

# Herpes Zoster Ophthalmicus: A Teaching Case Report

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## Abstract

*Herpes zoster ophthalmicus (HZO) is a disease that occurs when the ophthalmic division of the trigeminal nerve is impaired as a result of reactivation of the varicella-zoster virus. HZO develops in 10-20% of patients who experience reactivation of zoster in the fifth cranial nerve dermatome. The patient in this teaching case report developed neurotrophic keratitis as a result of both HZO and diabetic neuropathy of V1. This teaching case illustrates many of the classic signs and symptoms of HZO and discusses appropriate treatment, management and patient education.*

**Key Words:** *herpes zoster ophthalmicus, neurotrophic keratitis, diabetes mellitus, antiviral, Hutchinson's sign, Zostavax*

## Background

The following case report on the diagnosis and management of herpes zoster ophthalmicus (HZO) is appropriate as a teaching guide for third- and fourth-year optometry students as well as optometry residents. The case report explores important clinical findings and considerations in the treatment of HZO in a patient with HZO, ocular manifestations of diabetes and atrophic age-related macular degeneration. This case emphasizes the need for a list of differentials when a patient presents with comorbid disease. Thus, it also teaches students to learn to manage multiple conditions in the same patient, all of which may contribute to a patient's decreased vision and may be important in the determination of treatment and prognosis.

## Learning Objectives

At the conclusion of this case discussion, participants should be able to:

1. Describe the signs and symptoms of HZO
2. List the differential diagnoses of neurotrophic keratitis
3. Describe the stages of the Mackie Classification
4. Understand treatment and management of HZO and neurotrophic keratitis
5. Describe the pathophysiology and demographics of herpes zoster (HZ)
6. Understand common morphologic changes that occur in corneas of patients with diabetes

## Key Concepts

1. Systemic, ocular and neurologic causes of neurotrophic keratitis
2. Pathophysiology of HZO
3. Ocular manifestations of HZ
4. Treatment considerations in comorbid presentations

## Discussion Questions

1. What is the pathophysiology of herpes zoster?
2. What are the demographics of herpes zoster and HZO?

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3. What are classic signs and symptoms of herpes zoster?
4. What are some of the acute and chronic signs of HZO?
5. Why might a HZO patient not complain of symptoms?
6. What are the common signs and symptoms of neurotrophic keratitis?
7. What are treatments for mild vs. severe forms of neurotrophic keratitis?
8. What neural factors are used in treatment of neurotrophic keratitis?
9. How is the diabetic cornea different from the non-diabetic cornea?
10. What are some of the systemic, ocular and neurologic causes of neurotrophic keratitis?
11. What are the stages of neurotrophic keratitis?
12. What are some differentials for red eye?

## Case Description

Patient RT, a 76-year-old Caucasian male, was referred to the White River Junction Veterans Affairs Medical Center eye clinic on Aug. 8, 2012 for a red left eye that started two days prior. The patient was seen by an optometrist in the private sector who diagnosed the patient with bacterial conjunctivitis OS and prescribed ofloxacin QID OU. The patient reported feeling pressure in his left eye, as well as pain radiating down the left side of his face. He also had small erythematous, vesicular lesions on the left side of his face that also started two days prior.

RT's medical history was positive for diabetes mellitus type 2 for 18 years with associated complications of peripheral neuropathy, foot ulcers, dystrophic toenails, polyneuropathy, chronic urinary tract infections and kidney failure. The patient also had erectile dysfunction, arthralgia, stenosis of the carotid artery, spinal stenosis, colonic polyps, dysphagia, drop foot, hammer toe, hyperkeratosis, hypertension, suspect gout, and pulmonary embolism from unknown cause. The patient had a remote surgical history of lumbar discectomy.

RT's last visit to the eye clinic was March 29, 2006. His ocular history was positive for retinal Hollenhorst plaque OD, involutinal proliferative diabetic retinopathy with panretinal photocoagulation (PRP) OU, corneal epitheliopathy (likely diabetic neurotrophic cornea) OU, dry eye syndrome OU, pseudophakia OU and early dry macular degeneration OS.

His current medications included baclofen, camphor/menthol lotion, carbamazepine, clobetasol propionate ointment, colchicine, docusate, hydroxyzine, insulin (aspart and glargine), lisinopril, loperamide, metformin, naproxen, permethrin cream, psyllium, and triamcinolone cream. His fasting blood glucose measured at home the morning of his appointment was 127 mg/dl. He was not a smoker. His allergies included contrast media, terazosin and Augmentin.

Entering unaided visual acuities were OD 20/60-2 and OS 20/200-1 without improvement on pinhole. Notation was made that the patient was possibly viewing eccentrically with his left eye. Pupils were equally round and minimally reactive to light, without an afferent pupillary defect. During pupil testing, the patient reported that the trans-illuminator appeared dimmer in his left eye. Red cap desaturation testing revealed 40% desaturation OS.

Anterior segment evaluation revealed meibomian gland stasis OU, mild mucous discharge OS, and trace conjunctival hyperemia OS. Fluorescein dye evaluation of the corneas revealed 4+ diffuse punctate staining OS and trace punctate staining OD. There were no ulcerations, edema or dendrites in the cornea OU. The anterior chamber was deep and quiet OD but was difficult to assess OS through the corneal epithelial defects. Intraocular pressures were 11 mmHg OU by non-contact tonometry (NCT).

Dilated fundus examination revealed posterior chamber IOLs with peripheral fibrosis OU. The vitreous was clear and quiet OU. The optic nerves had distinct margins but there was moderate pallor of the rims. The C/D ratios were 0.35 round OU. The maculae had nearly complete geographic atrophy OU with a small central island of

retinal pigmented epithelium remaining, which was greater in size OD than OS. The peripheral retina had extensive PRP OU that encroached on the posterior pole. No hemorrhages were present OU.

The patient was diagnosed with HZ with V1 branch involvement. He was also diagnosed with chronic blepharitis-associated evaporative dry eye syndrome. He was prescribed oral famciclovir 500 mg Q8H and preservative-free artificial tears (carboxymethylcellulose 0.5%) Q1H OU, and was instructed to discontinue ofloxacin ophthalmic solution. Other diagnoses from the examination were diabetic optic atrophy OU and atrophic age-related macular degeneration OU, each contributing to and consistent with the decreased visual acuity. The patient was scheduled to return in one week to monitor the HZ and other conditions as needed

## Follow-up and management (Table 1)

**Visit #2 (8/15/12):** The small erythematous, vesicular lesions on the left side of the patient's face decreased in size. His pain also slightly improved. Visual acuity remained reduced at OD 20/70 and OS 20/400 uncorrected. Corneal staining was graded as 2+ diffuse SPK OD and 3+ diffuse SPK OS, without edema or dendrites OU. OCT imaging of the optic nerves and maculae were attempted to further evaluate the optic atrophy and atrophic macular degeneration. However, image quality was poor secondary to corneal staining and keratitis. The plan was to continue with oral famciclovir Q8H for three more days and change the artificial tears from carboxymethylcellulose 0.5% to 1.0% Q1H OU for additional viscosity.

**Visit #3 (8/23/12):** Visual acuity was OD 20/80+2 and OS 20/150-1 uncorrected. The skin lesions continued to reduce in size. Dermatomal facial pain symptoms were intermittent and not as severe as before. Corneal staining was noted to be 2+ diffuse OD and 3++ diffuse OS. There were also two new anterior stromal infiltrates near the superior limbus OS. One infiltrate was 1 mm in size and stained superficially; the other infiltrate was 1/3 mm in size and did not stain. The patient was diagnosed with stromal keratitis OS and

was prescribed prednisolone acetate 1% ophthalmic solution QID OS. Polysporin ophthalmic ointment BID OS and ciprofloxacin 0.3% ophthalmic solution QID OS were also prescribed for bacterial coverage. Carboxymethylcellulose 1.0% was continued Q1H to Q1.5H OU.

**Visit #4 (8/27/12):** Visual acuity was OD 20/70-1 and OD 20/150-1 uncorrected. Facial pain was reported to be less frequent and less severe. Corneal staining reduced to trace OD but increased to 4+ diffuse OS. The two stromal infiltrates OS reduced in size to 1/3 mm and 1/4 mm, with only the larger one staining. Only ciprofloxacin 0.3% ophthalmic solution was discontinued due to reduction of infiltrate sizes. The rest of the topical medications and artificial tears were continued as prescribed.

**Visit #5 (8/29/12) and #6 (9/5/12):** Visual acuities at these two visits were stable at about OD 20/70 and OS 20/150 uncorrected. Facial pain was also stable without increase. The degree of corneal staining improved to trace OD and 3+ diffuse OS. The stromal infiltrates OS had greatly reduced in size and appeared more faint. Follow-up was scheduled for two weeks. Polysporin ophthalmic ointment was discontinued and prednisolone acetate 1% ophthalmic solution was tapered to TID OS for one week, then BID OS for one week. Artificial tears were continued as before.

**Visit #7 (9/19/12):** Visual acuity was OD 20/70+2 and OS 20/150-1 uncorrected. Pain symptoms remained stable but the skin lesions were almost fully resolved. Corneal staining decreased to 2+ diffuse OS but increased to 1+ diffuse OD. The stromal infiltrates OS had completely resolved. The patient was dilated to obtain OCT images of the maculae and optic nerves. Preservative-free artificial tears were instilled every 5-10 minutes as the patient was dilating to prevent additional keratitis from the dilating drops. Fundoscopy revealed no changes OU.

OCT of the macula revealed thinning of the retinal tissue, mild disruption of the retinal pigmented epithelium, and no edema OU. However, the signal strength and image quality were much lower OS and an accurate assessment

**Table 1**  
**Summary of Follow-Up Visits**

Visit	Visual Acuity	Cornea	Other Signs/Symptoms	Treatment
8/8/12	OD: 20/60-2 OS: 20/200-1	Diffuse inferior SPK OD>OS	Pain/pressure left face Scattered lesions V1	Famciclovir Q8H Refresh Q1H OU
8/15/12	OD: 20/70 OS: 20/400	OD: 2+ diffuse staining OS: 3+ diffuse staining	Dec pain/pressure Dec lesion size	Famciclovir Q8H Celluvisc Q1H OU
8/23/12	OD: 20/80+2 OS: 20/150-1	OD: 2+ diffuse staining OS: 3++ diffuse staining 2 infiltrates 1 & 1/3 mm	Dec pain/pressure Dec lesion size	Celluvisc Q1H OU Pred F QID OS Polyspor BID OS Cipro QID OS
8/27/12	OD: 20/70-1 OS: 20/150-2	OD: trace staining OS: 4+ diffuse staining 2 infiltrates 1/3 & 1/4 mm	Dec pain/pressure Dec lesion size	Celluvisc Q1H OU Pred F QID OS Polyspor BID OS
8/29/12	OD: 20/70 OS: 20/150	OD: trace staining OS: 4+ diffuse staining 2 fainter infiltrates 1/3 & 1/4 mm	Stable pain/pressure Dec lesion size	Celluvisc Q1H OU Pred F QID OS Polyspor BID OS
9/5/12	OD: 20/70+2 OS: 20/150-1	OD: trace staining OS: 3+ diffuse staining; 2 fainter infiltrates 1/3 & 1/8 mm	Stable pain/pressure Dec lesion size	Celluvisc Q1H OU Pred F TID 1 wk then BID 1 wk OS
9/19/12	OD: 20/70+2 OS: 20/150-1	OD: 1+ diffuse staining OS: 2+ diffuse staining Infiltrates resolved	Dec pain/pressure Dec lesion size	Celluvisc Q1H OU Bland lubricating ointment BID OU
10/17/12	OD: 20/70-2 OS: 0/150+2	OU: 1-2+ diffuse SPK in scattered patches OS: 3 stromal scars all 1/4 mm	Intermittent face ache Skin lesions resolved	Celluvisc 4-6x per day OU

was difficult to make. OCT of the optic nerve fiber layers revealed OD borderline thinning of the superior quadrant, and OS thinning of the superior and inferior quadrants and borderline thinning of the nasal quadrant. Again, the signal strength was much lower OS because of signal interference from poor optics in the cornea.

Prednisolone acetate 1% ophthalmic solution was discontinued. Artificial tears were to be continued every 1.5 hours. Additionally, a bland lubricating ointment was prescribed QHS OU. The patient did not have any complaints about his vision and wished to lengthen the time until his next follow-up visit. A follow-up was scheduled for one month to check the anterior segments, corneal sensitivities, and follow-up on blood sugar control. Careful patient education was provided at this time as well. The patient was told that the eye was not entirely healed and he may not be able to feel disruption to his cornea because of nerve damage.

**Visit #8 (10/17/12):** The patient reported better blood sugar control. His fasting blood sugar that morning was 112 mg/dl. A left facial "ache" was still present, but improving. The facial skin

lesions had resolved. Visual acuity remained stable at OD 20/70-2 and OS 20/150+2 uncorrected. Corneal staining decreased to 1-2+ diffuse OU, with three superior stromal scars OS where the previous infiltrates were. Corneal sensitivity testing with a cotton wisp was noted to be equal and normal OU. The patient was instructed to continue artificial tears 4-6 times per day or as needed, and to return in 4-6 months for a dilated exam. Unfortunately, RT passed away on Jan. 9, 2013. The cause of death was unknown.

## Literature Review

### *Herpes zoster ophthalmicus*

The varicella-zoster virus (VZV), which belongs to the same herpes subfamily as herpes simplex, is responsible for causing both chickenpox (varicella) and shingles (herpes zoster).<sup>1</sup> After an initial infection of chickenpox, the VZV lays dormant in the dorsal root ganglia of a variety of nerves throughout the body, including the trigeminal nerve, which is affected in herpes zoster ophthalmicus. The most commonly affected dermatomes are in the thoracic region of the body, followed by the lumbar and cervical regions.<sup>2</sup> HZ can remain dormant for decades before reactivation

results from a decline in cell-mediated immunity.<sup>3</sup> This decline in immunity can result from increasing age, immunosuppressive conditions or medications.<sup>4</sup> Viral replication spreads along the dermatome of the affected ganglia, commonly presenting as a unilateral vesicular rash that does not cross the midline of the body.<sup>5,6</sup> The rash may affect one or two adjacent dermatomes (localized zoster) or be more widespread and affect three or more dermatomes (disseminated zoster).<sup>4</sup> Associated prodromal symptoms may include fever, headache, malaise or unilateral pain. Prodromal symptoms may occur days to weeks before the rash. It is common for individuals to have one episode of HZ in their lifetime. However, periodic episodes of reactivation may occur.<sup>4,6</sup>

In the United States, the incidence of HZ is 3.2 per 1,000 person-years. The incidence increases with age, with the highest rate in individuals over 80 years old. The incidence is also higher in patients with recent care for cancer, HIV infection, or transplantation compared to patients without these conditions.<sup>7</sup> HZ is uncommon in adults younger than 40 years old who are not immunocompromised. Younger patients tend to develop less severe forms of the disease and have better response to treatment.<sup>8</sup> HZO occurs when reactivation of the VZV involves the ophthalmic division (V1) of the trigeminal nerve and may be associated with ocular involvement. (Figure 1) The other two main divisions of the trigeminal nerve are the maxillary (V2) and mandibular (V3). (Fig-

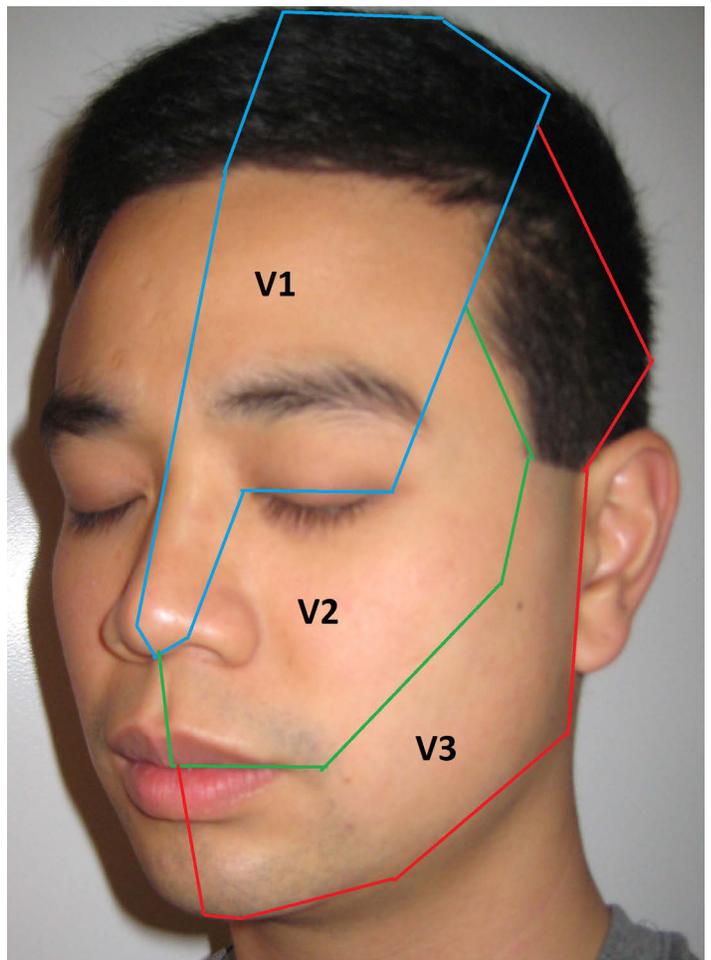
ure 2) The ophthalmic division further divides into the frontal, lacrimal and nasociliary branches. These branches innervate the forehead, upper eyelid, cornea, uvea, conjunctiva, sclera and the nose. The most common decade of onset of HZO is between 50 and 59 years of age.<sup>9</sup> Current standard of care recommendations for patients with HZ affecting the fifth cranial nerve include referral to an eyecare practitioner to rule out vision-threatening complications. Most patients with HZ affecting V1 experience very little ocular involvement.<sup>10</sup> Only 10-20% of HZ cases involving the fifth cranial nerve will have HZO.<sup>2</sup>

Ocular manifestations of HZO in the anterior segment may be acute or chronic, and the cornea is commonly

**Figure 1**  
**Unilateral Vesicular Rash Along V1 Dermatome in Herpes Zoster Ophthalmicus**  
 (Photo by Robert E. Sumpter, Image ID#12621, Centers for Disease Control and Prevention, Public Health Image Library.<sup>43</sup>)



**Figure 2**  
**Three Main Divisions of the Trigeminal Nerve**  
 (Original image created by author)



involved. Acute ophthalmic complications include acute epithelial keratitis, conjunctivitis, episcleritis, scleritis, nummular keratitis, stromal (interstitial) keratitis, disciform keratitis and anterior uveitis. Chronic complications include neurotrophic keratitis, scleritis, mucous plaque keratitis, lipid degeneration, lipid-filled granuloma and eyelid scarring.<sup>1,8</sup> Immunocompromised patients are more likely to have bacterial keratitis and poor visual outcome compared to immunocompetent patients.<sup>8</sup> Posterior segment manifestations are uncommon, and may include retinal perivasculitis, ischemic optic neuritis and necrotizing retinopathy.<sup>6</sup>

Acute epithelial keratitis, which develops in more than 50% of cases within two days of rash onset, may be characterized by dendritic lesions known as “pseudodendrites.” Pseudodendrites are elevated, opaque, white, fine branching or stellate plaque-like lesions that have tapered ends without terminal end bulbs. Pseudodendrites stain better with rose bengal than with fluorescein. These lesions are more likely to form in younger HZO patients. Pseudodendrites are treated with a topical antiviral, while the other forms of keratitis are treated with topical steroids, such as prednisolone acetate 1%.<sup>19</sup>

Decreased visual acuity and corneal sensation are common symptoms, and patients may complain of foreign body sensation, irritation, burning and dry eye symptoms.<sup>8</sup> In some patients with decreased corneal sensitivity there may be no symptoms of discomfort at all<sup>5</sup> due to neurotrophic corneal nerves branching from CN V1. Loss of corneal sensitivity can lead to breakdown of epithelium, which can in turn create inflammation (uveitis), secondary infection, corneal thinning, ulcers, corneal perforations and scarring.<sup>5,8</sup> Edema of the eyelids, ptosis, lagophthalmos or eyelid scarring may also lead to tear evaporation and corneal desiccation that ultimately results in damage to the corneal nerves.<sup>5,6</sup>

Oral antivirals are widely used to treat HZ. The most common oral antivirals used are acyclovir 800 mg five times a day, valacyclovir 1 g TID, and famciclovir 500 mg TID for 7-10 days.<sup>1</sup> These three antivirals have been shown to reduce pain, virus shedding and an-

terior segment complications when started within 72 hours of onset.<sup>11</sup> The less frequent dosing of valacyclovir and famciclovir compared to acyclovir increases the potential for patient compliance. Valacyclovir is a prodrug of acyclovir, and has been found to be equally effective in reducing ocular complications, zoster-associated pain and skin lesions.<sup>12</sup> A study of 86 immunocompetent HZ patients revealed that famciclovir may provide earlier reduction in zoster-associated pain compared to valacyclovir.<sup>13</sup>

In a study surveying 100 eyecare practitioners, the majority of them being corneal specialists, on treatment options for stromal keratitis and anterior uveitis associated with HZO, the most common treatment reported was a combination of oral antivirals and topical corticosteroids, with variability in the dosage and duration. The second most common treatment was topical corticosteroids alone. Oral antivirals are typically administered for 7-14 days, but there is no established guideline for the duration of antiviral treatment. The most common corticosteroid used to treat was prednisolone acetate 1% QID.<sup>14</sup>

Vaccination has been important in preventing the reactivation of VZV. The Shingles Prevention Study in 2005 found that the use of the Oka/Merck VZV vaccine (“zoster vaccine”) reduced the incidence of HZ by 51% and the incidence of post-herpetic neuralgia by 66% in immunocompetent individuals 60 years of age and older.<sup>15</sup> The U.S. Food and Drug Administration (FDA) approved Zostavax (Zoster vaccine live) in 2006, for individuals 60 years of age and older.<sup>16</sup>

In 2011, the FDA approved Zostavax for individuals 50-59 years of age.<sup>17</sup> However, the U.S. Centers for Disease Control and Prevention (CDC) still recommends the vaccine for 60 years of age and older despite the FDA approval.<sup>18</sup> Furthermore, vaccination rates are low for the 50- to 59-year-old age group due to lack of awareness or understanding of the vaccine. The rate increases for older age groups.<sup>19</sup>

### *Neurotrophic keratitis*

Neurotrophic keratitis is a corneal disease caused by an impairment of corne-

al branches of trigeminal nerve V1.<sup>20,21</sup> Loss or reduction of corneal innervation leads to compromised corneal integrity, tear dysfunction and decreased corneal sensation.<sup>6</sup> Dry eye syndrome often results because the tear reflex can be impaired.<sup>22</sup> Neurotrophic keratitis can lead to defective differentiation and delayed wound healing of epithelial cells, which in turn can result in corneal ulceration and even perforation without the patient feeling discomfort.<sup>9,22</sup> Neurotrophic keratitis occurs at a higher frequency with increasing age, and develops in about 20% of cases of HZO. Older individuals are also at increased risk for secondary corneal infections.<sup>9</sup>

A number of ocular, systemic and neurologic conditions can cause corneal hypoesthesia that leads to neurotrophic keratitis.<sup>23</sup> (Table 2) These include ocular surgery, trauma, topical medications, diabetes mellitus, contact lens wear, trigeminal neuralgia and others. Neurotrophic keratitis is divided into three stages known as the Mackie Classification.<sup>23</sup> (Table 3) Stage 1 is characterized by decreased tear breakup time and punctate epithelial staining. Stage 2 is characterized by stromal edema and loss of epithelium. Stage 3 is characterized by stromal lysis and corneal perforation.

Standard treatments for milder cases of neurotrophic keratitis include preservative-free artificial tears, punctal occlusion and bandage contact lenses. Antibiotic ointments may be used prophylactically to prevent infectious corneal ulcers. Steroids may be needed if the patient develops keratouveitis but should be used with caution due to the known side effect of reduction in wound healing. More severe cases may require surgery, such as tarsorrhaphy or conjunctival flap construction.<sup>20,22,24</sup> Large corneal defects may require penetrating keratoplasty; however, any surgical corneal intervention should be avoided due to further risks of corneal ulcers, melting and perforations after surgery.<sup>20</sup> Discontinuation of other non-essential topical drugs is necessary to reduce toxicity.<sup>20,24</sup>

Impairment of the trigeminal nerve causes an insufficient supply of neural factors, which leads to corneal epithelial disorder. These neural factors in-

clude substance P (SP) and insulin-like growth factor-1 (IGF-1).<sup>22</sup> Eye drops containing SP and IGF-1 have been shown to synergistically stimulate epithelial wound closure.<sup>25</sup> Derivatives of these neural factors (FGLM-amide and SSSR, respectively) have also been shown to promote resurfacing of persistent epithelial defects in neurotrophic corneas.<sup>26</sup> Autologous serum (AS) has also been shown to stimulate epithelial healing, improve corneal sensitivity, improve visual acuity and increase levels of SP and IGF-1 in individuals with neurotrophic keratitis.<sup>27</sup>

### *Diabetes mellitus and neurotrophic keratitis*

Neurotrophic keratitis may occur in patients with diabetes mellitus. Diabetic patients have reduced basal tear production and corneal sensitivity.<sup>28</sup> Neurotrophic keratitis should be a differential when a diabetic patient develops unexplained corneal epithelial disease.<sup>21</sup> Epithelial dysfunction puts diabetic patients at greater risk for corneal disorders such as recurrent corneal erosions, decreased sensitivity, delayed re-epithelialization, abnormal wound repair and ulcerations.<sup>29</sup> A study of corneal structure and sensitivity in type 1 diabetics found that corneal sensitivity is positively correlated with the number of long nerve fiber bundles in the cornea, and inversely correlated to the duration of diabetes. A significant decrease in long nerve fiber bundles was observed in patients with even mild neuropathy. However, corneal sensitivity may remain normal in patients with mild to moderate neuropathy. Epithelial thickness and corneal sensitivity are significantly decreased in patients with severe corneal neuropathy.<sup>30</sup>

### **Discussion**

The patient in this teaching case report presented with a red painful eye that was previously diagnosed as bacterial conjunctivitis and treated with a topical antibiotic. It is important for a clinician to consider the referring diagnosis; however, it is imperative that he/she differentiate the causes of red eye by careful clinical history and exam. Clinical history should include a careful detailed ocular and medical history. Older patients and other immunocompromised patients are more likely to have a

**Table 2**  
**Causes of Neurotrophic Keratitis/Corneal Hypoesthesia**

<b>Infection</b>
Herpes zoster Herpes simplex Leprosy
<b>Fifth Nerve Palsy</b>
Surgery (such as for trigeminal neuralgia) Neoplasia (such as acoustic neuroma) Aneurysms Facial trauma Congenital Familial dysautonomia (Riley-Day syndrome) Goldenhar-Gorlin syndrome Mobius syndrome Familial corneal hypesthesia Congenital insensitivity to pain with anhidrosis
<b>Topical Medications</b>
Anesthetics Timolol Betaxolol Sulfacetamide 30% Diclofenac sodium
<b>Corneal Dystrophies</b>
Lattice Granular (rare)
<b>Systemic Disease</b>
Diabetes mellitus Vitamin A deficiency
<b>Iatrogenic</b>
Contact lens wear Trauma to ciliary nerves by laser and surgery Corneal incisions LASIK
<b>Toxic</b>
Chemical burns Carbon disulfide exposure Hydrogen sulfide exposure

**Table 3**  
**The Mackie Classification**

<b>Stage 1</b>
Rose bengal staining of the palpebral conjunctiva Decreased tear breakup time Increased viscosity of tear mucus Punctate epithelial staining with fluorescein Scattered small facets of dried epithelium (Gault spots)
<b>Stage 2</b>
Acute loss of epithelium, usually under the upper lid Surrounding rim of loose epithelium Stromal edema Aqueous cells and flare Edges of the defect become smooth and rolled with time
<b>Stage 3</b>
Stromal lysis, sometimes resulting in corneal perforation

*Adapted from: Groos EB. Neurotrophic keratitis. In: Krachmer JH, Mannis MJ, Holland EJ (eds.) Cornea 2nd Ed: Fundamentals, Diagnosis and Management. Mosby: Philadelphia, 2005, p 1191.*

number of medical conditions and may be taking numerous medications that can broaden or change the differential significantly. The astute clinician pays attention to the systemic conditions that may have ocular manifestations and the systemic medications that may have ocular side effects and adjusts the differential and the physical exam accordingly.

A thorough case history was key in diagnosing this case. The patient had classic signs and symptoms of HZ, most notably a unilateral vesicular rash with ipsilateral facial pain following the V1 dermatome. The patient had acute manifestations of HZO in the form of epithelial keratitis and stromal keratitis. The patient's reduced acuity was not consistent with his presenting

corneal condition, which required additional testing. A clinician should be aware that there may be multiple causes of a patient's reduced visual acuity. The patient in this teaching case report had vision loss from a combination of neurotrophic keratitis secondary to HZO and diabetes, and atrophic macular degeneration. A good method for students to practice is to use the 'axis approach', where the major structures going from the front to the back of the eye along the visual axis are considered. This includes the cornea, the lens and the retina. A clinician should know how to address each cause and decide which ones can be treated and which ones should be monitored.

Additionally, HZ skin lesions typically appear as a vesicular rash covering a large area that respects the dermatome vertical midline. However, skin lesions can be widely scattered and difficult to identify if they are beyond the hairline. The patient in this case had several small, red lesions following the dermatome and respecting the midline but they were few in number and widely scattered. A clinician should be aware of the different presentations of the skin lesions that appear as erythema, macules, papules or vesicles.<sup>6</sup> (Figure 3) The presence of the rash in younger patients may be mistaken for other diseases, such as herpes simplex dermatitis, insect bites or poison ivy, which leads to incorrect management.<sup>9</sup>

Interestingly, the patient in this case was at first in disbelief that he had HZ simply because he had been vaccinated for it. The patient was educated that vaccinations do not work 100% of the time. However, in a study examining the incidence of recurrence of HZ in immunocompetent individuals less than 70 years of age, the incidence of recurrence was 0.99 and 2.20 cases per 1,000 person-years in vaccinated and unvaccinated individuals, respectively. Thus, regardless of vaccination status, there is still a low risk of recurrence of HZ.<sup>31</sup> The efficacy of the vaccine decreases one year after administration and continues to decline afterward. The efficacy of the vaccine is uncertain after five years.<sup>32</sup> Vaccinated individuals who developed HZ developed a milder form of the disease compared to unvaccinated individuals in one study.<sup>3</sup>

**Figure 3**  
**Vesicular Rash Due to the Varicella-Zoster Virus**  
(Photo by Joe Miller, Image ID#5409, Centers for Disease Control and Prevention, Public Health Image Library.<sup>43</sup>)



Unvaccinated individuals with a history of HZO must exercise caution if they decide to get vaccinated. Hwang et al. described the case of a 63-year-old male with a history of HZ keratouveitis and neurotrophic keratopathy who had been quiescent for 3.5 years, but developed keratouveitis two weeks after vaccination. Patients with a history of HZO may have persistent viral antigens. The live attenuated vaccine may induce recurrence of keratouveitis.<sup>33</sup>

Also, Hutchinson's sign was not evaluated in this patient. However, this sign can help predict the clinical outcome for the patient. Hutchinson's sign is positive if the patient reports pain or discomfort on the very tip of the nose on palpation. There may or may not be a rash in the cutaneous region of the terminal branches of the nasociliary nerve, which are at the tip, side and root of the nose.<sup>10</sup> Several studies have found that Hutchinson's sign is a strong predictor of ocular involvement and poor visual outcome in HZ patients.<sup>34,35,36</sup> Nithyanandam et al. found that other factors significantly associated with visual loss in HZO are anterior uveitis, acute epithelial lesions, neurotrophic keratitis and increasing age.<sup>34</sup> A positive Hutchinson's sign predicts about a 76% chance of ocular involvement, while a

negative Hutchinson's sign still has about a 34% chance of ocular involvement.<sup>37</sup> However, not all studies agree on the predictive value of Hutchinson's sign. Adam et al. 2010 instead found that blepharitis, eye redness and a rash in the supratrochlear nerve distribution (forehead above nasal bridge) were statistically significant associations with moderate to severe eye disease in HZ patients.<sup>10</sup>

The epithelial disease and neurotrophic keratitis that developed in the patient in this case required regular use of artificial tears in addition to pharmacological therapy. The artificial tears were a first-line defense in protecting the cornea and allowing it to heal. Another treatment consideration for this patient was bandage contact lenses. Soft contact lenses are used in the management of many corneal conditions to provide pain relief and mechanical protection, facilitate epithelial healing and maintain corneal hydration.<sup>38</sup> Silicone hydrogel lenses work as effective bandage contact lenses due to high oxygen permeability, low water content, good wetting properties and good patient comfort.<sup>39</sup> However, use of contact lenses is not without risks, such as increased risk of infections. The management of this patient was more cautious in order

to avoid introducing another potential complication. Furthermore, the patient was already very compliant with all his medications and his condition was improving.

It is important to note that the patient in this case had persistent pain along the affected dermatome that slowly resolved over the course of follow-up but not entirely. Two months after initial presentation, the patient continued to report an "ache" on the left side of his face. This was diagnosed as post-herpetic neuralgia (PHN), a pain that can persist throughout the acute phase of HZO and for many months afterwards. The pain can be severe and has been associated with depression and suicidal ideation if not controlled. PHN is the most common lingering symptom and most debilitating complication of HZ,<sup>6</sup> occurring in about 75% of patients over 70 years old.<sup>1</sup> A possible mechanism is inflammation and destruction of nerve roots. PHN is treated with opioids, topical analgesics, antidepressants and anticonvulsants according to the patient's individual needs.<sup>40</sup> Oral famciclovir and valacyclovir are more effective than acyclovir in treating PHN. These oral antivirals can reduce the severity of PHN, but they do not prevent it.<sup>11</sup> Studies have shown that the use of cimetidine, an H2 antihistamine receptor antagonist, shortened the time to heal pain and skin lesions in HZ patients, although the mechanism for immunomodulation is not completely understood.<sup>41,42</sup>

In general, the patient in this case was followed very closely at first. As his condition became more controlled, the interval between follow-ups became longer. The patient did become frustrated with the number of follow-up visits required because of the lack of acute pain and improved acuity over time. After several visits, the patient did not have any complaints about his vision and wanted to be seen much later for his next follow-up, despite the fact that there were persistent signs of inflammation and neurotrophobia. Patients are often aware of their reduced vision; however, the corneal esthesia associated with an HZO infection may elude the patient and lead to a false understanding of the resolution of the disease process. The patient in this case did not

initially understand why he needed to continue to come back for follow-up. Careful patient education was key in managing the patient's corneal disease. Pseudodendrites, keratitis, inflammation or loss of stromal clarity are often present with few symptoms, so it is important to understand the course of neurotrophic keratitis.<sup>5</sup>

## Conclusion

Any HZ patient with V1 branch involvement should be referred for an eye exam. HZO affects up to 20% of HZ cases involving the fifth cranial nerve dermatome. It can lead to a host of acute or chronic ocular conditions, many of which involve the cornea. Thus, timely and accurate management is important in preventing further damage and vision loss. Still, the most debilitating complication of HZ is PHN. Older patients should be monitored more carefully and treatment should be more aggressive, as the incidence and severity of the disease increase with age. Vaccination is helpful in reducing the incidence of HZ and PHN, but recurrence is possible and the long-term efficacy of the vaccine is uncertain. Neurotrophic keratitis may complicate treatment, exacerbating the corneal damage and prolonging therapy. Patients may complain of various ocular symptoms or have no symptoms at all. Good patient history, careful observation and aggressive treatment are imperative in managing patients with HZO.

**Disclosure:** Dr. Dorothy Hitchmoth is a consultant for Annidis Health Systems Corporation and is on the speakers bureau for Zeavision.

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