One Thing Leads to Another: Vogt-Koyanagi-Harada-Like Syndrome

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Introduction:

A 49-year-old Hispanic male presented to the retina clinic with a chief concern of blurred vision in both eyes for one week. He stated that he was unable to focus and read text on his phone or large print street signs. His past ocular history was significant for myopia in both eyes; however, he did state that he had not worn glasses or had a recent eye exam in the past two years. His past medical history was significant for stage 4 metastatic lung cancer with metastatic lesions to his brain. For his cancer he had previously undergone a craniotomy with resection of cancerous brain lesions two years ago. He was also previously treated with infusions of pembrolizumab, with his most recent infusion 4 months prior to presentation. Additionally, he was also taking sildenafil as needed. His review of systems was significant for a 5-10 lb. weight loss and headaches that had been going on for approximately one month. He denied any rashes, skin discoloration, whitening of his eyelashes/hair, or tinnitus.

Exam:

Visual acuity testing without correction was 20/90 in the right eye and 4/200 in the left eye. Intraocular pressures (IOP) were normal. Pupils were equal, round, and reactive to light without evidence of a relative afferent pupillary defect. Confrontation visual fields were full. Slit lamp examination revealed 1+ cells in the anterior chamber of the right eye and 1-2+cells with keratic precipitates (KP) in the left eye. Both eyes had a nuclear sclerotic cataract. The posterior segment demonstrated 1+ vitreous cells, disc edema, venous dilation, and vascular tortuosity, with multiple serous retinal detachments (RD). The right eye had a notable serous RD nasally (Figure 1) and the macula in the left eye had a large pocket of intraretinal and subretinal fluid (Figure 2). Optical Coherence Tomography (OCT) was obtained of both eyes and demonstrated a bacillary layer detachment (BALAD) as well as choroidal thickening with the left being greater

Figure 1: Color photos showing disc edema, venous dilation and tortuosity, with multiple serous retinal detachments.

Figure 2: Color photos showing disc edema, venous dilation and tortuosity, with multiple serous retinal detachments as well as subretinal and intraretinal fluid involving the macula.

than the right (Figure 3). Fundus autofluorescence imaging of both eyes revealing hypoautofluorescence areas consistent with serous RDs (Figure 4). Fluorescein angiography of the right and left eyes demonstrated stippled hyperfluorescence with pooling into the areas of detachments (Figure 5). Given the patient's presentation as well as the multimodal imaging findings, the differential diagnosis consisted of Vogt-Koyanagi-Harada (VKH) Syndrome, VKH-Like Syndrome, Choroidal Metastasis, Infectious Posterior Uveitis, and Lymphoma. The fact that he had recently received treatment with pembrolizumab made the suspicion high for VKH-like syndrome. A laboratory workup was recommended to rule out infectious diseases and investigate other inflammatory causes of his presentation.

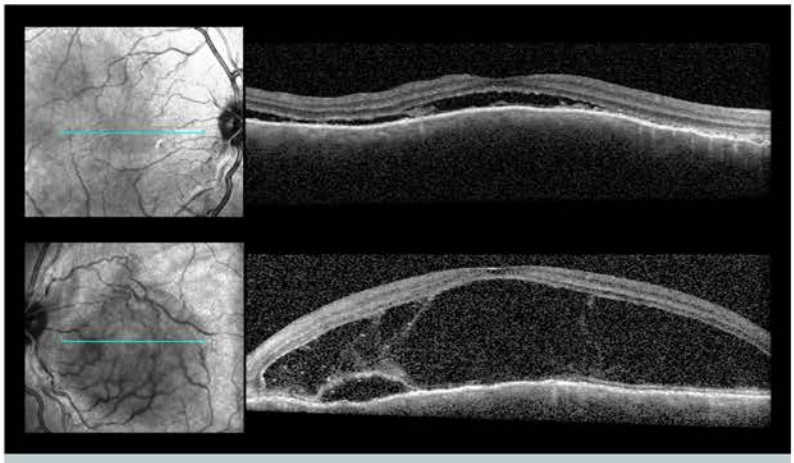

Figure 3: OCT imaging of both eyes demonstrating a bacillary layer detachment (BALAD) and choroidal thickening in both eyes.

Work-Up:

Infectious and inflammatory labs consisted of the following, CBC with differential, Complete Metabolic Panel, Erythrocyte Sedimentation Rate, C-Reactive Protein, RPR, ACE, Lysozyme, QuantiFERON Gold, HLA-B51, HLA-DRB1 0405, HLA-DR4, HLA-DRQ4, and HLA-DR53. As well as a chest X-ray. The lab studies demonstrated a mild elevation of the ESR and CRP. The chest X-ray revealed known metastatic lesions in both lungs. Infectious workup was negative and HLA testing was negative. The patient was then started on high dose systemic steroids with the assistance of his oncologist. Cessation of further pembrolizumab treatment was recommended and discussed with his oncologist. 1 gram of IV methylprednisolone was given for three days followed by 1 mg/kg oral prednisone for 3 weeks with a gradual taper to follow. The patient followed up three weeks after his initial presentation. Visual acuity without correction had improved to 20/70 in the right eye and 20/150 in the left eye. IOP remained within normal limits. Anterior chamber cell had also improved in both eyes and the left eye experienced a decrease in KP. Vitreous cells improved as well as venous tortuosity and dilation. The serous RDs decreased as well (Figure 6). OCT revealed resolution of the bacillary retinal detachments with remnant disruption in the areas of the outer segments. Choroidal congestion had improved on repeat OCT in both eyes as well (Figure 7). The patient noted a slight improvement in his blurry vision, however, did notice some residual distortion when looking at his cell phone.

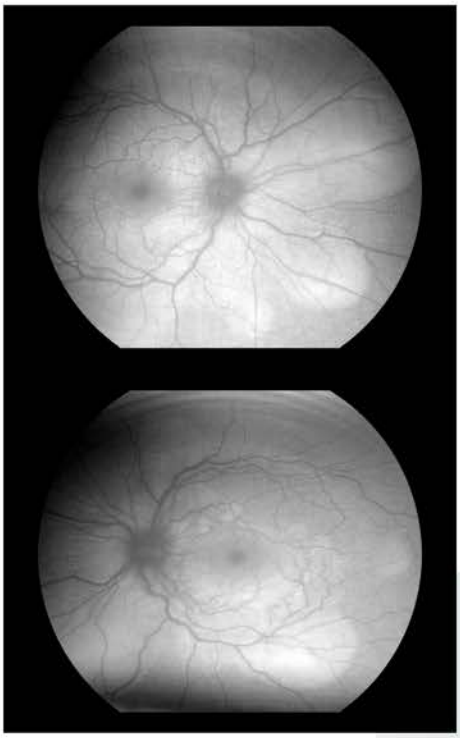

Figure 4: Fundus Autofluorescence imaging of both eyes revealing hypoautofluorescence areas consistent with serous RDs.

Discussion:

VKH is an idiopathic inflammatory disease syndrome that is characterized by granulomatous panuveitis with associated serous retinal detachments. There are often integumentary, auditory, and neurological manifestations that coincide with the ocular signs and symptoms. [1,2] Patients also may have iridocyclitis, diffuse choroidal thickening, and hyperemia of the optic disk. Neurological manifestations tend to occur in the initial stages and manifest as headaches, meningismus and other focal deficits. Patients can experience auditory symptoms such as hearing loss, vertigo, and tinnitus.

Skin changes include patchy alopecia, poliosis (whitening) of the eyelashes, eye brows and scalp hair, as well as patchy vitiligo.[3] It tends to affect more deeply pigmented groups such as Asians, Hispanics, Native Americans, Middle Easterners, and Blacks of non-sub-Saharan descent. The exact pathogenesis is unknown, however it is thought that it is due to a T-cell mediated autoimmune diagnostic criterion one or more antigens associated with melanin, melanocytes, and retinal pigment epithelium.[4] Due to large variations in clinical presentations, the American Uveitis Society adopted a set a diagnostic criteria for VKH consisting of the following: no history of ocular trauma or surgery. As well as three of the following four signs: bilateral chronic iridocyclitis, posterior uveitis with disk hyperemia or edema and serous/exudative retinal detachments, neurological signs of tinnitus, neck stiffness, cranial nerve or CNS problems, or cerebrospinal fluid pleocytosis, and cutaneous findings of alopecia, poliosis, or vitiligo.[2]

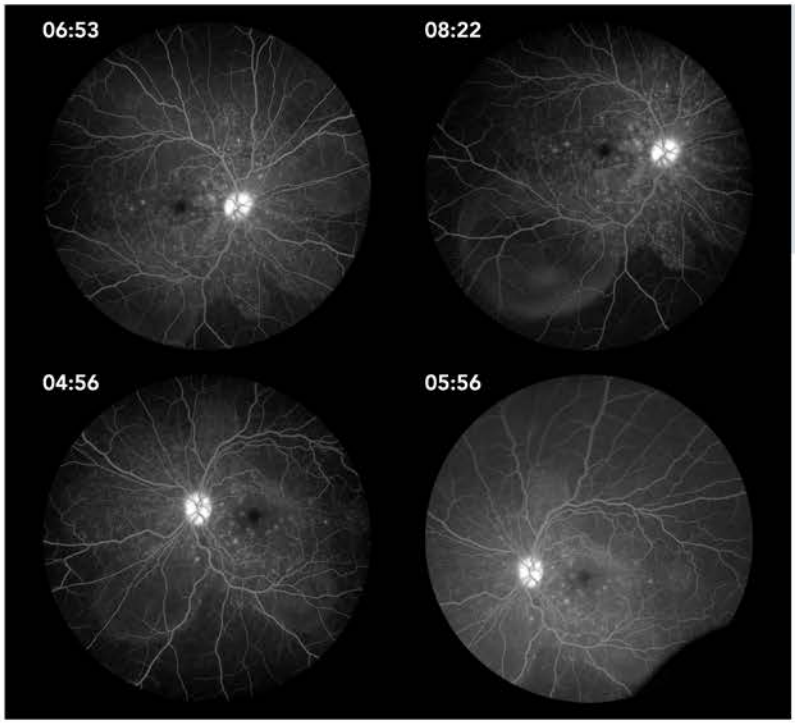

Figure 5: A fluorescein angiogram of the right (top) and left (bottom) eyes demonstrating stippled hyperfluorescence with pooling into the areas of detachments.

Immune checkpoint inhibitors, such as Pembrolizumab, have shown significant promise in treating malignancies such as melanoma, Hodgkin's lymphoma, and non-small cell lung cancer. They effectively work by upregulating the immune system's activity against tumor cells. In doing so this can also cause inflammatory side effects, known as immune-related adverse events (IRAEs) that can include ophthalmic manifestations of anterior, intermediate, posterior, and panuveitis. Pembrolizumab is a programmed cell death inhibitor (PD-1) that is used to treat melanoma, head and neck cancers, Hodgkin's lymphoma, cervical cancers, stomach cancers, and certain types of breast cancers. Prior studies have shown association with this class of medication and VKH-like syndrome. Genetic predispositions for a VKH-like syndrome has been reported with HLA-DR4/DRB1 0405 haplotypes.[5] Both PD-1 and CTLA-4, another chemotherapeutic immune therapy target, have genetic polymorphisms that have been found to be associated with a predisposition for a VKH-like syndrome. This syndrome is thought to be an immune reaction towards melanocytes precipitated by these molecules interacting with the immune system. Interestingly enough, anti-PD-1 agents such as Pembrolizumab, causing an inflammatory reaction can have delayed symptom onset with some reports suggesting as long as 16 months from last medication dose. Our patient's last dose was 4 months prior to his presentation but still had a rather vigorous inflammatory response, especially in the left eye. The large inflammatory response is typically managed with cessation of the offending agent, in this case Pembrolizumab, and initiation of steroid treatment.[1-5] However,

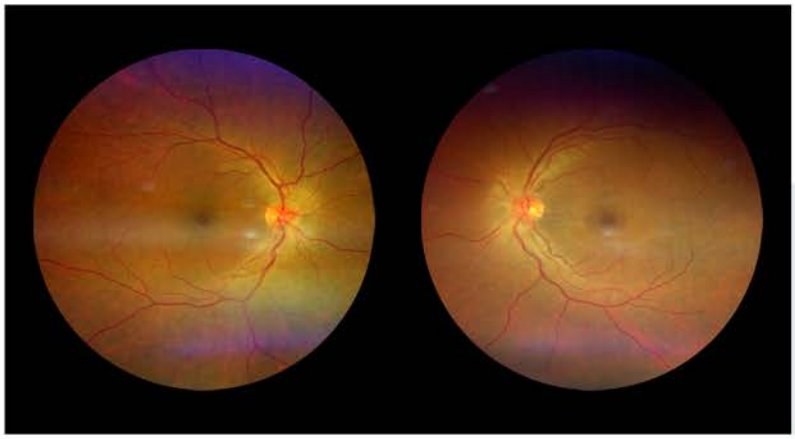

Figure 6: Color photos from follow up after 3 weeks of high dose steroids showing improvement in venous dilation and tortuosity as well as resolution of the serous RDs.

it is critical torule out an infectious etiology prior to the initiation of high dose steroid treatment. It is also paramount to keep in close communication with the patient's oncologist, especially if you are recommending cessation of an active chemotherapeutic treatment.

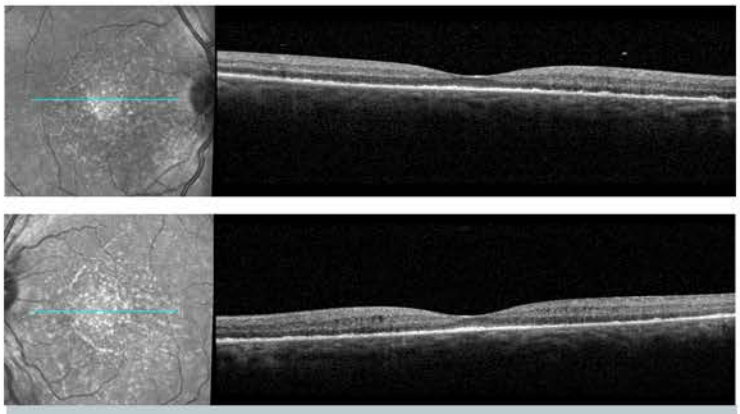

Figure 7: OCTs of both eyes demonstrating resolution of the bacillary retinal detachments with disruption of the outer segments.

Key Points:

- Immune checkpoint inhibitors can cause uveitis ranging from anterior, intermediate, posterior and panuveitis
- A thorough review of a patient's systemic mediations is important to fully elucidate the cause of their uveitis.
- It is important to rule out infectious etiology prior to initiation of high dose steroids in these cases.
- Close communication and collaboration with the patient's oncologist are critical.

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