American Journal of Ophthalmology Case Reports 32 (2023) 101876

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Panuveitis and optic neuropathy following SARS-COV-2 in the absence of multisystem inflammatory syndrome in a child

Preston Land [a], Veeral Shah [a,b], Daniel J. Lovell [c], Virginia Miraldi Utz [a,b,*]

[a] Abrahamson Pediatric Eye Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] University of Cincinnati Department of Ophthalmology, Cincinnati, OH, USA
[c] Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

ARTICLE INFO

Keywords:
Pan-uveitis
COVID-19
SARS-COV-2
Pediatric uveitis

ABSTRACT

Purpose: To describe the presentation of a healthy 8-year-old female referred to a pediatric ophthalmology clinic with blurred vision and concern for bilateral uveitis.
Observations: The patient was diagnosed with COVID-19 two weeks prior to the onset of ocular symptoms. An examination revealed bilateral pan-uveitis and patient underwent an extensive work-up for an underlying cause that was unremarkable. Two years following the initial presentation, she has not had any evidence of recurrence.
Conclusions and Importance: This case highlights the potential for COVID-19 to be temporally associated with ocular inflammation and underscores the importance of recognizing and investigating such manifestations in pediatric patients. The mechanism by which COVID-19 may lead to an immune response that affects the eyes is not fully understood, but it is believed to be related to an overactive immune response triggered by the virus. Further studies are needed to better understand the potential relationship between COVID-19 and ocular manifestations in pediatric patients.

1. Introduction

SARS-COV-2 (Severe acute respiratory syndrome coronavirus) belongs to the genus *Betacoronavirus,* which was first identified in Wuhan, China, in December 2019 and is reported as the causative agent of the severe respiratory illness deemed COVID-19.[1] In adults with acute infection, ocular manifestations have been reported and include conjunctival hyperemia, chemosis, and increased secretions.[2] However, literature regarding similar ocular manifestations during or following COVID-19 infection in children is limited. Multi-inflammatory syndrome in the absence of MIS-C has been reported occurring after COVID-19 infection has varied clinical presentations in children and young adults but is presumed to be of autoinflammatory origin triggered by previous infection with the virus.[3] Uveitis temporally following COVID-19 infection in the absence of Multisystem Inflammatory Syndrome in Children (MIS-C) has been minimally reported to the best of our knowledge.[1,4] Herein, we present a case of an 8-year-old girl with pan-uveitis in following recent COVID-19 infection.

2. Case report

A healthy, 8-year-old female was referred to the pediatric ophthalmology clinic at Cincinnati Children's Hospital Medical Center for blurred vision and concern for bilateral uveitis. The patient presented to an outside provider after a weeklong history of right eye injection, with worsening "blurriness" of vision and found to have bilateral anterior uveitis, treated with prednisolone acetate and referred to us for further management. Past medical history was significant for recent COVID-19 infection, confirmed by RT-PCR test (diarrhea was her only symptom) two weeks prior to her initial symptoms of red eye. She had been treated with atropine and prednisolone acetate 1% every hour by an outside provider without significant improvement. Review of systems was positive for headache with onset coinciding with ocular disease. Family history was significant for a maternal uncle with HLAB27-positive ankylosing spondylitis and multiple sclerosis following long-term TNFi treatment, maternal aunt with psoriasis, and mother with recent negative autoimmune work-up for arthritis.

Upon examination, the best-corrected visual acuity (BCVA) of each eye was $20/20^{-2}$, with intraocular pressure of 13 and 15 mm Hg by rebound tonometry (iCare™) in the right and left eyes, respectively.

* Corresponding author. Burnet Ave, Cincinnati, OH, 45229, USA.
E-mail address: Virginia.Utz@cchmc.org (V. Miraldi Utz).

https://doi.org/10.1016/j.ajoc.2023.101876
Received 14 February 2023; Received in revised form 4 May 2023; Accepted 15 June 2023
Available online 29 June 2023

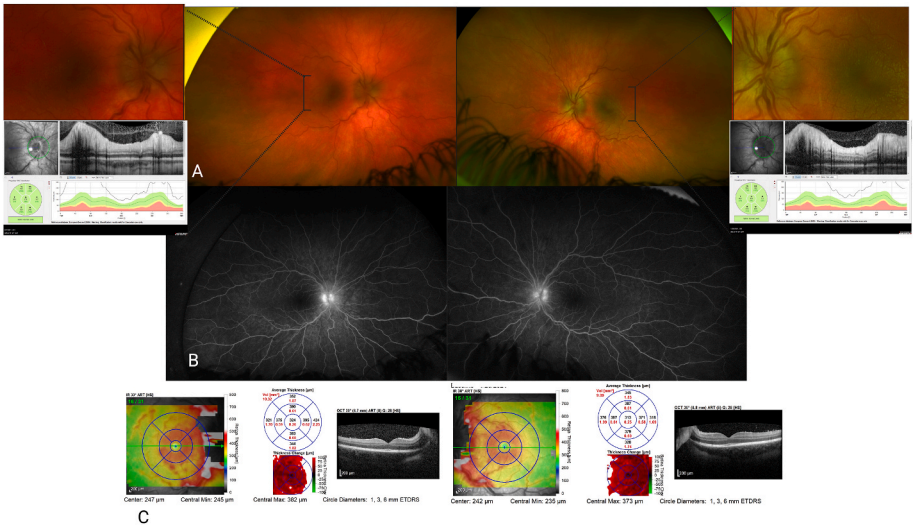

Fig. 1. Multi-modal imaging at presentation (2 weeks following COVID19 infection); A. Ultra-widefield pseudocolor images of the right and left eye demonstrating hazy media right eye > left eye, optic disc edema (See inset), blunted foveal reflex, vascular tortuosity and venous engorgement. The optic disc edema (see inset) is asymmetric, with the right greater than left. B. Oral fluorescein angiography demonstrating optic disc hyperfluorescence and subtle fering pattern of the peripheral retina. C. Spectral domain optical coherence tomography (SD-OCT) demonstrating perifoveal thickening nasal > temporal as highlighted by the retina thickness map.

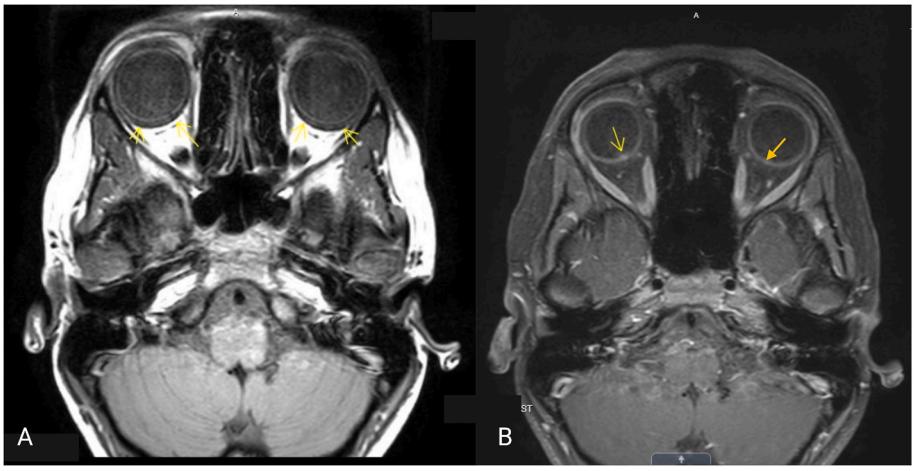

Fig. 2. There is a choroidal thickening of the posterior scleral layers of the globes bilaterally with associated thin subretinal effusions. There is thickening bilaterally as well as optic nerve thickening and mild optic nerve head enhancement.

Because of pharmacological cycloplegia, we were unable to assess for an afferent pupillary defect. However, both color (Ishihara) and contrast discrimination (Pelli-Robson) were full in each eye. On anterior segment examination, bilateral non-granulomatous keratic precipitates was present in an Arlt distribution in the right and left eyes, with 3+ cell, 2+ flare in each eye, broken synechiae noted on the right, with pigment deposition on the lens in both eyes. Posterior segment examination was significant for 2+ cell, 1–2+ haze in the right eye and 2+ cell, 1+ haze in the left eye. Both optic nerves were edematous (Frisen Grade 3) with associated with vascular tortuosity, and venous engorgement, and a few snowballs noted inferiorly in the right eye (Fig. 1A). No retinal or choroidal lesions were noted on clinical exam. Oral fluorescein angiography demonstrated diffuse optic disc leakage with a subtle peripheral fering pattern (Fig. 1B).

The patient was then started on difluprednate in both eyes given poor response to high-frequency prednisolone acetate. Neuro-ophthalmology was consulted for the headache and significant disc edema and an MRI, MRV of the brain and orbits and lumbar puncture were recommended and performed (Fig. 2). In the absence of cycloplegia, an afferent pupillary defect (0.9 log units) was noted in the right eye by the pediatric neuroophthalmology. Laboratory work-up for infectious and non-infectious causes was unremarkable, with the exception of elevated ESR (Table 1). Of note, the patient did not carry the HLAB27 antigen haplotype. Opening pressure for the lumbar puncture was normal (23 cm H_2O), and slight CSF pleocytosis was noted (WBC = 7). The patient was started on oral prednisone (1 mg/kg) with taper over eight weeks. The patient was examined by rheumatology and did not have evidence of arthritis or other systemic autoimmune etiology. Topical steroids were slowly tapered, transitioned to prednisolone acetate and then loteprednol over four months. When the patient received the pediatric COVID19 vaccine a year after the initial infection, she developed a headache that persisted several weeks, but the uveitis did not recur. The patient was last evaluated 2 years after the initial presentation without recurrence of uveitis. Synechiae were still present (as expected) and the

Table 1
Patient's laboratory work-up for uveitis. Patient's levels are provided with normative lab values.

Lab	Level	Normal Ranges
Potassium Level	4.20	3.3–4.7 mmol/L
Chloride Level	102.00	100–112 mmol/L
CO2 Level	30.00	17–31 mmol/L
Anion Gap	6.00	4–15 mmol/L
BUN	14.00	8–18 mg/dL
Creatinine Level	0.51	0.32–0.64 mg/dL
B/C Ratio	27.45 (H)	<=25.00
Glucose Level	69.00	54–117 mg/dL
Calcium	9.60	7.1–12.4 mg/dL
Albumin Level	3.50	3.5–4.7 gm/dL
ALK Phos	233.00	128–336 unit/L
ALT	36.00	12–49unit/L
AST	28.00	10–36 unit/L
Bilirubin Total	0.20	0.1–1.1 mg/dL
Globulin	4.20	gm/dl
A/G Ratio	1.00	1.0–2.0
Sodium Level	138.00	136–145 mmol/L
Total Protein Level	7.70	6.4–8.3 gm/dL
U appearance	Cloudy (A)	Clear
U Color	Yellow	
U Glucose	Negative	Negative mg/dL
U Bili	Negative	Negative
U Ketones	Negative	Negative mg/dL
Specific Gravity REF	1.02	1.002–1.030
U Blood	Negative	Negative
U pH	8.00	5.0–8.0
U Protein	Negative	Negative mg/dL
U Urobilinogen	Negative	Negative mg/dL
U Nitrite	Negative	Negative
U Leukoctye Ester	Negative	Negative
WBC/HPF, Urine	None	<=1 - 2/HPF
RBC/HPF, Urine	None	<=1 - 2/HPF
Bacteria, Urine	Trace (A)	None/HPF
Amorphous Cryst	3+ (A)	(none)/HPF
Anti-Nuclear	Negative	
ANA Titer	NA	
ANA Pattern	NA	
CARS-CoV-2	Positive (AA)	
Syphilis Screen	Negative	
RPR Qual	Negative	
SED Rate	31 (H)	
CRP	<0.29	
Rhheum Factor	<11	
IL-1B	<5	
IL-2	1.00	
IL-4	4.00	
IL-5	1.00	
IL-6	13.00	
IL-8	71.00	
IL-10	2.00	
G-IFN	2.00	
TNF-A	1.00	
GM-CSF	1.00	
CSF Appearance	Clear	Clear
Color CSF	Colorless	
CSF SEGS	0.00	%
CSF Lymphs	77.00	%
CSF Monos	23.00	%
CSF RBC Count	<2000	0-2000 mm3
CSF WBC Count	7 (HH)	0–4 mm3
CSF Lyme	0.04	<=0.99 LIV
Glucose CSF	58.00	40–70 mg/dl
Protein CSF	17.00	15–45 mg/dl
Angiotension Converting enzyme	0.90	0.0–2.5 U/L
Mycoplasma IgM	1.13 (H)	<=0.76 U/L
Vitamin B2 Level	21.20	6.2–39.0
Ferritin Level	32.90	8.0–150.0 ng/mL
Folate Level	>48.0 (H)	5.4–24.0 ng/mL
Lysozyme Serum	1.16	<= 2.75 μg/mL

RNFL was asymmetrically less in the right eye compared to the left (Fig. 3), suggesting subtle, residual damage to the optic nerve from the presenting optic neuropathy.

3. Discussion

The mechanism by which COVID-19 might lead to a post-infectious inflammatory response is not fully understood, but it is believed that the SARS-CoV-2 virus, which causes COVID-19, robust T-cell activation, elevation of Type 1 T helper (Th-1) and pro-inflammatory cytokines (interferon gamma [INF-γ]) and chemokines (C-X-C ligands 9 and 10).[5,6] A temporal association between COVID-19 infection and the development of uveitis in pediatric patients suggests a potential role for COVID-19 in triggering a systemic immune response that affects various organs, including the eyes. Uveitis is not part of the diagnostic description of MIS-C, however, two uveitic cases in adults and two cases in children were reported in association with MIS-C[7–10] Unlike previous cases of MIS-C with uveitis, this patient did not exhibit any symptoms or signs of multisystem inflammatory syndrome. The uveitis associated with MIS-C was described as anterior and acute, rather than panuveitis as in our patient. She did complain of new-onset headaches and in the setting of significant disc edema, led to a thorough CNS work-up to rule out CNS inflammatory disease. Rheumatologic evaluation and laboratory studies did not reveal an underlying systemic etiology for the uveitis.

Likewise, several case reports and series suggest a temporal association between COVID-19 vaccination and the development of ocular inflammatory events.[11–13] In one of the largest multinational series, Testi and colleagues reported on 70 patients diagnosed with ocular inflammation within 14 days of receiving COVID-19 vaccination and included anterior uveitis, optic neuritis, intermediate uveitis, posterior uveitis, and scleritis.[11] Approximately 50% had a previous history of ocular inflammation.[11] Therefore, both infection and vaccination may be associated with auto-inflammatory sequelae. Interestingly, when our patient underwent vaccination approximately one year later, she developed a headache that persisted for several weeks without eye inflammation.

Because of the family history of autoimmunity, she may have a genetic predisposition to develop inflammatory disease, making her more susceptible to post-infectious inflammatory sequelae, where COVID-19 acted as environmental trigger. The lack of disease over the last two years provides some reassurance, but the patient will continue to be monitored for recurrence. In conclusion, a temporal association between COVID-19 infection and the development of panuveitis in pediatric patients suggests that COVID-19 may influence an inflammatory response following acute infection.

4. Conclusion

It is important to continue monitoring the relationship between COVID-19, vaccines, and ocular manifestations, including uveitis. Further studies are needed to understand the mechanisms and risk factors for the development of autoimmune disorders and ocular manifestations in patients with COVID-19 and after receiving COVID-19 vaccine.

Consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient. The case report was waived by the Cincinnati Children's Hospital Medical Center IRB.

Financial support and sponsorship

Nil.

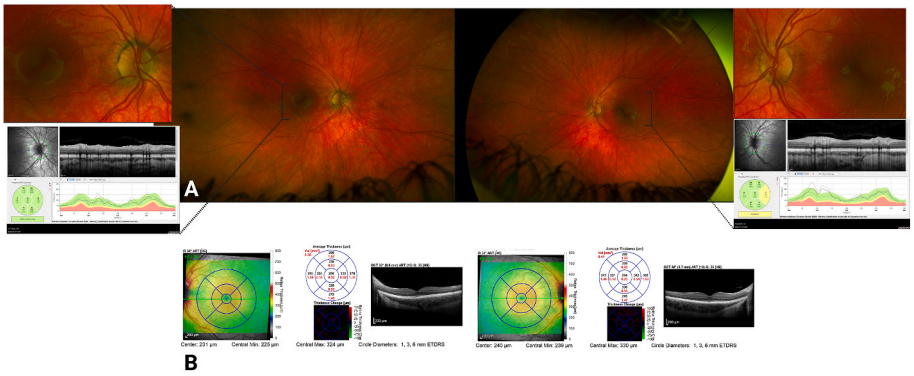

Fig. 3. Multi-modal imaging two years after initial presentation, demonstrating sustained resolution. A. Ultra-widefield pseudocolor images demonstrating resolution of optic disc edema, normal foveal reflex, and normal vasculature course and caliber, inset showing optic disc detail and corresponding RNFL thickness measurements. B. OCT of the macula demonstrating resolution of perifoveal thickening.

Declaration of competing interest

There are no conflicts of interest.

Acknowledgments/disclosure

None.

References

1. Iriqat S, Yousef Q, Ereqat S. Clinical profile of COVID-19 patients presenting with uveitis - a short case series. *Int Med Case Rep J*. 2021;14:421–427. https://doi.org/10.2147/IMCRJ.S312461.
2. Eser-Ozturk H, Izci Duran T, Aydog O, Sullu Y. Sarcoid-like uveitis with or without tubulointerstitial nephritis during COVID-19. *Ocul Immunol Inflamm*. 2022:1–8. https://doi.org/10.1080/09273948.2022.2032195.
3. Petrescu L, Crișan M, Lazăr C, Stan C. Anterior and posterior uveitis associated with juvenile idiopathic arthritis-case report. *Rom J Ophthalmol*. 2022;66(2):185–190. https://doi.org/10.22336/rjo.2022.36.
4. Mazzotta C, Giancipoli E. Anterior acute uveitis report in a SARS-CoV-2 patient managed with adjunctive topical antiseptic prophylaxis preventing 2019-nCoV spread through the ocular surface route. *Int Med Case Rep J*. 2020;13:513–520. https://doi.org/10.2147/IMCRJ.S260252.
5. Kumar D, Rostad CA, Jaggi P, et al. Distinguishing immune activation and inflammatory signatures of multisystem inflammatory syndrome in children (MIS-C) versus hemophagocytic lymphohistiocytosis (HLH). e16 *J Allergy Clin Immunol*. 2022 May;149(5):1592–1606. https://doi.org/10.1016/j.jaci.2022.02.028. Epub 2022 Mar 15. PMID: 35304157; PMCID: PMC8923010.
6. Arruti N. Acute bilateral anterior uveitis in paediatric inflammatory multisystem syndrome temporally associated with COVID-19. *Int J Ophthalmol*. 2022;15(8):1410–1412. https://doi.org/10.18240/ijo.2022.08.28.
7. Shaigany S, Gnirke M, Guttmann A, et al. An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. *Lancet*. 2020;396:e8 10.
8. Bettach E, Zadok D, Weill Y, Brosh K. Hanhart J Bilateral anterior uveitis as a part of a multisystem inflammatory syndrome secondary to COVID-19 infection. *J Med Virol*. 2021;93:139 40.
9. W Wong Chung JERE, Engin Ö, Wolfs TFW, Renson TJC, de Boer JH. Anterior uveitis in paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *Lancet*. 2021;397(10281):e10. https://doi.org/10.1016/S0140-6736(21)00579-1.
10. Icariu CI, Merticariu M, Cobzariu C, Mihai MM, Dragomir MS. Pediatric inflammatory multisystem syndrome induced Panuveitis associated with SARS-CoV-2 infection: what the Ophthalmologists need to know. *Rom J Ophthalmol*. 2022;66(2).
11. Testi I, Brandão-de-Resende C, Agrawal R, Pavesio C. COVID-19 Vaccination Ocular Inflammatory Events Study Group. Ocular inflammatory events following COVID-19 vaccination: a multinational case series. *J Ophthalmic Inflamm Infect*. 2022 Jan 4;12(1):4. https://doi.org/10.1186/s12348-021-00275-x. PMID: 34982290; PMCID: PMC8725430.
12. Pichi F, Aljneibi S, Neri P, Hay S, Dackiw C, Ghazi NG. Association of ocular adverse events with inactivated COVID-19 vaccination in patients in abu dhabi. *JAMA Ophthalmol*. 2021 Oct 1;139(10):1131–1135. https://doi.org/10.1001/jamaophthalmol.2021.3477. PMID: 34473209; PMCID: PMC8414361.
13. Rabinovitch T, Ben-Arie-Weintrob Y, Hareuveni-Blum T, et al. UVEITIS after the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: a possible association. *Retina*. 2021 Dec 1;41(12):2462–2471. https://doi.org/10.1097/IAE.0000000000003277. PMID: 34369440.