

## Bilateral Orbital Inflammation Associated with COVID-19 Infection: A Case Report and Brief Review of the Literature

Usanee Tungsattayathitthan, M.D.<sup>1</sup>, Teechaya Nonboonyawat, M.D.<sup>1</sup>,  
Parinda Phinitkitanan, M.D.<sup>1</sup>, Nuttha Sanghan, M.D.<sup>2</sup>, Orapan Aryasit, M.D.<sup>1</sup>,  
Wantanee Sittivarakul, M.D.<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

<sup>2</sup>Department of Radiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

Received 4 April 2022 • Revised 11 May 2022 • Accepted 9 June 2022 • Published online 21 July 2022

### Abstract:

A 31-year-old woman with no history of systemic autoimmune disease developed bilateral pain, redness, periorbital edema, and proptosis while being hospitalized for mild coronavirus disease 2019 (COVID-19) pneumonia. The onset of ocular symptoms occurred six days after systemic COVID-19 symptoms. Computed tomography examination of the orbit revealed diffuse inflammation involving multiple orbital structures. A complete systemic workup was performed to exclude other systemic inflammatory diseases. She was initially diagnosed with probable orbital cellulitis secondary to sinusitis. However, she did not improve with antibiotic therapy. Empirical administration of systemic corticosteroids led to a dramatic clinical response. The patient has been maintained on a gradual steroid taper without inflammation relapse. This article describes a potential causal association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and orbital inflammation. Ophthalmologists should be aware of this presentation when assessing patients with COVID-19 who present with orbital inflammatory symptoms.

**Keywords:** autoinflammation, COVID-19, orbit, orbital inflammation, SARS-CoV-2

**Contact:** Wantanee Sittivarakul, M.D.  
Department of Ophthalmology, Faculty of Medicine,  
Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.  
E-mail: wantanee.s@psu.ac.th

J Health Sci Med Res .....  
doi: 10.31584/jhsmr.2022884  
www.jhsmr.org

© 2022 JHSMR. Hosting by Prince of Songkla University. All rights reserved.  
This is an open access article under the CC BY-NC-ND license  
(<http://www.jhsmr.org/index.php/jhsmr/about/editorialPolicies#openAccessPolicy>).

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a major global health issue in 2022. Considerable research has emerged during the past two years, regarding ophthalmological involvement in regards to COVID-19. The prevalence of ocular manifestations in patients with COVID-19 ranges from 2% to 32%.<sup>1</sup> Conjunctivitis was the first reported ocular manifestation of SARS-CoV-2 infection. Subsequent reports have revealed associations between COVID-19 and corneoscleral, uveitic, retinovascular, neuro-ophthalmic, and orbital disease.<sup>2</sup>

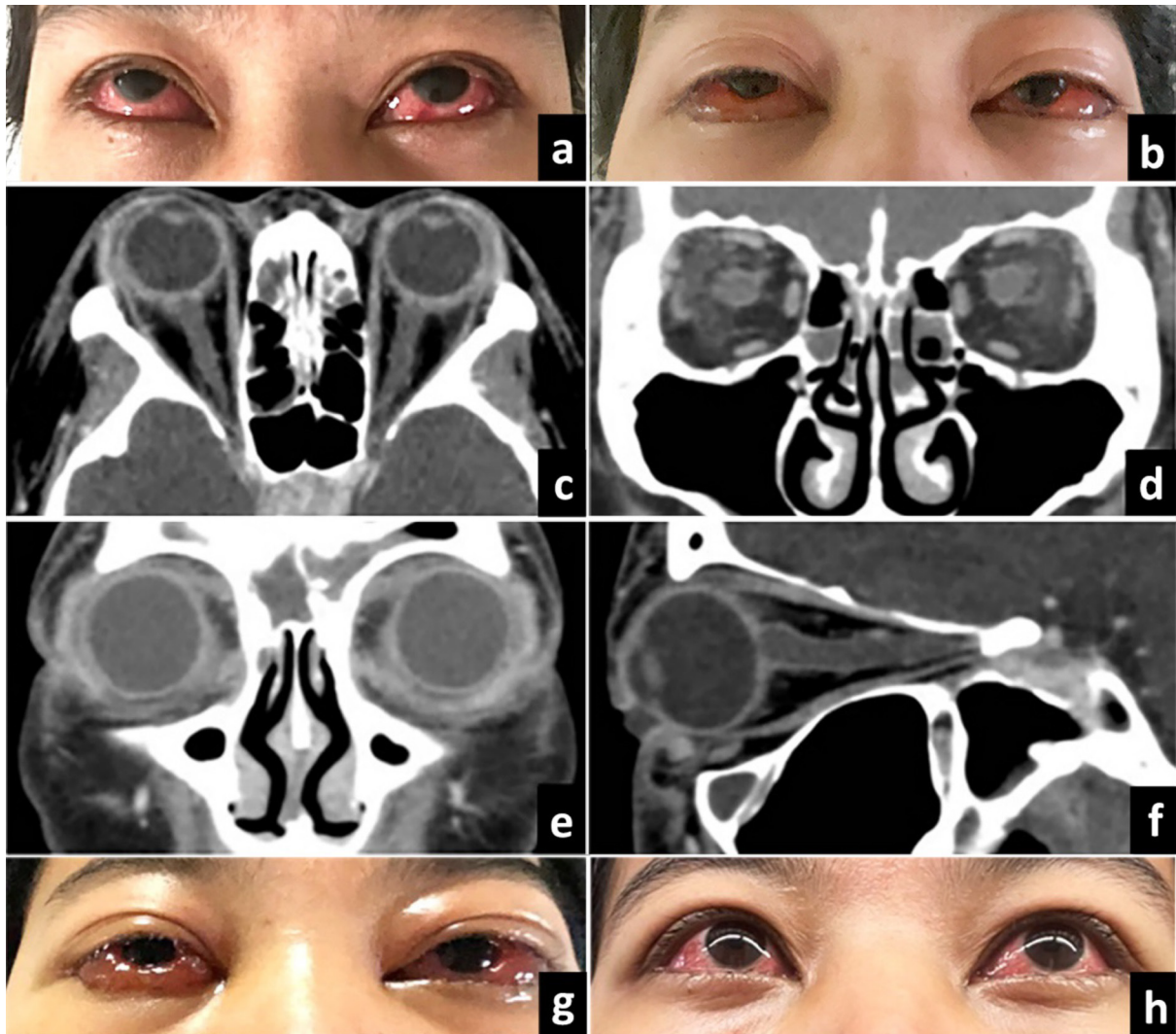
Orbital involvement in patients with SARS-CoV-2 infection is uncommon. Infectious and noninfectious orbital conditions related to COVID-19 have been reported. Infectious conditions include bacterial or fungal superinfection of the orbit, which is a devastating complication typically affecting patients with severe COVID-19 who have preexisting comorbidities such as diabetes mellitus, or those who received high-dose systemic corticosteroids/monoclonal antibodies as part of the armamentarium against COVID-19.<sup>3</sup> In contrast, a few case reports describe an inflammatory orbital condition associated with SARS-CoV-2 infection. The clinical presentations ranged from orbital myositis, dacryoadenitis, and optic perineuritis, which were hypothesized to represent immune consequences of the interaction between SARS-CoV-2 and the host.<sup>4-9</sup> This article describes the case of a healthy young woman who developed bilateral eye redness, periorbital pain with edema, and proptosis during hospitalization for mild COVID-19 pneumonia. The patient provided written informed consent for the publication of the photographs in this article.

## Case report

A 31-year-old healthy Thai woman presented with a one-day history of sore throat and headache. She

worked in a canned food factory where there had been a COVID-19 cluster outbreak and reported a history of close contact with one confirmed case. A reverse-transcriptase polymerase chain reaction test for SARS-CoV-2, using a nasopharyngeal specimen, was positive. She was admitted to the Songklanagarind COVID-19 field hospital on day 3 of her illness. Her previous medical and ocular histories were unremarkable. She had not received any recent vaccinations (including COVID-19 vaccines) and was not taking prescription medications. On admission, physical examination revealed a temperature of 36.1°C, pulse rate of 77 beats/minute, respiratory rate of 18 breaths/minute, blood pressure of 130/80 mmHg, and room air oxygen saturation of 97%. Other physical examination results were unremarkable. Her initial chest radiograph (CXR) was normal. Three days after admission (day 6 of illness), she showed diffuse redness and discomfort, without visual impairment, in both eyes (Figure 1a). An on-duty general practitioner made a presumptive diagnosis of conjunctivitis associated with COVID-19. Topical antihistamine eyedrops, four times per day, were prescribed; however, her ocular symptoms did not improve.

On day 10 of her illness, she developed a high-grade fever (body temperature 38.7°C) and mild shortness of breath; moreover, a 1-minute sit-to-stand test showed positive oxygen desaturation. A repeat CXR revealed mild infiltration in the right lower lung field. She was diagnosed with early COVID-19 pneumonia and was transferred from the field hospital to the COVID-19 cohort ward for closer monitoring. In addition, she reported significant progression of periorbital pain, eyelid swelling, and conjunctival chemosis in both eyes. In the cohort ward, the patient started receiving 800 mg of favipiravir twice daily and supportive medication such as an antipyretic for COVID-19 pneumonia treatment. She did not require supplemental oxygen therapy as her room air oxygen saturation was within normal range. The fever and shortness of breath subsided within 24



**Figure 1** (a) Bilateral, moderate, diffuse conjunctival injection observed 6 days after the onset of systemic COVID-19 symptoms. (b) Bilateral periorbital edema and massive chemosis at the initial ophthalmological examination (day 11 of illness). (c–f) CT images with contrast show bilateral proptosis with diffuse scleral thickening, diffuse infiltration of periorbital and retrobulbar fat, prominent bilateral lacrimal glands and partial opacification of both frontal sinuses. (g) Follow-up clinical examination 48 hours after systemic antibiotic therapy did not reveal a clinical response. (h) There was significant improvement in periorbital edema, chemosis, and proptosis at 48 hours after starting systemic corticosteroid treatment.

hours; however, her ocular symptoms did not improve. An ophthalmology specialist was consulted for a thorough ocular examination and specific management (day 11 of illness).

An initial ophthalmologic examination, which was performed through a video call to reduce the risk of SARS-CoV-2 exposure, revealed uncorrected near visual acuity (VA) measured using a near vision test card of 20/100 and 20/70 in the right and left eyes, respectively. Distance VA was not measured since a distance VA chart was not available at the cohort ward. Bilateral mild axial proptosis was appreciable on video examination. In addition, moderately swollen eyelids, without lid lag or retraction, and marked conjunctival chemosis with injection were observed in regards to both eyes. The cornea and anterior chamber were apparently clear. Pupillary reaction was normal. Extraocular motility showed a mild degree of abduction and adduction deficit in regards to both eyes (Figure 1b). The patient reported not having facial numbness along the area corresponding to the dermatomal distribution of the ophthalmic and maxillary division of the trigeminal nerve. Fundus examination and color vision testing were not performed at that time.

Given the presence of orbital signs and symptoms on examination, a computed tomography (CT) of the orbit, with injection of contrast medium, was requested. In addition, laboratory investigations of unrecognized systemic diseases that could cause acute proptosis, such as granulomatosis polyangiitis, rheumatoid arthritis, and systemic lupus erythematosus, as well as inflammatory biomarkers panels, were performed. The CT images showed bilateral proptosis, diffuse scleral thickening of both globes, as well as diffuse infiltration of the periorbital and retrobulbar fat. There was also enhancement of the bilateral lacrimal glands. The extraocular muscles remained intact. There were no superior ophthalmic vein dilatations. The cavernous

sinuses had no filling defects and were not distended. Moreover, partial opacification of both frontal sinuses and mucoperiosteal thickening of other paranasal sinuses were observed (Figure 1c-f). Complete blood counts revealed a hematocrit of 44% and a white cell count of  $11.4 \times 10^3 /\mu\text{L}$ . The proportions of neutrophils and lymphocytes were 82.3% and 21.2%, respectively. In addition, she had elevated levels of C-reactive protein (CRP) (62.8 mg/L; normal range, <5 mg/L), elevated ferritin (334 ng/mL; normal range, 13–150 ng/mL), and elevated interleukin-6 (26.9 pg/mL; normal range, 0–7 pg/mL).

Since the CT images revealed the involvement of paranasal sinuses, she was initially diagnosed with a probable bacterial orbital cellulitis secondary to sinusitis. She was started on intravenous ceftriaxone 2 g/day and clindamycin 600 mg orally at 8-hour intervals according to the suggestion of an infectious disease specialist. The patient completed 48-hours of systemic antibiotic therapy; however, no improvement in ophthalmic signs and symptoms was observed. The proptosis, eyelid swelling, and chemosis remained unchanged (Figure 1g). Since there was no clinical improvement, other orbital conditions were considered at this point. The differential diagnosis included noninfectious orbital inflammation, cavernous sinus thrombosis (CST) complicated with sinusitis/orbital cellulitis, and fungal orbital cellulitis. Our patient was immunocompetent and had not received any systemic steroids in connection to the COVID-19 pneumonia treatment that she received. Bilateral fungal orbital superinfection was therefore unlikely. In regards to CST, which is a life-threatening condition, the patient reported not having numbness along the V1 and V2 dermatomes. She was fully conscious and did not report having a severe headache, therefore the signs and symptoms suggestive of CST were not present. In addition, there was no imaging evidence of CST from the initial orbital CT, i.e. superior ophthalmic veins dilatation or

distended cavernous sinuses. Hence, we believed that our patient had a low possibility to develop CST. Based on these clinical grounds, a noninfectious orbital inflammatory condition associated with COVID-19 infection became the most likely differential diagnosis. An empiric trial of 60 mg oral prednisolone per day was initiated. There was rapid and dramatic clinical improvement within 48 hours of steroid therapy. Her orbital pain, edema, chemosis, and proptosis significantly improved. Her ocular motility recovered fully (Figure 1h). Favipiravir was administered for 10 days. Systemic antibiotic treatment was discontinued after the completion of a 7-day course. The patient was discharged on day 18 after admission, and she continued receiving 60 mg oral prednisolone daily for a total of 1 week that was tapered down to 50 mg/day.

Two weeks after hospital discharge, the patient came for a follow-up visit at the outpatient ophthalmology clinic. She did not have any specific complaints. She was taking 50 mg oral prednisolone daily. Her best-corrected VA was 20/32 and 20/25 in the right and left eyes, respectively. Slit-lamp examination revealed moderate diffuse conjunctival injection. There was no anterior chamber cell. Both pupils were equal and reactive to light without afferent pupil defects. Dilated fundus examination revealed a normal optic disc appearance without cotton wool spots, hemorrhages, or vasculitis. There was no engorgement or tortuous retinal veins. The results of the autoimmune blood test panel were available at that time, and indicated that rheumatoid factor (RF), antineutrophil cytoplasmic antibodies (ANCA), anti-double strand DNA antibodies, and anti-extractable nuclear antigens were all negative; however, the immunofluorescence test for antinuclear antibodies (ANA) was positive at a titer of 1:160 (nucleolar pattern). Since the ANA test was positive, a rheumatology specialist was consulted to evaluate whether she had coexisting systemic autoimmune disease. Comprehensive

history taking and physical examination did not reveal any evidence of a systemic autoimmune disorder. Follow-up clinical examinations and serial ANA titers were advised accordingly. Oral prednisolone was slowly tapered at 2.5 to 5 mg/week every 2–4 weeks and it was discontinued at approximately 6 months. There was no recurrence of orbital inflammation found, including during the latest follow-up visit, at 8 months after hospital discharge. ANA test was repeated at five months after hospital discharge, the result returned negative.

## Discussion

COVID-19 is associated with a spectrum of ophthalmological manifestations. Ocular tissue could serve as an entry portal for the virus since angiotensin-converting enzyme 2, which is the entry receptor for SARS-CoV-2, is variably expressed in the conjunctiva, limbus, and vascular endothelial cell.<sup>10</sup> The commonly proposed pathologic mechanisms underlying ophthalmologic manifestations involve a combination of direct tissue damage due to SARS-CoV-2 replication and immunopathological sequelae, including endothelial cell damage, thromboinflammation, and a dysregulated immune response.<sup>11</sup> We described the case of a young woman with acute onset of bilateral redness, periorbital pain, and progressive proptosis commencing six days after the onset of systemic symptoms of a confirmed SARS-CoV-2 infection. Orbital CT images revealed signs of diffuse inflammation involving multiple orbital structures including orbital fat, lacrimal glands, and sclera. The patient did not respond to systemic antibiotic therapy; however, she rapidly improved following corticosteroid treatment, suggesting an inflammation-driven process.

The clinical features and radiological findings in our patient closely resemble that of a diffuse variant of idiopathic orbital inflammation (IOI), which is defined as a benign, nonspecific, inflammatory condition of the orbit without



identifiable local or systemic causes. The exact etiology and pathogenesis of IOI are not completely known, and both infectious and immune-mediated etiologies have been implicated. Several infectious processes, including upper respiratory tract infections and flu-like viral illness, have been reported in association with IOI.<sup>12</sup> Molecular mimicry between organisms and self epitopes is hypothesized as one of the mechanisms underlying IOI after an acute infection.<sup>12</sup> It is difficult to ascertain whether the orbital inflammation in our patient was directly triggered by SARS-CoV-2 infection. However, the temporal association between the onset of COVID-19 and orbital symptoms, as well as the absence of other definitive systemic diseases that could be a secondary cause of orbital inflammation, suggest a potential causal association between SARS-CoV-2 and the orbital inflammation in regards to this patient.

The immune system is crucially involved in SARS-CoV-2 infection. Cumulative evidence shows that SARS-CoV-2 has the ability to induce hyper-stimulation of the immune system, disturb self-tolerance, and trigger autoimmune responses through cross-reactivity with host cells.<sup>13</sup> Several systemic as well as ocular immune-mediated disorders have been described in individuals after SARS-CoV-2-infection, such as cutaneous rashes and vasculitis, autoimmune thyroiditis, autoimmune hemolytic anemia, and phlyctenular keratoconjunctivitis.<sup>13,14</sup> More than 15 distinct autoantibodies, including ANA, ANCA, RF, and anti-citrullinated protein antibodies, have been recorded in patients with COVID-19 who had no previous autoimmune rheumatic disease.<sup>13</sup> The positivity rate for ANA in patients with COVID-19 ranges from 35% to 50%.<sup>15</sup> However, their pathogenicity and likelihood to induce autoimmune disorders in the long term remain to be seen. The possibility of positive autoantibodies as a transitory epiphenomenon accompanying a viral infection cannot be ruled out.<sup>13</sup>

To our knowledge, orbital inflammatory diseases have only been reported in six patients with COVID-19

(Table 1).<sup>4-9</sup> These patients shared some similarities in ophthalmic presentation and imaging. All the patients showed a favorable response to high-dose systemic corticosteroids. It is notable that unilateral involvement was more common than bilateral involvement. Only one of these six cases showed bilateral orbital inflammation, similar to our case. Dermarkarian et al. reported a case of a 6-month-old female who presented with sequential bilateral orbital inflammation as a manifestation of SARS-CoV-2 infection. The authors hypothesized that the orbital inflammation might be a sequel of SARS-CoV-2 involvement of the orbital tissue since the orbital tissue biopsy revealed similar findings to those observed in previously collected lung specimens in regards to SARS-CoV-2 infection. Additionally, this orbital inflammation could also be part of a pediatric multisystem inflammatory syndrome.<sup>9</sup> It remains unclear whether any clinical parameters can predict the extent and severity of orbital inflammation. However, it is notable that the levels of serum inflammatory markers were significantly elevated in both patients with bilateral orbital inflammation (our patient and Dermarkarian et al.'s patient).<sup>9</sup> Whether the elevation of these inflammatory markers, which are known to be a predictor of COVID-19 severity, is associated with or contributes to the extent and severity of orbital inflammation requires further study.

## Conclusion

We report a case of acute onset, bilateral, painful proptosis in regards to an adult patient with active SARS-CoV-2 infection. A rapid clinical improvement was observed after the administration of systemic corticosteroids, suggesting an inflammation-driven process. A potential causal association of SARS-CoV-2 infection as a viral trigger of orbital inflammation is concerned. Ophthalmologists should be aware of this presentation when assessing patients with COVID-19 who exhibit inflammatory orbital signs and symptoms. Although systemic

**Table 1** Summary of published cases of orbital inflammation in patients with COVID-19

Age	Sex	Underlying conditions	Laterality	Onset*	Radiological findings	Serum inflammatory markers	Autoantibody test results	Clinical diagnosis	
Present case	31 years	F	None	Bilateral	After 6 days	Diffuse inflammation involving sclera, perioptic nerves, lacrimal glands, and intraorbital fat. Frontal sinuses opacification	CRP 62.8 mg/L ferritin 334 ng/mL IL-6 26.9 pg/mL	Positive ANA titer at 1:160 (Nucleolar pattern) Negative anti-ENAs	Orbital inflammation
Dermarkarian et al. <sup>9</sup>	6 months	F	None	Bilateral	As presenting symptoms	Bilateral enlargement of lacrimal glands. Bilateral soft tissue enhancement of the extraconal spaces	CRP 29 mg/L ESR 86 mm/h D-dimer 1.48 µg/mL	Negative for IgG4	Orbital inflammation
Martínez et al. <sup>7</sup>	22 years	M	None	Unilateral (OD)	As presenting symptoms	Enlargement of the lacrimal gland and lateral rectus muscle. Eyelids and pre-septal soft tissue edema	CRP 100 mg/L	Negative for ANA, anti-ENAs, RF, anti-CCP, and IgG4	Acute dacryoadenitis with orbital inflammatory syndrome
Eleiwa et al. <sup>5</sup>	10 years	M	None	Unilateral (OS)	As presenting symptoms	Enlargement of the left lateral rectus muscle and lacrimal gland. Mild stranding of the surrounding intraorbital fat and proptosis	ESR 56 mm/h Positive CRP level	Negative for ANA, ANCA, and RF	Orbital inflammatory disease
Dinkin et al. <sup>4</sup>	56 years	M	Hypertension Hyperlipidemia Duane syndrome	Unilateral (OD)	As presenting symptoms	Perineural enhancement with extension in the orbital fat	Normal ESR and CRP	Negative for ANA, anti-dsDNA, and lupus anticoagulant	Orbital inflammation and optic perineuritis

Table 1 (continued)

Age	Sex	Underlying conditions	Laterality	Onset*	Radiological findings	Serum inflammatory markers	Autoantibody test results	Clinical diagnosis
Armstrong et al. <sup>6</sup>	M	Idiopathic facial palsy, Neurogenic tumor at spine post removal	Unilateral (OS)	After 2 days	Isolated opacification of the superior rectus/levator complex	Normal CRP, procalcitonin, and D-dimer	Negative for ANA, ANCA, and IgG4	Orbital myositis
Mangan et al. <sup>8</sup>	F	None	Unilateral (OD)	1 week after	Diffuse fusiform enhancing enlargement of the right lateral rectus and superior rectus muscles	N/A	Negative for ANA, anti-ENAs, anti-dsDNA, RF, anti-CCP, ANCA, lupus anticoagulant, antiheta-2 glycoprotein 1 IgG/IgM, and ACA, C3, C4	Orbital myositis

\* Onset of ocular symptoms related to systemic COVID-19 symptoms.

ACA=anti-centromere antibodies, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, C=complement, CCP=cyclic citrullinated peptides, CRP=C-reactive protein, dsDNA=double-stranded DNA, ENA=extractable nuclear antigens, ESR=erythrocyte sedimentation rate, F=female, Ig=immunoglobulin, IL-6=interleukin-6, M=male, N/A=not available, mg/L= milligrams per liter, ng/mL= nanograms per milliliter, pg/mL= picograms per milliliter, mm/h= millimeters per hour, µg/mL= microgram per milliliter



corticosteroids yielded excellent short-term outcomes, the long-term natural course of this presentation after steroid taper and discontinuation remains to be observed.

## Acknowledgements

We are grateful to Dr. Porntip Intapiboon (Allergy and Rheumatology Unit, Division of Internal medicine, Faculty of Medicine, Prince of Songkla University) for the co-evaluation of the patient and for making helpful suggestions in regards to autoimmune blood testing.

## Funding sources

No funding or grant support was received.

## Conflict of interest

There are no potential conflicts of interest to declare.

## References

1. Ulhaq ZS, Soraya GV. The prevalence of ophthalmic manifestations in COVID-19 and the diagnostic value of ocular tissue/fluid. *Graefes Arch Clin Exp Ophthalmol* 2020;258:1351-2.
2. Nasiri N, Sharifi H, Bazrafshan A, Noori A, Karamouzian M, Sharifi A. Ocular manifestations of COVID-19: a systematic review and meta-analysis. *J Ophthalmic Vis Res* 2021;16:103-12.
3. Dave TV, Nair AG, Hegde R, Vithalani N, Desai S, Adulkar N, et al. Clinical presentations, management and outcomes of rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19: a multi-centric study. *Ophthalmic Plast Reconstr Surg* 2021;37:488-95.
4. Dinkin M, Feinberg E, Oliveira C, Tsai J. Orbital inflammation with optic perineuritis in association with COVID-19. *J Neuroophthalmol* 2022;42:e300-1.
5. Eleiwa T, Abdelrahman SN, ElSheikh RH, Elhusseiny AM. Orbital inflammatory disease associated with COVID-19 infection. *J AAPOS* 2021;25:232-4.
6. Armstrong BK, Murchison AP, Bilyk JR. Suspected orbital myositis associated with COVID-19. *Orbit* 2021;40:532-5.
7. Martinez Diaz M, Copete Piqueras S, Blanco Marchite C, Vahdani K. Acute dacryoadenitis in a patient with SARS-CoV-2 infection. *Orbit* 2021;41:374-7.
8. Mangan MS, Yildiz E. New onset of unilateral orbital myositis following mild COVID-19 infection. *Ocul Immunol Inflamm* 2021;29:669-70.
9. Dermarkarian CR, Chilakapati M, Hussein M, Chevez-Barrios P, Allen RC. Bilateral orbital inflammation in a 6-month old with SARS-CoV-2 infection. *Orbit* 2021;1-4.
10. Ho D, Low R, Tong L, Gupta V, Veeraraghavan A, Agrawal R. COVID-19 and the ocular surface: a review of transmission and manifestations. *Ocul Immunol Inflamm* 2020;28:726-34.
11. Neri P, Pichi F. COVID-19 and the eye immunity: lesson learned from the past and possible new therapeutic insights. *Int Ophthalmol* 2020;40:1057-60.
12. Yeşiltaş YS, Gündüz AK. Idiopathic orbital inflammation: review of literature and new advances. *Middle East Afr J Ophthalmol* 2018;25:71-80.
13. Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. *Autoimmun Rev* 2021;20:102792.
14. Eleiwa TK, Elmaghrabi A, Helal HG, Abdelrahman SN, ElSheikh RH, Elhusseiny AM. Phlyctenular keratoconjunctivitis in a patient with COVID-19 infection. *Cornea* 2021;40:1502-4.
15. Vlachoyiannopoulos PG, Magira E, Alexopoulos H, Jahaj E, Theophilopoulou K, Kotanidou A, et al. Autoantibodies related to systemic autoimmune rheumatic diseases in severely ill patients with COVID-19. *Ann Rheum Dis* 2020;79:1661-3.