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NEURORETINITIS ASSOCIATED WITH COVID-19 INFECTION AND VARICELLA-ZOSTER VIRUS REACTIVATION

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Purpose: To report a case of neuroretinitis as the presenting manifestation of COVID-19 infection alongside varicella-zoster virus reactivation, in the absence of other systemic symptoms.

Methods: A case report.

Results: A previously healthy 15-year-old boy presented with a 1-week history of acute unilateral visual loss and clinical findings consistent with neuroretinitis. Diagnostic work-up revealed a positive polymerase chain reaction test of nasopharyngeal swab for COVID-19 and serology showed the presence of immunoglobulin M and immunoglobulin G antibodies for varicella-zoster virus. After a comprehensive treatment regimen involving IV acyclovir, high-dose IV steroids, and oral doxycycline, rapid and remarkable improvements were observed. The macular star and optic disk swelling regressed, and visual acuity improved from 20/200 to 20/20.

Conclusion: This case offers valuable insights into the neuroretinitis associated with COVID-19 infection and varicella-zoster virus reactivation.

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Neuroretinitis is characterized by optic nerve edema and stellate macular exudate secondary to optic nerve inflammation. The etiology is diverse and should be determined early in the evaluation process to guide management.[1] Herein, we report a unique case of neuroretinitis associated with COVID-19 infection, alongside positive serology for varicella-zoster virus (VZV), suggesting VZV reactivation, in the absence of other systemic symptoms.

Case Report

A healthy 15-year-old boy presented with a 1-week history of decreased visual acuity in his left eye, associated with pain on eye movement. He reported no systemic symptoms or signs such as flu-like symptoms, fever, fatigue, headache, dyspnea, or skin rash. He confirmed recent contact with animals, including cats. The medical history was significant for having had chickenpox. On presentation, visual acuity was 20/20 in the right eye and 20/200 in the left eye. There was a relative afferent pupillary defect in the left eye. There was vitritis, optic disk edema, hard exudates within the macula in a stellate pattern, perivascular sheathing, and intraretinal hemorrhages along the vein in the inferior temporal arcade, which extended to the midperiphery (Figure 1A). Examination of the right eye was unremarkable, as was neurologic examination.

Optical coherence tomography showed hyperreflective dots in the vitreous cavity, disk swelling, retinal thickening in the

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Patient consent was obtained for the use of his medical information and any accompanying images in this article.

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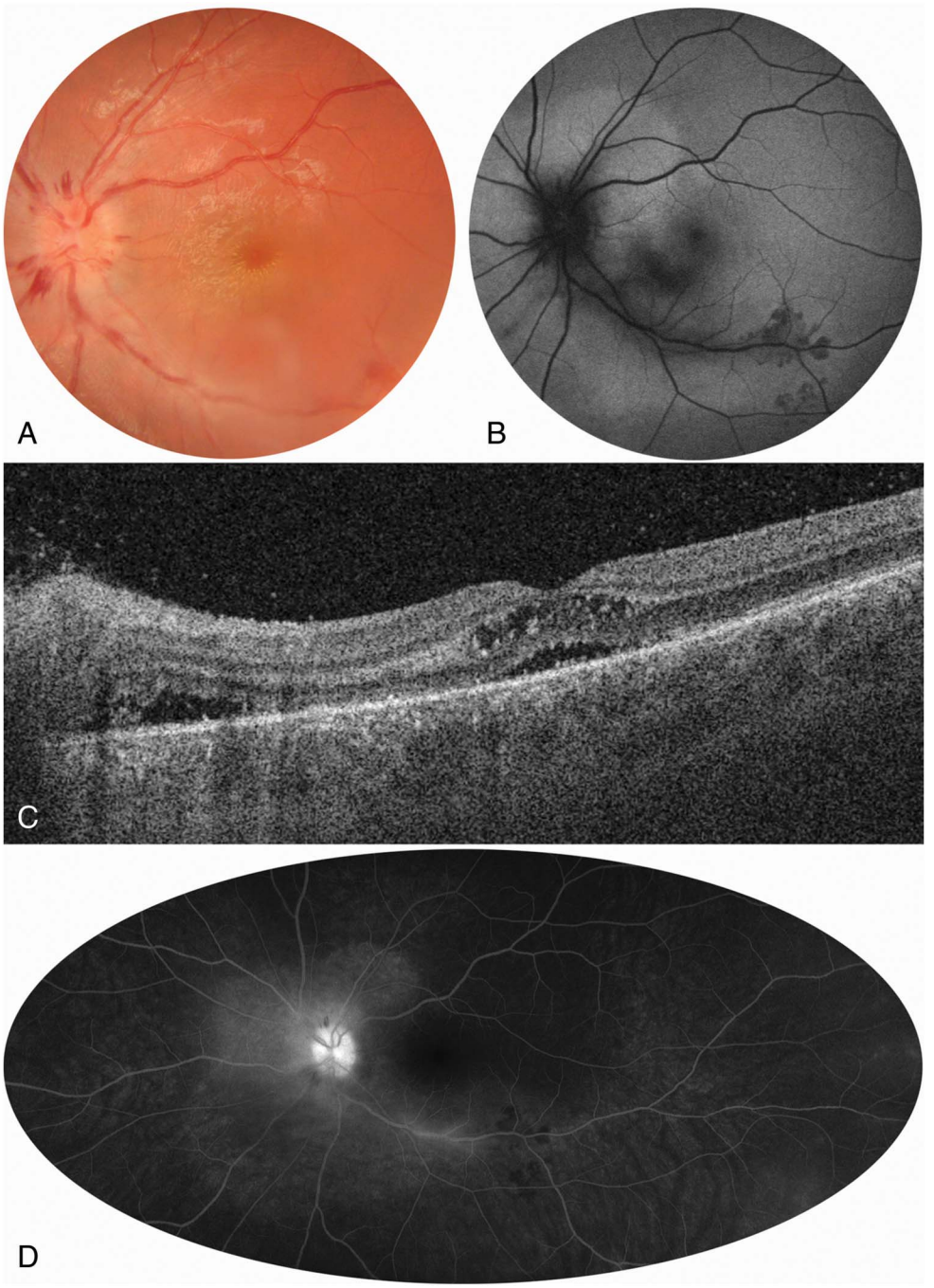

Fig. 1. A. Fundus photograph of the left eye demonstrating peripapillary swelling, hemorrhages, hard exudates in a stellate pattern with perivascular sheathing, and intraretinal hemorrhages along the vein in the inferior temporal arcade. **B.** Baseline macular optical coherence tomography shows nasal and subfoveal subretinal fluid, outer retinal irregularity, and hyper-reflective foci in the outer plexiform layer corresponding to hard exudates. **C.** Fundus autofluorescence demonstrating peripapillary hyperautofluorescence in the area of serous retinal detachment and hypoautofluorescence around the inferior temporal vein corresponding to perivascular intraretinal hemorrhages and thickening of inner retinal layers. **D.** Late-phase fluorescein angiography demonstrating late leakage at the optic disk and inferior temporal vein.

macula with intraretinal and subretinal fluid, and intraretinal hyper-reflective foci corresponding to hard exudates (Figure 1C). Fluorescein angiography showed late leakage at the optic disk and along the inferior temporal retinal vein (Figure 1D). Fundus autofluorescence revealed peripapillary hyperautofluorescence in the area of serous retinal detachment and hypoautofluorescence around the inferior temporal vein corresponding to perivascular intraretinal hemorrhages and thickening of the inner retinal layers (Figure 1B). On indocyanine green angiography, no abnormalities were seen in the choroidal vessels. Visual field examination of the left eye revealed a visual field defect in the superior aspect. Optical coherence tomography, fluorescein angiography, indocyanine green angiography, and visual field analysis of the right eye were unremarkable.

An extensive laboratory work-up including tests for Bartonella, Lyme disease, syphilis, tuberculosis, toxoplasmosis, toxocariasis, herpes simplex virus type 1 and type 2 (HSV-1, HSV-2), cytomegalovirus, antiaquaporin 4 Ab, antimyelin oligodendrocyte glycoprotein, angiotensin-converting enzyme, antinuclear antibody and antineutrophil cytoplasmic antibody, and rheumatoid factor all returned negative. We admitted the patient during the global

COVID-19 pandemic, so routine testing for COVID-19 was conducted on admission. A diagnostic evaluation revealed a positive polymerase chain reaction (PCR) of a nasopharyngeal swab for COVID-19 and the presence of both immunoglobulin M and immunoglobulin G antibodies for VZV. In addition, aqueous humor sampling for reverse transcription polymerase chain reaction was conducted and was negative for COVID-19, VZV, HSV-1, HSV-2, and cytomegalovirus.

The patient was initially treated with IV acyclovir (10 mg per kg, every 8 hours for 10 days), followed by oral valacyclovir (500 mg daily for 5 weeks) and empirical oral doxycycline (100 mg twice daily for 2 weeks). And 72 hours after the start of antiviral treatment, high-dose pulse steroid therapy was added (methylprednisolone intravenously 500 mg daily for 3 days), followed by oral steroids tapered off for the next 5 weeks.

Five days after starting treatment, optical coherence tomography imaging showed complete absorption of both intra- and subretinal fluid, and visual acuity improved to 20/40 (Figure 2). After 1 month, further progress was noted with visual acuity reaching 20/20. The COVID-19 PCR test was negative 7 days after presentation. Varicella-zoster virus-immunoglobulin M titers were also negative, and immunoglobulin G titers had declined. The patient remained stable at all follow-up visits for at least 18 months after the initial presentation, with the right eye remaining unaffected.

Discussion

COVID-19 and VZV are each identified as potential, though extremely rare, causes of neuroretinitis.[2–6] In reported cases of COVID-19-associated neuroretinitis, systemic signs of infection were present.[2,5] Our case stands out because of the absence of extraocular symptoms. It has been demonstrated that ocular manifestations can occasionally be the first or even the sole indication of COVID-19.[3] In addition, pediatric COVID-19 generally presents with mild symptoms, and lower respiratory tract symptoms are usually less prominent in children than in adults.[7] It is suspected that COVID-19 infection may have contributed to the reactivation of VZV, because patients with COVID-19 are at a clinically relevant risk for VZV reactivation. This interaction is believed to result from the impaired cellular immunity characteristic of COVID-19.[8] We cannot confirm whether the neuroretinitis in our case is caused by both viruses or primarily by one virus. Neuroretinitis caused by VZV is known as varicella-zoster virus-associated neuroretinitis, and it can be confirmed by PCR testing of aqueous humor. Alternatively, the etiology can be established through clinical presentation, such as a vesicular rash occurring close in time to the neuroretinitis, or through serology.[4] In our case, positive immunoglobulin M and immunoglobulin G antibodies indicated VZV reactivation, but the aqueous humor PCR for VZV was negative. A retrospective study reported a 28% diagnostic positivity rate for aqueous humor PCR, compared with 11% for immunoglobulin M serologic tests in identifying uveitis-associated infectious agents.[9] However, relying solely on PCR for diagnosis would have missed the correct infectious etiology in 34% of patients with herpetic uveitis.[10]

There is no standardized approach to treating neuroretinitis, aside from addressing known causes. For example, in cases of varicella-zoster virus-associated neuroretinitis, favorable outcomes have been reported with the use of systemic acyclovir and corticosteroids.[4,6] Because Bartonella is the primary pathogen linked to infectious neuroretinitis and considering our patient's history of contact with cats, we started empirical systemic antibiotic treatment even though serologic tests did not detect Bartonella-specific

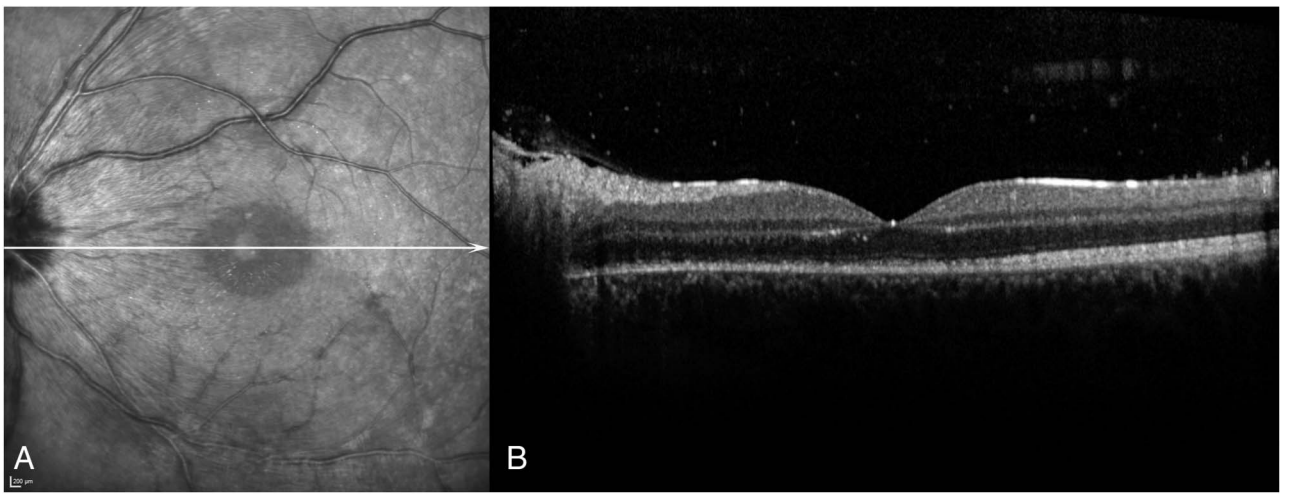

Fig. 2. A and **B.** Near-infrared reflectance and optical coherence tomography were performed 5 days after initial presentation, which was 2 days after the start of intravenous steroid therapy, and absorption of intra- and subretinal fluid was observed.

antibodies. In our case, the patient experienced a rapid resolution of symptoms and achieved a final visual acuity of 20/20.

We hypothesiZe that this case of neuroretinitis presents a complex interplay between acute COVID-19 infection and herpesvirus reactivation. Further research and clinical observation are necessary to understand the underlying mechanisms and to gain deeper insights into the wide range of viral-induced ophthalmic complications.

Key words: COVID-19, neuroretinitis, varicella-zoster virus.

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