



Reflectance adaptive optics findings in a patient with Vogt-Koyanagi-Harada disease

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ABSTRACT

Purpose: To describe the reflectance adaptive optics scanning laser ophthalmoscopy (AOSLO) findings in different stages of Vogt-Koyanagi-Harada (VKH) disease and correlate them to visual gain post treatment. Confocal (cAOSLO) and non-confocal split-detector AOSLO (sdAOSLO) were used to assess longitudinally the status of the photoreceptors in a patient with VKH managed on corticosteroid and immunomodulatory therapy.

Observation: A 32-year-old Japanese American female presented with a 2-week history of blurred vision in both eyes (OU) and worsening headache previously diagnosed as a case of VKH and treated with high dose oral prednisone. At the time of presentation, though vision was improving, and frank serous retinal detachments were absent, spectral domain optical coherence tomography (SD-OCT) showed presence of residual subretinal fluid with disruption of the photoreceptor inner segments and outer segments (IS/OS) involving OU. The photoreceptor mosaic at the foveal center appeared very sparse with large areas devoid of visible photoreceptors on cAOSLO, in agreement with the SD-OCT data. sdAOSLO imaging over the same location shows a higher number of contiguous photoreceptors. After imaging, the patient was started on mycophenolate mofetil as steroid-sparing long-term therapy. Three months later, visual acuity improved to 20/20 OU, and SD-OCT showed almost complete resolution of subretinal fluid with significant improvement of the IS/OS SD-OCT signal, OU. cAOSLO imaging revealed a contiguous photoreceptor mosaic without gaps and of normal appearance.

Conclusions and Importance: VKH patients may demonstrate transient photoreceptor abnormalities on SD-OCT and cAOSLO imaging. sdAOSLO imaging revealed intact photoreceptor segments in areas that appeared as voids on cAOSLO, which later showed structural recovery on SD-OCT and cAOSLO. Therefore, sdAOSLO may predict potential for improvement in patients wherein there appears to be photoreceptor loss in cAOSLO and/or SD-OCT.

1. Introduction

First described in 1906 by Alfred Vogt and officially named in 1932, Vogt-Koyanagi Harada (VKH) disease is a rare autoimmune disorder involving the skin, nervous, and auditory systems, with effects that are secondary to destruction of melanocytes by autoreactive T-cells.¹ In the eye, VKH usually presents with bilateral, panuveitis with diffuse chorioiditis manifesting as multiple serous retinal detachments in the acute phase, followed by chronic depigmenting changes with a number of untreated or undertreated patients developing ocular complications

resulting in poor visual outcomes.² VKH frequently affects those of Asian, Middle Eastern, Hispanic, and Native American descent and is rare in Africans. In the USA, VKH accounts for 1–4% of all uveitis.³

Adaptive optics (AO) enhances the performance of optical systems via the reduction of wavefront aberrations, and when used in ophthalmoscopes, it can provide the ability to resolve individual cells in a non-invasive manner. It has been implemented in many optical modalities used in the field of ophthalmology such as Optical Coherence Tomography (OCT), Scanning Light Ophthalmoscopy (SLO), and fundus photography.^{4–11} In this report, we used an Adaptive Optics Scanning Laser

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Ophthalmoscopy (AOSLO) that allows simultaneous reflectance imaging using non-confocal split-detection that reveals the photoreceptor inner segment mosaic and confocal detection, that reveals what is thought to be the photoreceptor IS/OS junction mosaic. AOSLO imaging allows for measurement of cone density in patients with repeatability and reliability of measurements to an acceptable degree.¹²⁻¹⁴ The use of other imaging modalities such as OCT in VKH has been well documented and often shows disruptions in the photoreceptor complex, noted as focal or generalized loss of the photoreceptor inner segments and outer segments (IS/OS) layer, as a result of retinal detachments pathognomonic for the disease.¹⁵⁻¹⁹ A previous study using OCT and flood-illumination AO ophthalmoscopy has shown the apparent recovery of macular cone photoreceptors in a case series of eight VKH patients. The finding was attributed to the loss, and later recovery of photoreceptor outer segments.²⁰ However, such observation begs the question as to whether there is a true loss of the photoreceptor outer segment and subsequent recovery in cases of retinal detachment. One could make the argument that apparent losses on confocal view do not represent true photoreceptor loss and non-confocal imaging may enable greater clarity and visualization of the affected cone photoreceptor mosaic. Recent studies have begun to debunk the long held notion that photoreceptors are incapable of regeneration as they have been shown capable of partial regeneration, developing new outer segments after injury so long as the inner segments are left intact in a supportive microenvironment.²¹

Given these facts, we postulated that the use of non-confocal split-detection AOSLO (sdAOSLO), may provide clues as to the nature of

visual recovery in VKH patients with serous retinal detachment. Therein, we report a case of a 32-year-old Japanese American woman who presented to our clinic with a diagnosis of VKH and was followed with both standard confocal AO-SLO (cAOSLO) and sdAOSLO.

2. Case report

A 32-year-old Japanese American female presented at another institution one month prior to consultation with our institution with complaints of a five-day history of worsening headaches associated with worsening vision, OU. On ocular examination, best corrected visual acuity was 20/60 OU with slit-lamp examination demonstrating anterior chamber inflammation (1+ cells and flare) in OU. Posterior examination showed multiple serous retinal detachments OU which was captured by fundus photography (Fig. 1). Fluorescein angiography (FA) showed focal areas of partially blocked transmission surrounded by hyper-fluorescent borders corresponding to the multiple areas of exudative retinal detachment seen on color fundus photographs (Fig. 2). Spectral domain OCT scans likewise demonstrated multiple areas of serous detachments in both eyes (Fig. 3). The patient was diagnosed with VKH and therapy with high dose oral steroids was begun.

The patient moved after treatment was initiated and was subsequently referred to our institution for follow-up care. The visual acuity was found to be 20/25 OD and 20/30 OS during this first visit. Clinical resolution of the serous detachments with normalization of the fundal appearance OU was noted (Fig. 1). FA images showed window defects

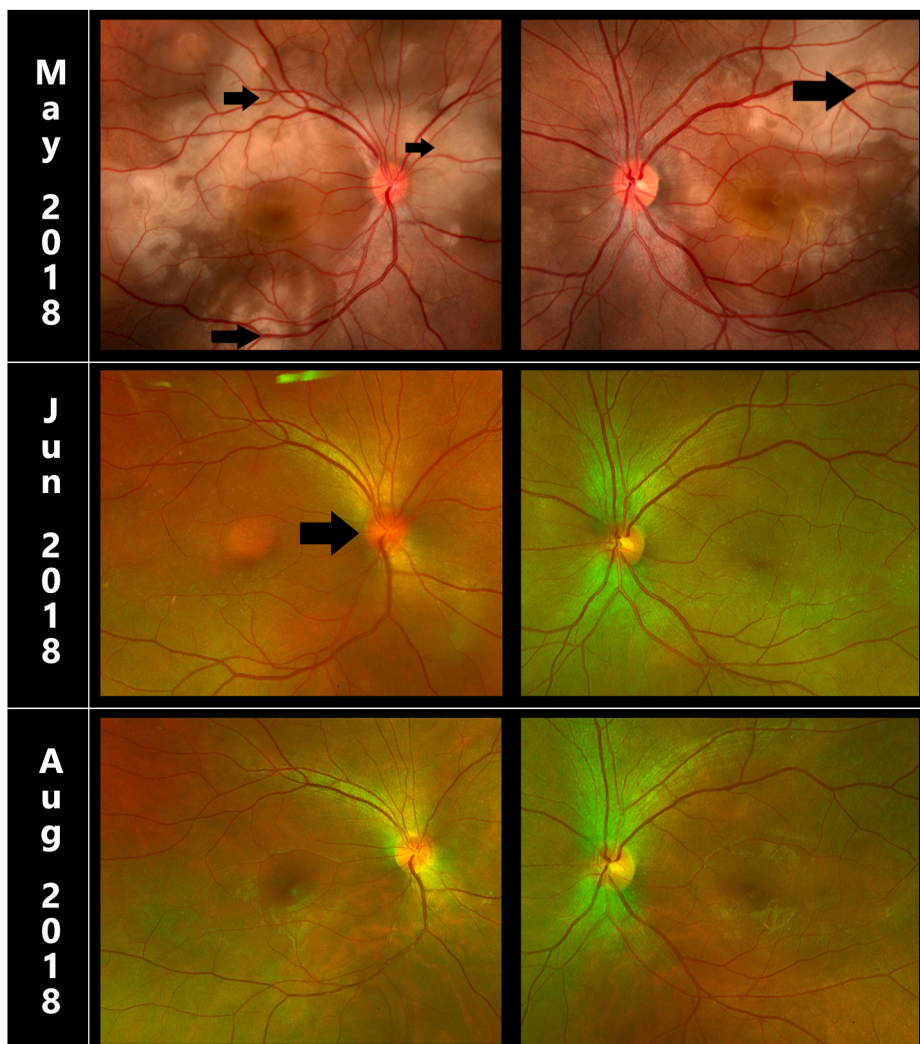


Fig. 1. Color fundus photographs (FP) show multiple areas of exudative retinal detachments covering the posterior pole with macular involvement in both eyes in May 2018 (black arrows). The visits in June and August 2018 show resolution of the serous detachment. The right eye disc appears hyperemic in the pseudo-colored photograph; however, clinical examination determined it is within normal limits (white arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

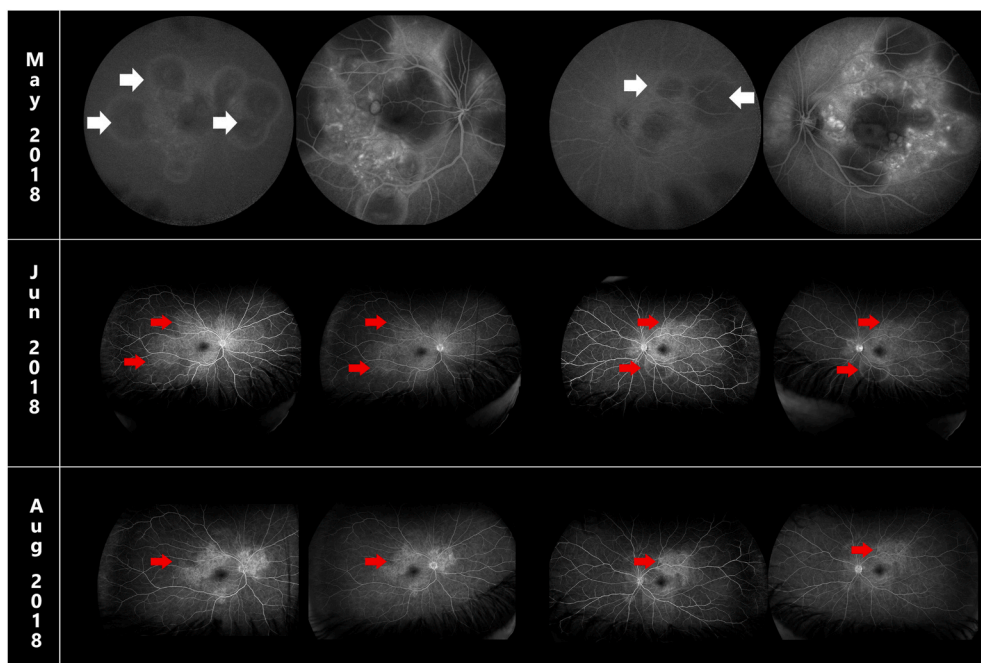


Fig. 2. Fluorescein angiography (FA) shows focal areas of partially blocked transmission surrounded by hyperfluorescent borders corresponding to the multiple areas of exudative retinal detachment seen on color photographs (white arrows). There are focal areas of staining that appear within the lesions in the later phases. Macula is likewise detached with partially blocked transmission in all phases. There is no presence of disc leakage. FA on follow-up visits showed areas of staining corresponding to areas of serous retinal detachments (red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

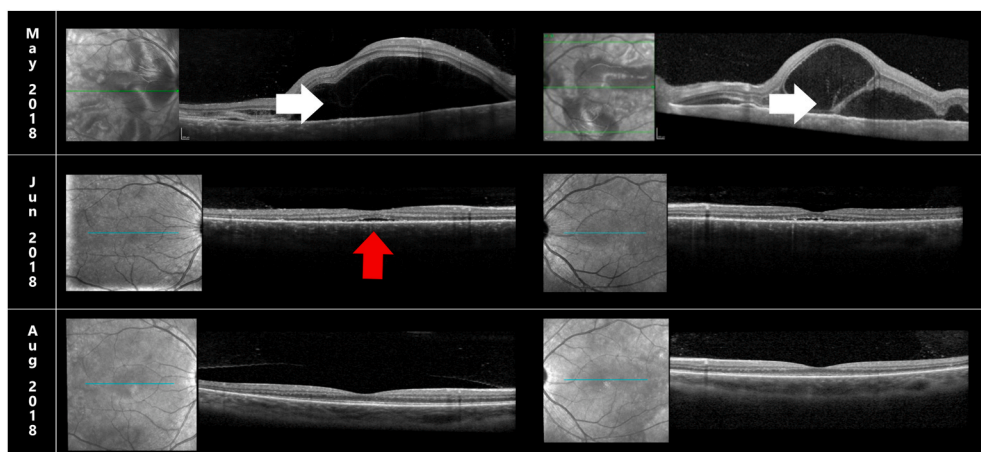


Fig. 3. An optical coherence tomography (OCT) scan shows multiple serous retinal detachments OU in addition to photoreceptor segment disruptions in the macula with foveal involvement captured in May 2018 (white arrows). Follow-up OCT shows marked improvement of serous retinal detachments with residual sub-foveal fluid (red arrow; June 2018) which completely resolved in August 2018. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and minimal staining corresponding to the areas of previous detachment (Fig. 2). SD-OCT likewise showed marked improvement of serous retinal detachments, but subfoveal fluid still remained in OU (Fig. 3). Furthermore, the foveal IS/OS layer appeared to be disrupted in both eyes. Reflectance cAOSLO and sdAOSLO images were obtained to assess photoreceptor status. cAOSLO demonstrated visualization of very few and sparse photoreceptors at the foveal center (Fig. 4). sdAOSLO over the same location revealed some artifacts and difficulty visualizing fine structures over the superior section of the collected image, but showed an overall more intact photoreceptor matrix with visualizable cone segments in sections that appeared as voids on cAOSLO (Fig. 4). Due to persistence of subfoveal fluid, treatment with mycophenolate mofetil 1000 mg twice daily as steroid-sparing long-term therapy was initiated, and prednisone was continued on tapering dose.

The patient followed-up two months later with visual acuity improvement to 20/20 in OU; no signs of active inflammation on physical exam were detected. Posterior pole examination and FA showed no change from previous assessments. SD-OCT showed complete resolution of the subretinal fluid in both eyes with restoration of the photoreceptor layers (Fig. 3). Repeat AOSLO imaging showed

restoration of the normal photoreceptor mosaic on cAOSLO (Fig. 4).

Since then, the patient has been stable on immunomodulatory therapy with mycophenolate at various follow-up visits.

3. Discussion

The identification of affected anatomical structures and to which extent damage may be reversible is an important part of any mechanism of disease. The high axial resolution of OCT images has been found quite useful in this regard through strong correlation with human histological and animal model data.²² AOSLO complements OCT by providing high transverse resolution that reveals individual cells, and in particular the photoreceptor mosaic. Their combined use can improve our understanding of retinal pathology, as we demonstrate here.

Though it is known that the process by which VKH leads to eye inflammation and damage is primarily T-cell driven with genetic and racial predilections, the exact antigens involved are still poorly understood.²³ In addition, there have been conflicting studies about the presence of autoantibodies for interphotoreceptor retinoid binding protein (IRBP) in cases of VKH.^{24,25} It is theorized that these

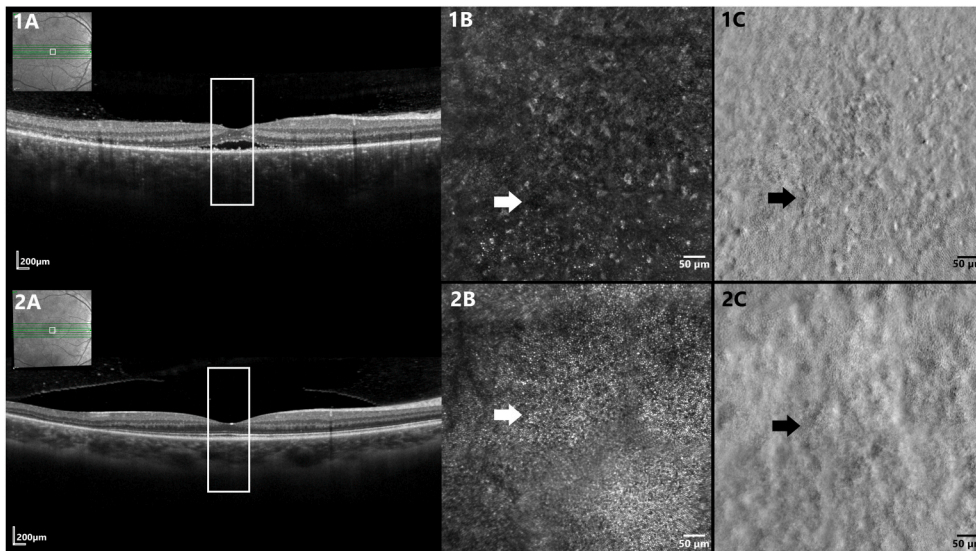


Fig. 4. Adaptive optics scanning laser ophthalmoscopy (AOSLO) imaging of the Vogt-Koyanagi-Harada Disease. Column (A) shows optical coherence tomography (OCT) (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) horizontal scans through the fovea for each subject visit (June 1, 2018; August 2, 2018) and the white box represents the region of interest imaged with AOSLO which is presented in columns (B) and (C). Column (B) depicts confocal AOSLO (cAOSLO) and column (C) split detection (SD) AOSLO. At visit 1, on OCT, there is clear separation of the retina with the disruption of IS/OS or ellipsoid zone secondary to residual subretinal fluid. There is non-visualization of cone photoreceptor (white arrow) in confocal imaging while the corresponding inner segments of cone photoreceptors (black arrow) are visualized on non-confocal imaging. At the follow-up visit (2), the OCT demonstrated restoration of normal anatomy with improvement in previously disrupted IS/OS or ellipsoid zone as well as total resolution of previously noted sub retinal fluid. The cor-

responding confocal and non-confocal imaging are able to visualize cone photoreceptors. All AOSLO images were acquired using a custom-built AOSLO housed at the Byers Eye Institute at Stanford University, USA. Scale bar is 50 μ m.

autoantibodies may thus, be either a phase-dependent or a secondary response to retinal detachment and may not be an inherent component of VKH as a disease process.³ Animal models of VKH have demonstrated two possible mechanisms of photoreceptor damage, either as a direct consequence of the diffuse inflammatory state brought about by the disease²⁶ or as a secondary consequence due to the shearing effects of retinal detachment where photoreceptor outer segments, the outer nuclear and plexiform layers in particular were found to be most affected.²⁷ In their study using AO fundus camera, Nakamura et al. stated that the use of AO further supported the notion that photoreceptor outer segment damage indeed played a role in the pathogenesis of VKH and photoreceptor recovery is an observable part of the healing process with the initiation of therapy.²⁰

Investigations performed on photoreceptor recovery show that reattachment in cases of retinal detachment appears to prevent further lowering of measured cone densities and restores normal anatomy though end cone density measurements, but not necessarily final visual acuity, is often reduced as a consequence.^{28–30} In their study, Nakamura et al. have theorized that there may be a high redundancy of cone photoreceptors to retinal ganglion cells and such redundancy may allow for relatively good vision even in the face of cone density reductions.^{20,31} In the case of VKH, however, damage caused by retinal detachment is compounded by inflammatory processes and a study conducted by Okamoto et al. has shown that the cone density recovery time in these patients are often significantly longer.³² Nakamura et al. have added to this concept, indicating that end cone densities are often lower than those in normal populations post recovery.²⁰ Focal disruptions of the photoreceptor mosaic on both cAOSLO and sAOSLO imaging on the other, have been noted as linked to poor end vision outcomes in a case of central serous retinopathy reported by Sun et al.³³ Similar findings have been noted in eyes with poor vision due to various conditions when imaged, showing focal IS/OS losses on OCT and visible photoreceptor mosaic abnormalities on both cAOSLO and sAOSLO.³⁴ These studies demonstrate that consistent photoreceptor loss on multimodal imaging correlates with poor vision and that the use of both cAOSLO and sAOSLO may have some prognostic value in cases wherein photoreceptor loss secondary to eye disease is suspected.

In our patient, though the IS/OS layer was disrupted on OCT and the photoreceptor mosaic appeared disrupted initially on cAOSLO, use of

sAOSLO showed a contiguous-appearing photoreceptor matrix when the same area was imaged. This contiguous appearance was maintained on sAOSLO during treatment alongside seeming restoration of the IS/OS layer on OCT and the photoreceptor matrix on cAOSLO. This may indicate that, contrary to prior notions, photoreceptors, rather than being destroyed, may simply be displaced or otherwise not ready visualizable via the prior methods of OCT and cAOSLO. This shows a potential benefit of sAOSLO in regards to its increased ability to visualize photoreceptors. As to whether definitive photoreceptor loss, even on sAOSLO would correlate to poorer end visual prognosis in patients with VKH or similar disorders, further investigation will be required.

Additionally, in our management, we employed early use of antimetabolite therapy using mycophenolate mofetil due to residual subfoveal fluid which may have allowed for rapid resolution of fluid and preservation of cones. Such approach resulted in recovery not only of vision to 20/20 OU, but also demonstrated photoreceptor mosaic restoration of normal appearance.

In conclusion, the findings of our index patient contrast with the other studies mentioned earlier wherein end cone densities are often noted to be reduced with corresponding appearance changes of the photoreceptor mosaic on follow-up AOSLO imaging. In our patient, we noted apparent recovery of the IS/OS layer on OCT as well as seeming restoration of a normal-looking photoreceptor mosaic on cAOSLO follow up imaging after early initiation of steroid-sparing antimetabolite therapy due to abnormal follow up findings on OCT and cAOSLO despite improving vision in a case of VKH. The use of antimetabolite therapy has been shown to control inflammation more rapidly in VKH, leading to less dependence on steroids.¹⁷ Furthermore, mycophenolate in particular has been shown to prevent the chronic effects of VKH such as the dreaded sunset glow fundus appearance.³⁵ The recovery status of our patient has shown that a rapid resolution of both retinal fluid and retinal inflammation is paramount in order to achieve ideal end vision outcomes. Anatomically, AOSLO may be able to correlate these outcomes by depicting a restoration of the normal photoreceptor mosaic appearance on cAOSLO. In the active disease state, the employment of non-confocal imaging techniques such as sAOSLO was able to demonstrate intact cone photoreceptor inner segments where cAOSLO could not. This may indicate that, contrary to previous notions, photoreceptors may not be lost and subsequently regenerate in

VKH-associated detachment, but may be rendered temporarily displaced or disorganized due to edema fluid. The presence of intact photoreceptors on sdaOSLO imaging illustrates that seeming losses on OCT and caOSLO may not represent true photoreceptor loss. More studies are needed in order to determine if photoreceptor losses on sdaOSLO correlate with poor visual end outcomes in order to determine the significance of finding intact photoreceptors on sdaOSLO imaging. As to the importance of cone density, further research is needed in order to discover density thresholds required to maintain acceptable vision. Finally, our combination of innovative imaging techniques supported the notion that early and aggressive treatment in cases of VKH may improve visual and structural outcomes. One may not generalize from a single case though and more studies need to be undertaken. These newer imaging techniques, however, show great potential for guidance in the path clinician-scientists take as they continue to push the boundaries of science.

Patient consent

The patient gave verbal permission. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria.

Declaration of competing interest

The authors declare that there are no conflicts of interest related to this article.

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