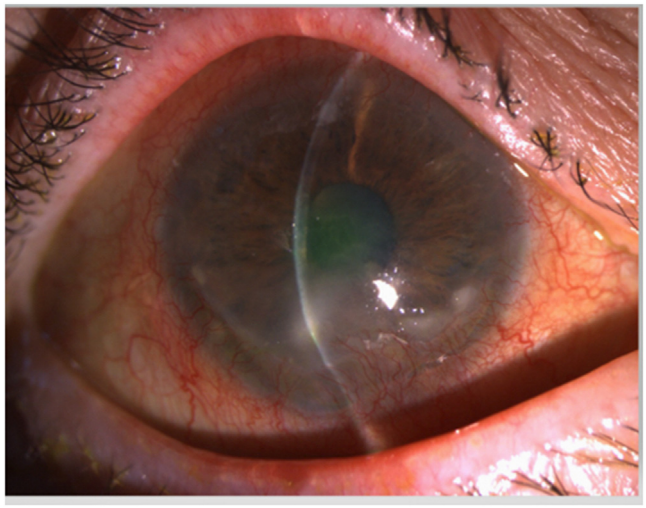

Fig. 3 Herpes zoster keratitis. Inferior corneal thinning with dense neovascularization and associated lipid deposition. An early central neurotrophic corneal epithelial defect is also present and can be observed with fluorescein staining.

V1 dermatome.[1] Up to 91% of clinical diagnoses of HZO can be serologically confirmed, reflecting the reliability of history and physical examination.[25] Further testing may be necessary for patients with atypical presentations, especially in immunocompromised patients. Approximately 20% of affected patients present with atypical findings, including an eruption that crosses the midline.[26] In these patients, it is important to exclude clinical mimics of HZO. Polymerase chain reaction (PCR) testing is the preferred diagnostic tool as it is rapid and is the most sensitive test for VZV.[27] The sensitivity and specificity of PCR are 97.6% to 100% and 100%, respectively.[28] Direct fluorescent antibody testing and viral culture can be used if PCR testing is unavailable; however, their sensitivities are only 87.8% and 46.3%, respectively.[28,29]

Management and outcomes

Early diagnosis and treatment of HZO are imperative to mitigate the risk of corneal involvement and vision loss.[30] Standard therapy should incorporate oral antivirals to reduce viral replication, topical corticosteroid eyedrops to limit inflammation and immune system-mediated keratitis and iritis, and supportive care.[13,30-32] After the onset of clinical cutaneous findings, most viral replication will cease by 72 hours, and there is no evidence that oral antiviral therapy improves the clinical course once the eruption has resolved.[33] Thus, antiviral therapy, such as acyclovir, valacyclovir, and famciclovir, should be initiated within 72 hours of disease onset. Empiric therapy is warranted when a definitive diagnosis is pending.[34] Antiviral therapy can be considered 72 hours after onset if there are new lesions indicative of active viral replication or for immunocompromised patients.[33] In immuno-

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compromised patients, the duration of viral replication and shedding extends beyond 72 hours.[33] Thus, all immunocompromised patients should be treated with antiviral therapy, even if presenting after 72 hours of onset.[33] Approximately 50% of patients left untreated will develop ocular complications.[35]

Immunocompetent patients can be treated with oral acyclovir 800 mg five times daily, valacyclovir 1000 mg every eight hours, or famciclovir 500 mg daily for at least seven days.[36-38] Acyclovir, valacyclovir, and famciclovir require renal dosing.[37-39] Immunocompromised patients or patients with vision-threatening disease should be treated with acyclovir 10 mg/kg (based on ideal body weight) intravenously every eight hours for at least seven days.[40] Foscarnet 90 mg/kg intravenously every 12 hours can be used for acyclovir-resistant disease.[37]

Evaluation by an ophthalmologist should be sought urgently if any of the following are present: Hutchinson sign, blurry vision, and/or red eye.[18] Patients with potential nasociliary nerve involvement (with or without Hutchinson sign) and HZ that includes HZO and additional dermatomes such as V2 and V3, as well as all immunocompromised patients, should be referred to an ophthalmologist, as they are at greater risk of ocular disease.[24] Delayed treatment can result in complete or partial blindness.[3]

Supportive care for ocular disease includes artificial tears, cold compresses, and analgesics.[18,40] Topical ophthalmic steroids can improve pain secondary to uveitis or scleritis, but these should be started only after initiation of antiviral therapy and ophthalmology consultation given their side effect profile and risk for complications.[41] If there is periocular skin involvement without ocular surface disease, an ophthalmic antibiotic ointment may be considered to prevent bacterial superinfection.[3] Topical antiretrovirals lack sufficient evidence and therefore have no current role in therapy.[34] For severe, debilitating pain, short-acting narcotics or a 10- to 14-day prednisone taper starting at 60 mg/d can be considered.[42] If there is minimal relief with prednisone, then gabapentin or tricyclic antidepressants, which are typically used for PHN, may be used.[42] Prednisone can also be considered for uveitis and can decrease initial pain; however, there is no evidence that systemic steroids decrease the risk of PHN or ocular complications.[3,41]

Rarely, surgical intervention is necessary when the integrity of the periocular and intraocular tissue has been compromised. Eyelid reconstruction from cicatricial entropion or ectropion repair can reduce vision loss from lagophthalmos and exposure keratopathy.[43] An eyelid tarsorrhaphy is a useful procedure for limiting damage from neurotrophic keratopathy and preventing corneal perforation. Finally, in patients with frank corneal perforation, corneal gluing, conjunctival autografting, or corneal transplantation can be used to preserve globe integrity.[44]

To prevent HZO, adults 50 years or older should receive two doses of the HZ vaccine (Zoster Vaccine Recombinant, Adjuvanted). This vaccine is based on VZV glycoprotein E, is inactivated, and is administered to patients with and without a history of HZ.[45] Two doses are given in series, with the second dose given two to six months after the first dose.[45] The vaccine has an overall efficacy of 97.2%, significantly reducing the risk of HZ and PHN.[46]

Several studies have suggested an increased risk of stroke within one year of diagnosis of HZ. The hazard ratio for developing stroke within one year after HZ is 1.31.[47] The hazard ratio for stroke within one year after HZO with ophthalmic complications is 4.28.[47] In addition to a higher risk of stroke, patients with HZO also have lower one-year stroke-free survival rates.[48] Antiviral therapy does not appear to influence the risk of stroke.[48]

Conclusions

Herpes zoster ophthalmicus results from reactivation of VZV in the dermatomal distribution of the ophthalmic division of the trigeminal nerve. When typical physical findings are present, HZO is a clinical diagnosis. Following the diagnosis of HZO, antiviral therapy, topical corticosteroid eye drops, and supportive care should be initiated. It is imperative to treat HZO within 72 hours of onset, as vision loss is the major complication associated with HZO. Patients who present with evidence of nasociliary nerve involvement (Hutchinson sign, red eye, blurry vision, or other ocular findins), HZ that includes HZO and additional dermatomes such as V2 and V3, or a history of immunosuppression should be promptly evaluated by an ophthalmologist. Immunocompetent patients with HZO limited to frontal nerve involvement (physical findings localized to forehead and upper eyelid), absence of red eye, and without ocular symptoms can be managed with oral antiviral therapy alone by a dermatologist. Zoster Vaccine Recombinant is recommended for all adults 50 years or older with or without history of HZ.

Declaration of competing interest

The authors declare no conflicts of interest.

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