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Clinical course of von Szily reaction: Case report and comprehensive review of the literature

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ABSTRACT

Purpose: To describe a rare case of von Szily reaction (VSR) accompanied by a comprehensive review of the literature.

Observations: A 57-year-old woman with herpes zoster ophthalmicus (HZO) associated with ipsilateral sectoral scleritis and anterior uveitis (sclerouveitis) subsequently developed contralateral necrotizing retinitis, leading to a diagnosis of VSR. A literature review revealed 10 additional cases of VSR. The full VSR cohort of 11 subjects included six women and five men, had a median age of 39 years (range 21–78 years), and most presented with HZO (n = 7, 63.6%), often associated with either ipsilateral anterior uveitis (n = 5; 45.5%) or keratitis (n = 4; 36.4%). All 11 cases developed necrotizing retinitis in the fellow eye, at a median of six weeks following onset in the sentinel eye. The most frequently implicated agent was varicella zoster virus (VZV; n = 8, 72.7%). A high proportion of the eight patients with VZV-associated VSR were identified as having increased risk of VZV reactivation, including age of 50 years or greater (n = 5, 62.5%), an underlying malignancy (n = 3, 37.5%), and/or use of immunosuppressive medication (n = 2, 25.0%).

Conclusion: This was the first reported case of VSR presenting as HZO-associated with sclerouveitis. A comprehensive literature review revealed that most previously reported cases presented with HZO associated with isolated anterior uveitis and/or keratitis, and that all reported cases of VSR developed necrotizing retinitis in the fellow eye, typically within two months of initial presentation. Patients with VZV-associated VSR often had known risk factors for VZV reactivation.

1. Introduction

Von Szily first reported that rodents given an intracameral inoculation of herpes simplex virus type-1 (HSV-1) in one eye developed ipsilateral anterior uveitis followed by contralateral necrotizing retinitis.[1] This unique pattern of bilateral, sequential herpetic uveitis has since been shown to occur via viral spread along parasympathetic fibers of the oculomotor nerve to the ipsilateral ciliary ganglion, then to the Edinger-Westphal nucleus, thereafter to the suprachiasmatic area of the hypothalamus, and finally crossing over to the contralateral optic tract, optic nerve and retina.[2] Sparing of the ipsilateral retina is believed to be mediated by $CD4^+$ and $CD8^+$ T-cell dependent mechanisms.[3,4] While von Szily's observations have been reproduced and studied further in several animal models,[5,6] reports of the phenomenon in humans have been rare. When observed, this unique series of events has been referred to clinically as the von Szily reaction (VSR).[7]

To the best of our knowledge, a total of 10 previous clinical reports of VSR have appeared in the literature.[7–14] We added here an eleventh case, the first wherein herpes zoster ophthalmicus (HZO) was accompanied by sclerouveitis at presentation. A comprehensive review of the 11 total reported cases was performed.

2. Case report

A 57-year-old Caucasian woman presented with left-sided HZO associated with sectoral scleritis (Fig. 1A) and anterior uveitis (sclerouveitis). She previously received a four-day course of oral corticosteroid for left-sided periorbital pain and edema. A week later, an outside

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ophthalmologist diagnosed her with left-sided HZO and anterior uveitis, and initiated treatment with oral acyclovir and topical corticosteroid drops. Best-corrected vision and intraocular pressures were normal bilaterally. The patient admitted poor compliance with recommended treatment, but noted symptomatic improvement in the left eye. Three weeks later she experienced decreased vision and floaters in her right eye. Repeat examination revealed a best-corrected vision of 20/60 on the right and 20/20 on the left, improved sclerouveitis on the left, and new onset moderate vitritis and peripheral, multifocal necrotizing retinitis on the right (Fig.1B). Serologic workup for syphilis, tuberculosis, sarcoidosis, toxoplasmosis, and human immunodeficiency virus was negative, but polymerase chain reaction (PCR)-based testing of aqueous humor detected varicella zoster virus (VZV) DNA. The patient was diagnosed with unilateral HZO with sclerouveitis followed three weeks later by contralateral necrotizing zoster retinitis, a clinical picture consistent with VSR. Oral valacyclovir, 2000 mg twice daily, was added to the topical corticosteroid and cycloplegic/mydriatic drops used to control her anterior uveitis, and then 1 mg/kg/day of oral prednisone was added 10 days later. At the last examination, the patient showed no signs of scleritis, uveitis, or retinitis in either eye and her best-corrected visual acuity had improved to 20/32 on the right and 20/20 on the left.

3. Methods

A literature review was performed on PubMed and Google Scholar using the search term "von Szily." Published citations describing VSR were reviewed and additional citations were gleaned from the lists of referenced papers. Publications describing clinical cases of VSR were reviewed for the patient's demographic information, immune status, viral agent, mode of testing, findings in the presenting eye, treatment for the presenting eye, time to fellow eye involvement, findings in contralateral eye, treatment for the contralateral eye, time to last visit, and both anatomic disposition and vision in presenting and fellow eye at last visit. Subjects 50 years of age and older, with an underlying malignancy, and/or receiving immunotherapeutics were considered to be at increased risk for VZV reactivation.[15–21]

4. Results

A comprehensive literature review identified eight reports[7–14] with a total of 10 previously described patients with VSR. The addition of our case brought the total to number of subjects to 11 (Table 1). Age at presentation ranged from 21 to 78 years, with mean of 45.3 years and median of 39 years. Five of the subjects were male and six were female (M:F ratio 0.83:1) Causative agents were uncovered through PCR (45.4%), serology (36.4%), or vitreous biopsy with viral culture (9.1%). Two eyes (18.2%) lacked any viral testing; one was given a clinical diagnosis of presumed VZV. Varicella zoster virus (VZV) was the most commonly implicated agent (72.7%), with herpes simplex (HSV) type 1 and type 2 detected in one case each (9.1%). A high proportion of the eight patients with VZV-associated VSR were identified to possess increased risk of VZV reactivation due to age (50 years or greater; n = 5, 62.5%), an underlying malignancy (37.5%), and/or use of immunosuppressive agents (25.0%). The most common findings in the presenting eye included HZO (n = 7; 63.6%), anterior uveitis (n = 5; 45.5%) and keratitis (n = 4; 36.4%). Ipsilateral cranial nerve palsy (n = 2; 18.2%), sectoral scleritis (n = 1; 9.1%), and ipsilateral acute retinal necrosis (ARN; n = 1, 9.1%) were also reported. Management approaches to the presenting eye included observation (n = 4, 36.4%), treatment with topical corticosteroids (n = 6, 54.5%), oral antiviral medication (n = 4, 36.4%), topical antiviral agents (n = 3, 27.3%), and/or oral corticosteroids (n = 2, 18.2%). All 11 patients (100%) developed contralateral necrotizing retinitis, and nine of those eyes (81.8%) were diagnosed clinically as having acute retinal necrosis (ARN). Time to fellow eye involvement ranged from 2 weeks to 21 years, with a median of 6 weeks. Fellow eyes received treatment with systemic antiviral medications (n = 10, 90.9%), topical corticosteroids (n = 7, 63.6%), systemic corticosteroids (n = 5, 45.4%), intravitreal antiviral medications (n = 1, 9.1%), and/or topical antiviral medications (n = 1, 9.1%). Time to last visit ranged from 3 weeks to 3.5 years, with a median of 8.5 weeks. Anatomic disposition of the presenting eyes at last visit was most commonly unremarkable (63.6%), but corneal scarring, sectoral iris atrophy, pigmented retinal scars, and total retinal detachment were each observed in one case (9.1%). Visual acuity in the presenting eyes at last visit ranged from 20/16 to no light perception (NLP), with a median of 20/30. Nine (81.8%) fellow eyes were described to have resolution of the retinitis with an attached retina at last examination. Four of these eyes (36.4%) were treated with prophylactic laser barricade, with one still progressing to retinal detachment. Two (18.2%) eyes underwent successful surgical repair of retinal detachments. One contralateral eye each (9.1%) had optic neuropathy and had total rhegmatogenous retinal detachment at last visit. The outcome of one eye (9.1%) was not described. Visual acuity in contralateral eyes at last visit ranged from 20/16 to NLP, with median of 20/40.

5. Discussion

A 58-year-old woman developed unilateral HZO with sclerouveitis and was found to have necrotizing retinitis in her contralateral eye three weeks later, a clinical picture consistent with VSR. Of the 11 total reported subjects with VSR (Table), the majority presented with HZO, frequently with anterior uveitis, keratitis, or both. A contralateral necrotizing developed in all cases, typically within two months. Among those with VZV-associated VSR, the presence of one or more risk factors

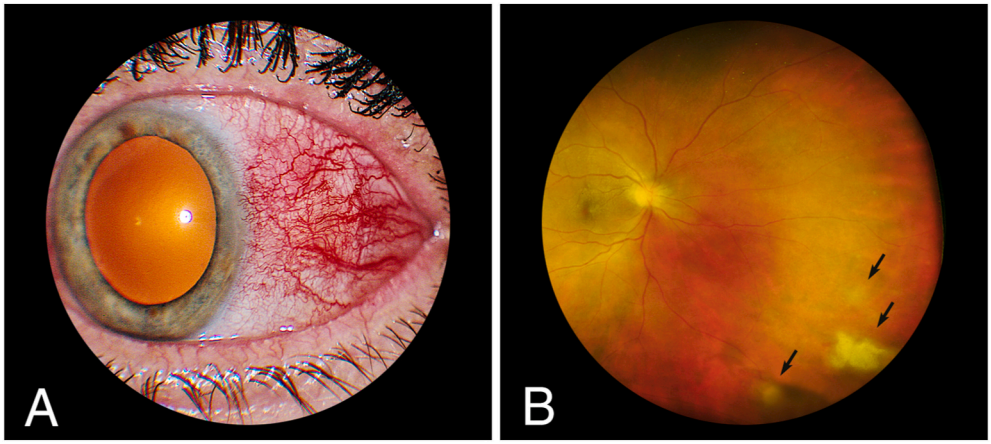

Fig. 1. (A) External photograph of the right eye showed temporal, sectoral scleritis in the setting of herpes zoster ophthalmicus. (B) Widefield (Optos®) fundus photograph of the left eye revealed mild vitritis and patchy necrotizing retinitis in the nasal inferotemporal periphery (arrows). Both images were taken three weeks after initial presentation, concurrent with onset of symptoms in the secondarily involved eye. External photograph was taken after the installation of phenylephrine and tropicamide, confirming the presence of scleritis as opposed to either episcleritis or conjunctival injection.

Table 1
Clinical Characteristics of Report Cases of von Szily Reaction.

Author	Age	Sex	Immune Status	Virus	Testing	Initial Eye	Findings in Presenting Eye	Treatment for Presenting Eye	Time to Contralateral Eye Involvement	Findings in Contralateral Eye	Treatment for Contralateral Eye	Final anatomic disposition Initial Eye	Final anatomic disposition Contralateral Eye	Time to Last Visit	Final Vision Initial eye	Final Vision Contralateral eye
Ng et al.,2020	58y	F	Compromised (Steroid exposure[b] Elderly)	VZV	PCR	OS	HZO Anterior uveitis Sectoral Scleritis[e]	PO Acyclovir and Corticosteroids Prednisolone eyedrops	3w	Patchy necrotizing retinitis	PO Valacyclovir and Prednisone Prednisolone and Cyclopentolate eyedrops	Unremarkable	Attached Resolved retinitis	1.6y	20/20	20/32
Smith et al.,2007	21y	F	Competent	HSV-2	PCR of Vitreous biopsy	OS	Congenital HSV-2 keratitis	None	21y	ARN	Intravitrea Foscarnet PO Acyclovir, Prednisolone and Cyclopentolate eyedrops	Corneal scarring	Undisclosed	8w	Undisclosed	20/50
Smith et al 2007	30y	M	Competent	VZV[c]	none	OS	Recurrent keratouveitis since age 10, last flare 5y prior to presentation	Prednisolone eyedrops	5y	Patchy retinitis	Prednisolone and Trifluridine eyedrops PO Acyclovir	Peripheral pigmented retinal scars	Resolved retinitis	Undisclosed	Undisclosed	undisclosed
Matthews et al., 2002	32y	F	Compromised (SLE[d])	VZV	PCR	OD	HZO Keratouveitis,	PO Famciclovir, Acyclovir and Prednisolone eyedrops	4w	ARN	IV Acyclovir, Prophylactic laser barricade SB/PPV for RRD,	Sectoral iris atrophy	Attached s/p SB/PPV Resolved retinitis Epiretinal membrane	3.5y	20/30	HM
Matthews et al., 2002	39y	M	Compromised (Hodgkin's disease, in remission)	VZV	PCR	OS	HZO Keratouveitis	PO Famciclovir Acyclovir and Dexamethasone eyedrops	4w	Early ARN	IV Acyclovir Prophylactic laser barricade,	Unremarkable	Attached Resolved retinitis	1.25y	20/20	20/20
Nakanishi et al.,2000	64y	M	Compromised (Stage 4 lung adenocarcinoma Elderly)	VZV	Serology PCR	OS	HZO	Acyclovir ointment	4w	ARN	IV Acyclovir PO prednisone and ASA Corticosteroid eyedrops Prophylactic laser barricade	Unremarkable	Attached, Resolved retinitis	3.5w	20/16-1	20/16-1
Farrell et al.,1991	64y	M	Compromised (Elderly)	VZV	Serology	OD	HZO Anterior uveitis CN 3 palsy	PO Acyclovir Corticosteroid eyedrops	7w	ARN	IV Acyclovir PO Prednisone, Corticosteroid eyedrops Prophylactic laser barricade	Unremarkable	Attached Resolved retinitis Optic nerve pallor	6w	20/100	LP
Lewis et al., 1989	27y[a]	M	Competent	HSV-1	Viral Culture From Diagnostic Vitrectomy	OS	Unknown	None	Unknown	ARN	IV Acyclovir and Methylprednisolone PO prednisone	Unremarkable	Total RRD	4w	20/20	NLP
Browning et al.1987	78y	M	Compromised (Elderly)	VZV	Serology	OS	HZO CN 4 palsy,[f] anterior uveitis	None	7w	ARN	PPV with infusion of Acyclovir PO Acyclovir, Prednisolone eyedrops	Unremarkable	Attached Resolved retinitis	3w	20/30	20/25
Yeo et al., 1986	59y	F	Compromised (endometrial	VZV	Serology	OS	HZO	None	6w	ARN	Corticosteroid and mydriatic	Unremarkable	Attached s/p SB/PPV	9w	20/30	LP

(*continued on next page*)

Table 1 (*continued*)

Author	Age	Sex	Immune Status	Virus	Testing	Initial Eye	Findings in Presenting Eye	Treatment for Presenting Eye	Time to Contralateral Eye Involvement	Findings in Contralateral Eye	Treatment for Contralateral Eye	Final anatomic disposition Initial Eye	Final anatomic disposition Contralateral Eye	Time to Last Visit	Final Vision Initial eye	Final Vision Contralateral eye
			carcinoma in remission Elderly)								eyedrops IV and PO Acyclovir PO Prednisone SB/PPV for RRD		Resolved retinitis			
Fisher et al.,1981	26y	F	Compromised\ (Steroid exposure)	unknown	N/A	OS	ARN	Corticosteroid and Mydriatic eyedrops Systemic and periocular Corticosteroids, Antibiotics.	2w	ARN	None	Total RRD with multiple breaks	Attached Resolved retinitis	2y	NLP	20/20
n = 11	Mean 45.3y Median: 39y Range 21-78y	M: F 6:5	Compromised 63.4% Competent 36.6.%	VZV 72.7% HSV-1 9.1% HSV-2: 9.1% unknown 9.1%	PCR 45.4% Serology36.4% Culture 9.1% None 18.2%	OD: OS 2:9	HZO 63.6% Keratouveitis 54.5% CN palsy 18.2% Sectoral Scleritis 9.1% Keratitis9.1% ARN 9.1% Unknown 9.1%	Topical Corticosteroid 54.5% PO Antiviral 36.4% None 36.4% Topical Antiviral 27.3% Oral Corticosteroids 18.2%	Median 6w Range: 2w-21y	Retinitis 100% ARN 81.8%	Systemic Antiviral90.9% Topical Corticosteroids 63.6% Systemic Corticosteroids 45.4% Laser Barricade 36.4% RRD repair18.2% Intravitreal Antiviral 9.1% Topical Antiviral 9.1%	Unremarkable 63.6% Total RRD 9.1% Corneal Scarring 9.1% Sectoral Iris Atrophy 9.1% Pigmented Retinal Scars9.1%	Attached with Resolved retinitis 81.8% Total RRD 9.1% Optic neuropathy 9.1% Undisclosed 9.1%	Median 8.5w Range] 3w-3.5y	Median 20/30 Range 20/16-NLP	Median 20/40 Range 20/16-NLP

Legend: w - weeks, y - years, M – male, F - female, OD - right eye, OS - left eye, SLE - systemic lupus erythematosus, VZV - varicella zoster virus, HSV - herpes simplex virus, PCR - polymerase chain reaction, N/A - not applicable,HZO - herpes zoster ophthalmicus, CN - cranial nerve, ARN - acute retinal necrosis, SB - scleral buckle, PPV - pars plana vitrectomy, RRD - rhegmatogenous retinal detachment, HM - hand motion, LP - light perception, NLP - no light perception, PO - by mouth, IV - intravenous, ASA - acetylsalicylic acid.

[a] Smith et al. made diagnosis of von Szily reaction based on concurrent ipsilateral keratouveitis and acute retinal necrosis with magnetic resonance imaging changes involving both optic tracts, lateral geniculate ganglia, temporal lobes, and the midbrain.

[b] Patient treated with “five tablets” of oral prednisone daily for four days after she presented with early symptoms of HZO OS to local urgent care.

[c] Clinical diagnosis of VZV.

[d] Treated with pulsed cyclophosphamide and methylprednisolone.

[e] Sectoral scleritis was present on examination of the initial eye when necrotizing retinitis was diagnosed in the contralateral eye.

[f] Authors described a left hypertropia worse on right gaze and left head tilt.

for VZV reactivation was common.

Similar to animal models wherein intracameral herpes virus inoculation led to ipsilateral anterior uveitis followed by contralateral retinal necrosis within one or two weeks,[1–5] patients with VSR typically have unilateral, anterior herpes virus infection followed by necrotizing retinitis in the fellow eye within two months. Several cases have, however, differed in noteworthy ways. For example, a 27-year-old man (Lewis et al.,[11] Table 1) with unilateral necrotizing retinitis was retrospectively diagnosed with VSR based on magnetic resonance imaging of the brain, which revealed bilateral enhancement of the anterior and posterior visual pathways.[7] In addition, two patients with a remote history of keratitis and onset of contralateral retinitis five and 21 years following their last episode of keratitis were also classified as having a VSR.[7] Lastly, a 26-year-old woman (Fisher et al.,[8] Table 1) with necrotizing retinitis in the presenting eye followed two weeks later by necrotizing retinitis in the fellow eye was retrospectively diagnosed with a VSR,[7] despite the fact that 10–12.9%[22,23] of patients with necrotizing retinitis who receive antiviral treatment and 27.3–69.6%[8,23] of patients who do not receive such treatment will eventually develop necrotizing retinitis in the fellow eye - a series of events not typically classified as VSR, but traditionally as bilateral ARN (BARN).[24]

Since the diagnosis of a VSR requires the presence of necrotizing retinitis and because necrotizing herpetic retinitis is most often due to VZV,[24] it is perhaps not surprising that VZV was implicated in most clinical reports of VSR. As the diagnosis of VSR also requires the presence of anterior infection in the presenting eye, and the most common cause of VZV-related anterior uveitis is HZO,[25] it follows therefore that most cases of the VSR began as HZO.

Of eight cases of VZV-associated VSR, all but one had one or more risk factors for VZV reactivation. Nearly two-thirds were ≥50 years of age, just over one-third had an underlying malignancy, one quarter received treatment with immunotherapeutics, and just over one-third possessed a combination of the above mentioned risk factors. Each of these risk factors have been associated separately with VZV reactivation.[17–21]

While all seven cases of conventional VSR possessed risk factors for impaired immunity and VZV reactivation, an absence of early systemic antiviral therapy in some patients may have also played a role in the subsequent development of contralateral retinitis. Specifically, just four of these patients (57.1%) received early systemic antiviral treatment, two (28.7%) received no treatment, and one (14.3%) only topical acyclovir in the presenting eye.

Our case is the first report of VSR presenting initially as HZO associated with sclerouveitis. Herpetic scleritis is an acute, unilateral condition, often associated with moderate to intense pain.[26] Patients with herpetic scleritis are three times more likely to have vision loss compared to non-infectious scleritis.[26]

Most patients with VSR retained vision better than or equal to 20/30 in both eyes following treatment with systemic antiviral medications and topical or systemic corticosteroid mediations. However, eyes that developed optic nerve involvement (n = 1) or retinal detachment (n = 4) had a final visual acuity that ranged from hand motion to no light perception. Contralateral eyes with necrotizing retinitis accounted for four of the five eyes left with poor vision at final visit. Three of the five eyes that were left with poor vision at final visit failed to receive early systemic antiviral therapy, perhaps further supporting the use of early systemic antiviral treatment in patients with HZO.

6. Conclusion

The VSR is a rare clinical syndrome characterized by bilateral, consecutive, ocular herpes virus infection. The vast majority of cases were associated with VZV, most commonly presenting as HZO with anterior uveitis, keratitis, or both. Patients with VSR were often relatively immunosuppressed and prone to VZV reactivation by dint of age or underlying medical conditions. All reported VSR patients developed necrotizing retinitis in the fellow eye, usually within two months, which resulted in poor long-term vision in one-third of these eyes. Patients who develop HZO and possess one or more underlying factors for impaired immunity should be counseled regarding signs and symptoms of contralateral eye involvement and undergo bilateral, dilated eye examination both at presentation and during follow up visits. Consideration should be given to early, systemic anti-viral therapy in patients who develop HZO.

Patient consent

The patient consented to the publication of the case in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None of the authors have any financial disclosures.

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