Vogt–Koyanagi–Harada Disease after SARS-CoV-2 Infection: Case Report

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19), a multifaceted condition. The COVID-19 is associated with various ocular manifestations including conjunctivitis, retinal vein occlusion and optic neuritis. The case of VKH disease associated with SARS-CoV-2 was rare and the specific association is still unclear. Case Presentation In the present study, a 35-year-old female patient with no significant medical history presented with one week of bilateral blurred vision 2 weeks after a clinical course of COVID-19. Both eyes presented with bullous serous retinal detachments. She was diagnosed with incomplete Vogt–Koyanagi–Harada (VKH) disease. Early diagnosis and treatment of VKH disease are essential for the visual prognosis of this aggressive disease. Ocular inflammatory signs and visual acuity improved via corticosteroid therapy in this patient. The case of VKH disease associated with SARS-CoV-2 was rare and the specific association is still unclear. By reviewing similar studies previously reported, we discuss and summarize the potential mechanisms explaining the association between VKH disease and SARS-CoV-2. Conclusion Although the causality remains unclear, ophthalmologists and physicians should be aware of this possible association between VKH disease and COVID-19. SARS-CoV-2 may play a potential immunological triggering role in VKH disease. However, further in-depth researches are necessary to investigate the clinical and epidemiological features, as well as the underlying mechanisms of it. Keywords: Vogt–Koyanagi–Harada disease; SARS-CoV-2; COVID-19; case report

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Case Presentation

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Conclusion

Although the causality remains unclear, ophthalmologists and physicians should be aware of this possible association between VKH disease and COVID-19. SARS-CoV-2 may play a potential immunological triggering role in VKH disease. However, further in-depth researches are necessary to investigate the clinical and epidemiological features, as well as the underlying mechanisms of it.

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Introduction

Vogt Koyanagi Harada disease (VKH) is not only an autoimmune vision-threatening disease that is frequently characterized by bilateral granulomatous panuveitis, but also a multisystemic inflammatory disorder which is commonly accompanied by neurological, auditory, and integumentary symptoms, such as headache, tinnitus, deafness, alopecia and so on. Although the etiology and pathogenesis of VKH are unknown, considerable progress over the last few decades has been made on the subject. Many hypotheses have been reported, most of which were genetic predisposition and viral infections. It is now widely accepted that virus may trigger the autoimmune response to melanin through a mechanism of molecular mimicry in VKH disease. When summing up the studies reviewed, various infective triggers such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) have been reported to be involved in the start of VKH disease[1].

With the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative pathogen of the coronavirus disease 2019 (COVID-19) outbreak, it has been reported that the COVID-19 is associated with ocular signs, most of which were conjunctivitis, retinal vein occlusion and optic neuritis[2,3]. However, it is worth noting that the case of VKH disease associated with SARS-CoV-2 was rare and the specific association is still unclear. Thus, we report a case of bilateral panuveitis resembling VKH disease following SARS-CoV-2 infection, and review current pertinent literature to analyse some potential interactions between SARS-CoV-2 and VKH disease.

Case report

A 35-year-old female patient with no significant medical history presented to our ophthalmic outpatient department with one week of bilateral blurred vision. She mentioned that fever, headache and cough occurred 2 weeks ago. And she was tested positive for SARS CoV-2 by polymerase chain reaction (PCR) at that moment. She had no history of ocular trauma or surgery prior to the occurrence of uveitis.

Ophthalmological examinations showed her best corrected visual acuity (BCVA) was 0.8 in the right eye and 0.7 in the left eye when converted to logarithm of the minimal angle of resolution (LogMAR). Intraocular pressure was 21mmHg on the right eye and 22 mmHg on the left eye. Upon examination under a slit lamp, no keratic precipitates or flare were detected in the anterior segment, while vitreous opacities were grade 1+ inflammatory cells in both eyes. Fundscopic examination showed bullous serous retinal detachments (SRD) with subretinal fluid in the posterior retina of both eyes (Figure 1A, B). Furthermore, optical coherence tomography (OCT), B-scan ultrasonography and Fundus Fluorescein angiography (FFA) were also performed. OCT indicated more details of SRDs, cystoid spaces in the neurosensory layer of the retina, which was divided into several compartments by subretinal septa. OCT also showed the folds of RPE and bacillary layer detachment (BLD) (Figure 1C, D). FFA indicated multiple punctate fluorescein leakages and pooling of the dye in areas of SRDs, and optic disc hyperfluorescence (Figure 1E, F). B-scan ultrasonography showed

SRD and thickening of the posterior choroid in both eyes, while there was no evidence of posterior scleritis (Figure 2 A, B).

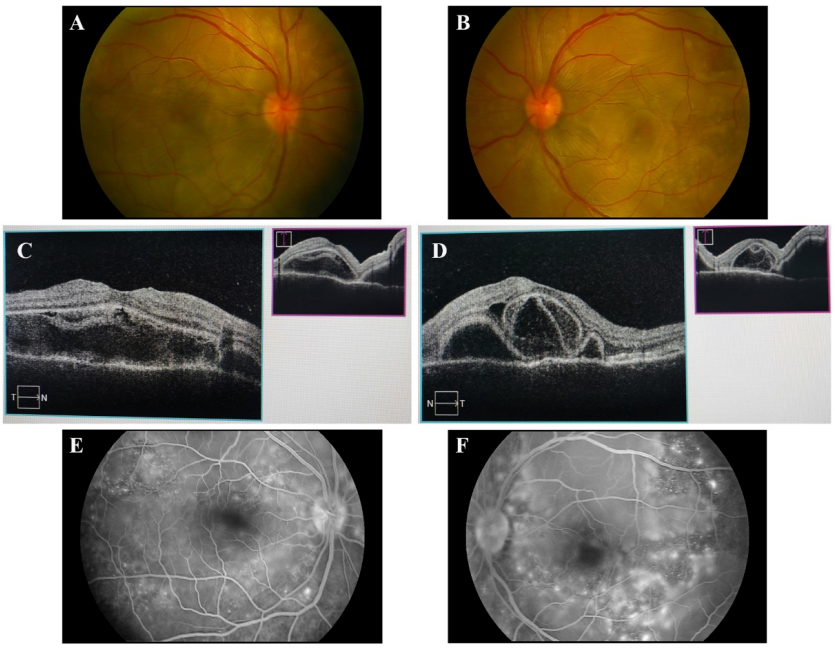

Figure 1 Fundus findings of panuveitis at initial presentation. Color fundus photographs showing bullous serous retinal detachment (SRD) in the posterior retina and optic disc hyperemia in the right eye (A) and the left eye (B). Optical coherence tomography (OCT) images revealing SRDs, cystoid spaces in the neurosensory layer of the retina and bacillary layer detachment in the right eye (C) and the left eye (D). Fluorescein angiography images indicating multiple punctate fluorescein leaks and late pooling of the dye consistent with the SRD locations, and optic disc staining in the right eye (E) and the left eye (F).

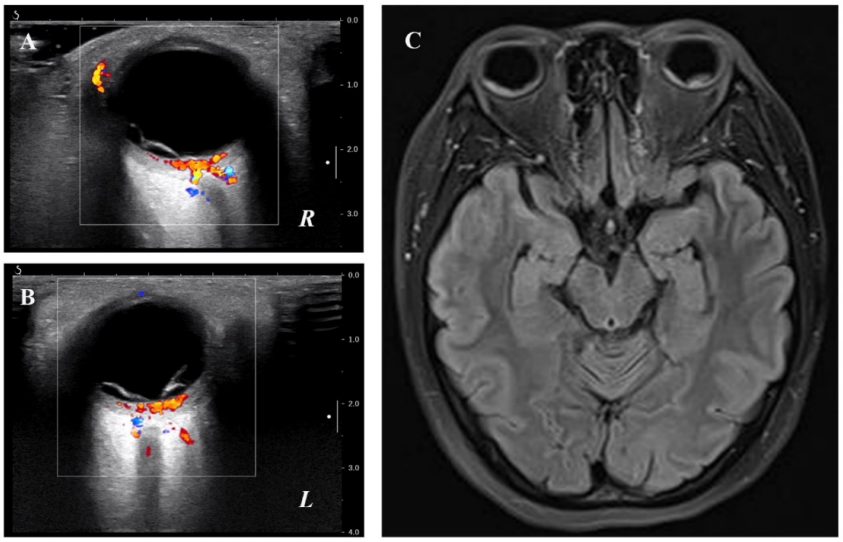

Figure 2 B-scan ultrasonography findings highlighting serous retinal detachment and thickened choroid in the right eye (A) and the left eye (B). Brain MRI images (C) demonstrating bilateral retinal detachment.

On admission, her body temperature was 36.6 degrees Celsius (°C), and her chest X-ray image showed no abnormal shadow. Furthermore, she was tested by PCR and was negative for SARS-CoV-2. She did not notice tinnitus and hair loss. A complete systemic workout was conducted with brain magnetic resonance imaging (MRI) which demonstrated bilateral retinal detachment, while she was negative for any optic nerve thickening and intracranial or orbital space-occupying lesion (Figure 2 C). Complete blood tests were performed, reporting unremarkable outcomes. Erythrocyte sedimentation rate was 20 mm/hour, and C-reactive protein level was 0.73 mg/L. Serological tests for toxoplasmosis, EBV, CMV, Rubella virus, Herpes simplex virus 1 and HIV were negative. In addition, extensive blood tests for underlying autoimmune etiologies were carried out, all within normal limits.

According to the clinical findings and laboratory data, she was diagnosed with incomplete VKH disease, as she presented with ocular signs and neurological findings[4]. Early and aggressive systemic glucocorticosteroid (GC) therapy remain the primary treatment according to the standard treatment for VKH disease[5]. The patient was treated with pulse intravenous methylprednisolone therapy(1000mg/day) followed by high-dose oral corticosteroid when the diagnosis of VKH disease was made. In the clinical course of treatment, we paid attention to deterioration of visual acuity and SRD, and tapered the dose of prednisolone slowly. Two weeks after the first evaluation, the patient presented with an improvement in her visual acuity, which was 0.5 in the right eye and 0.6 in the left eye. The control OCT fingdings revealed a significant resolution of subretinal fluid in both eyes (Figure 3).

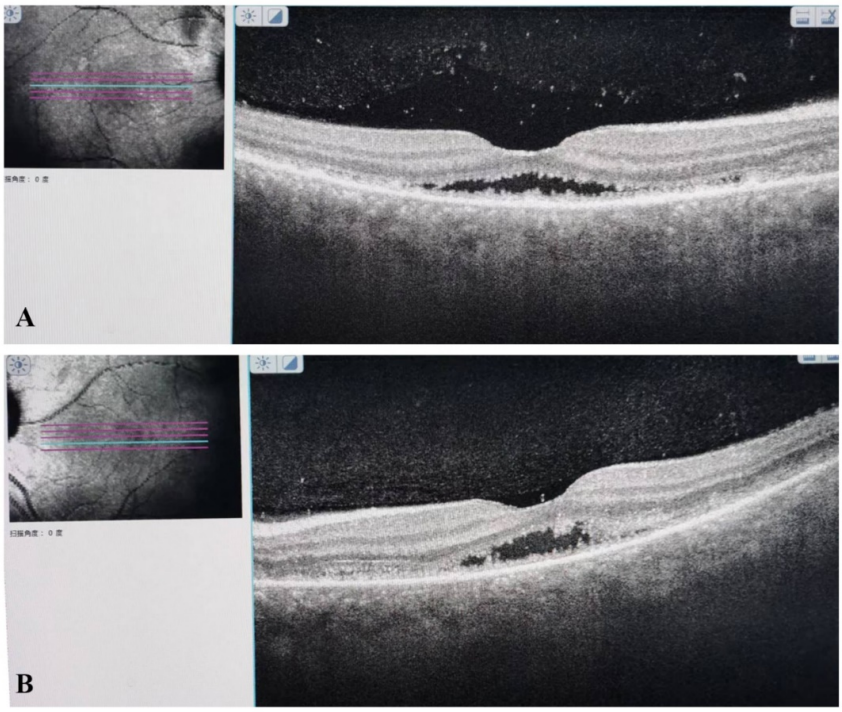

Figure 3 OCT of both eyes showing improvement of the serous retinal detachment and bacillary layer detachment.

Discussion

Vogt-Koyanagi-Harada (VKH) disease is a severe bilateral granulomatous panuveitis frequently associated

with a series of systemic and ocular manifestations. It manifests clinically in four stages: prodromal stage, acute stage, convalescent stage, and chronic recurrent stage. The prodromal phase is characterized by flu-like symptoms, including fever, headache, nausea, tinnitus, periorbital pain and so on. In this patient, extraocular manifestations, including fever and headache, have resolved by time of examination. Following the prodromal phase, bilateral posterior uveitis occurs, characterized by multiple exudative retinal detachment, optic disc swelling and choroidal thickening. Our patient presented with typical signs, in which inflammation is limited to the posterior segment of the eye. Based on Revised Diagnostic Criteria (RDC) for VKH disease[4], our patient was diagnosed as incomplete VKH disease.

Studies indicated that the clinical manifestations of VKH disease are caused by an inflammatory autoimmune response, which is mediated by $CD4^+$ cytotoxic T-lymphocyte against melanocyte-related antigens in the target organs, such as the eye, inner ear, meninges and skin[1,6]. VKH-derived lymphocytes recognize synthetic peptides derived from tyrosinase which is an enzyme uniquely expressed by melanocytes and involved in melanin synthesis, and are activated to initiate the immune response in VKH disease. Furthermore, it is widely accepted that genetic factors and exogenous or environmental trigger may play important role in the initial stage of VKH disease. Although the definitive mechanisms involved need further detailed research, the hypothesis that virus may play a triggering role in the disease is widely accepted. Meningeal manifestations including fever, headache, and EBV DNA discovered in the cerebrospinal fluid (CSF)[7]or vitreous[8] from patients with VKH disease provided evidence for the triggering role of a viral infection resulting in this disease. However, other studies could not verify these results, and EBV is a common virus in humans. According to evidence accumulated during past decades with the rapid advancement in several domains of basic science, a mechanism of molecular mimicry was proposed. Exogenous antigens encoded by viruses may resemble proteins from pigmented cells which can be recognized by specific HLA-class II molecules, subsequently activating the immune reaction. Sugita et al found the similarity between a cytomegalovirus-associated peptide and tyrosinase peptide, and suggested that some T cells from patients with VKH disease responded strongly to both peptides[9,10]. Furthermore, microbial immune products can be recognized by Toll-like receptors (TLRs), consequently triggering the innate immune responses. Currently, the increased expression of TLR3 and TLR4 in macrophages from active VKH patients compared to controls provided evidence for the role of TLRs in the pathogenesis of VKH disease[11].

According to early studies, Mycoplasma pneumoniae[12]and influenza A virus[13] have been reported to be associated with the development of VKH disease. In our report, this patient presented with VKH symptom 2 weeks after SARS CoV-2 infection. Thus, we hypothesized that SARS CoV-2 may play a triggering role in initiating the VKH disease.

COVID-19 typically manifests as an acute respiratory disease with inflammatory and vascular complications caused by SARS CoV-2. However, the SARS-CoV-2 is known to cause various clinical symptoms in multiple organ systems including respiratory organ, neurological system, cardiovascular, gastrointestinal tract, immune, eye and so on[14]. Most patients presented with fever, headache, cough, sore throat, and fatigue. While, severe COVID-19 may progress to acute respiratory distress syndrome, cytokine storm and multi-organ failure[15]. Our patient, confirmed SARS-CoV-2 infection by PCR, presented with fever, cough, and headache, and she presented with VKH symptom 2 weeks after COVID-19 infection onset.

A growing number of studies indicated that ocular manifestations were pre-existing or occurred as a result of SARS-CoV-2 infection. Aggarwal reported that ocular manifestations were observed in 11.64% COVID-19-infected patients in the meta-analysis[16]. There is evidence that conjunctivitis is the most common ocular pathology. Furthermore, retinal vascular occlusions, optic neuritis and uveitis have also been associated with COVID-19[2]. To our best knowledge, there have been some cases of VKH disease after COVID-19 vaccination reported[17-19]. However, the case of VKH disease associated with SARS-CoV-2 was rare. For the first time, Santamaria et al described the possible associations between SARS-CoV-2 infection and VKH disease[20]. Eatz reported a case of VKH disease 2 weeks after COVID-19 infection onset, and suggested that SARS-CoV-2 may be a immunological trigger of VKH if COVID-19 infection onset was prior to the 2-week history of VKH symptom onset, or during the prodromal VKH phase[21]. With all these facts,

the triggering role of COVID-19 infection in the development of VKH disease is widely accepted but still uncertain. Based on the analysis above, SARS-CoV-2 infection may directly provoke VKH disease, and also may indirectly lead to VKH disease via molecular mimicry, but further research is need to elucidate the specific mechanism of these two hypotheses. As we all known, the SARS-CoV-2 enters the host cells via binding to the angiotensin-converting enzyme 2 (ACE2) receptor. Several researchers have confirmed that ACE2 receptor is expressed in the eye, specifically on the conjunctiva, choroid, vascular endothelium, and nerves[22]. Thus, it is proposed that the SARS-CoV-2 may attack the choroid resulting in the development of VKH disease. In addition, SARS-CoV-2 may cause dysfunction of immune responses characterized by lymphopenia and an activated lymphocyte profile or dysfunction[23]. T cells can not only express some cell markers which may confer susceptibility to VKH disease, but also product a certain profile of cytokines which may have an effect on the differentiation of naïve T cells, forming a complicated immune environment[23,24]. Under the specific immune environment, activated effector T cells and other effector immune cells may attack tissue with pigment including the choroid, ear, skin and meninges. However, we need to provide additional insight into the definitive underlying mechanism explaining the triggering role of SARS-CoV-2 infection in the VKH disease.

This study has some limitations. Because genetic testing is expensive and cannot be popularized at that time, genetic testing was not performed in our patient. So we cannot confirm the genetic role the pathogenesis of VKH disease. As a case report, the relationship between SARS-CoV-2 infection and the VKH disease cannot be generalized in this study. Further studies are needed to reveal the exact pathogenesis that could be an aid to manage the VKH disease. Clinically, ophthalmologists and physicians should be aware of this possible association between VKH disease and COVID-19. Based on studies reviewed above, SARS-CoV-2 virus could be a possible trigger for VKH disease.

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