GRAYING EYELASHES, HEARING LOSS, AND BLURRY VISION: AGING OR ...?

A close look at an uncommon autoimmune disease.

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A 72-year-old Caucasian man presented to our office for cataract evaluation. His chief complaint was blurry vision. His medical history was positive for type 2 diabetes mellitus, well-controlled with metformin, and hypercholesterolemia. He denied smoking and reported occasional alcohol consumption. The patient's BCVA was 20/40 in the right eye (OD) and 20/50 in the left eye (OS). IOP at presentation was 14 mm Hg OD and 15 mm Hg OS.

External examination revealed 2+ dermatochalasis and poliosis along the upper lashes of each eye (OU) (Figure 1). Pupillary

Figure 1. Photograph shows 2+ dermatochalasis and poliosis along the upper lashes OU.
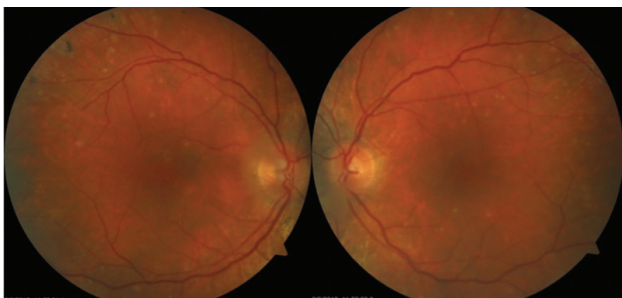

Figure 2. Posterior pole fundus photography demonstrates optic disc hyperemia, macular edema, and diffuse focal retinal pigment epithelium dropout in the macula OU.

and motility examinations were within normal limits. Anterior segment examination was significant for mutton-fat keratic precipitates and 2+ nuclear and 2+ cortical cataracts OU. Dilated posterior segment examination revealed optic disc hyperemia, macular edema, and diffuse focal retinal pigment epithelium (RPE) dropout in the macula (Figure 2). Peripheral examination demonstrated diffuse RPE atrophy and depigmentation, with areas of focal RPE scarring (Figure 3).

OCT revealed macular edema OU (Figure 4) and a Dalen-Fuchs nodule OD (Figure 5). Fluorescein angiography demonstrated diffusely scattered dots of hyperfluorescence caused by window defects at the level of the RPE, moderate macular leakage, and disc leakage (Figure 6).

Review of systems was positive for hearing loss, tinnitus, dizziness, and neck pain. The patient reported no nausea, vomiting, fever, chills, fatigue, chest pains, new rashes, joint
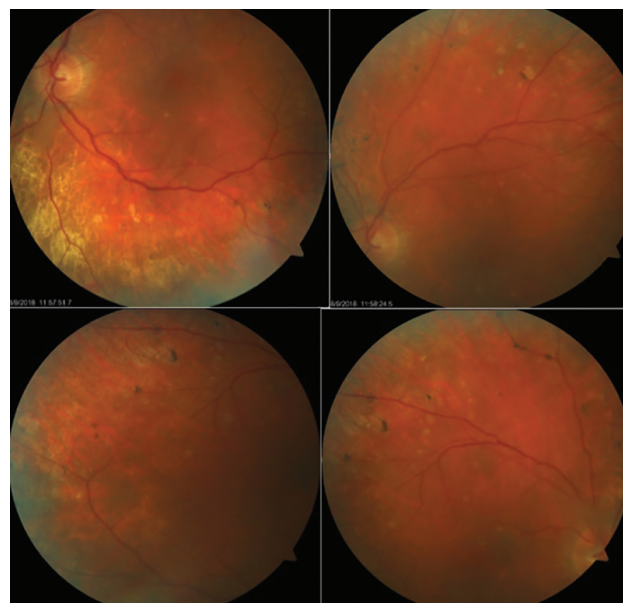

Figure 3. Peripheral fundus photography demonstrates diffuse RPE atrophy and depigmentation with areas of focal RPE scarring OU.

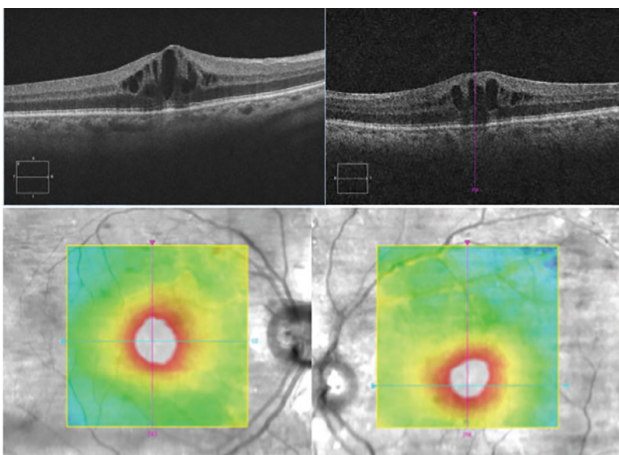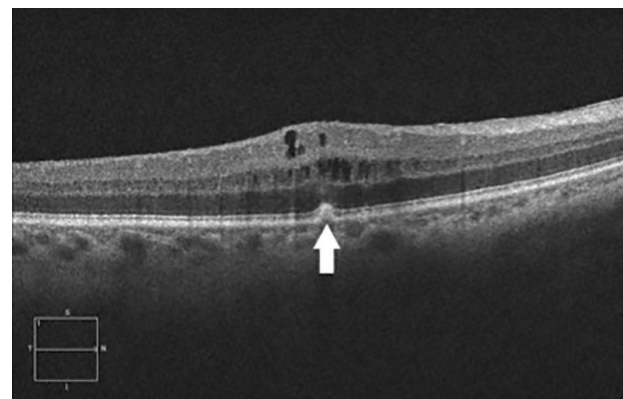Figure 4. OCT shows macular edema OU.

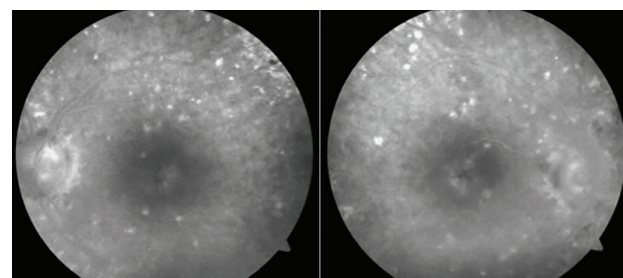Figure 5. OCT demonstrates a Dalen-Fuchs nodule OD.

Figure 6. Fluorescein angiography demonstrates diffusely scattered dots of hyperfluorescence caused by window defects at the level of the RPE, moderate macular leakage, and disc leakage OU.

pain, weight loss or gain, cough, or recent travel. He also reported no prior ocular trauma.

Uveitis workup, including antinuclear antibodies, angiotensin-converting enzyme, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, HLA-B27, and titers for toxoplasma, sarcoid, Lyme, and toxocara was negative.

Differential diagnosis with these ocular and systemic findings includes sympathetic ophthalmia, central serous chorioretinopathy, posterior scleritis, acute posterior multifocal placoid pigment epitheliopathy, and Behçet disease. We believe this patient to be in the convalescent stage of Vogt-Koyanagi-Harada (VKH) disease and will plan treatment accordingly.

DISCUSSION

VKH disease is a multisystem autoimmune inflammatory disorder with neurologic, skin, auditory, and ocular manifestations.[1] This disease primarily affects individuals with dark

AT A GLANCE

▶ Vogt-Koyanagi-Harada (VKH) disease is a multisystem autoimmune inflammatory disorder with neurologic, skin, auditory, and ocular manifestations.

▶ Treatment of VKH disease involves the use of an immunosuppressive agent with steroidal and nonsteroidal therapy.

▶ Early diagnosis and treatment of VKH disease is key for optimal clinical outcomes and potentially complete remission of the disease.

skin pigmentation. In a patient like ours, a white man, VKH is noted as being "distinctly uncommon."[2] The pathogenesis of VKH is not well understood. Evidence suggests that the target of autoimmunity is a melanin-associated antigen.[2] Xu et al found that serum interleukin-25 was significantly lower in patients with VKH than in a control group. However, the significance of this finding has yet to be discovered.[3] A retrospective analysis found that 93.8% of VKH patients tested were HLA-DR4 positive.[4] Unfortunately, neither of those findings are specific to VKH; only clinical findings can lead to a diagnosis of VKH.[5]

The diagnostic criteria for VKH are not widely agreed upon. There have been several sets of proposed criteria for diagnosing the disease, but each set takes a slightly different approach. The Diagnostic Criteria for VKH Disease proposed by Yang and colleagues were based on data from 659 patients in northern China.[6] These data are detailed in the Table on the next page. Definitive diagnosis of early-phase VKH disease can be made based on three variants:[6]

- Variant 1: Patients presenting with criteria A, B, C, and D1.
- Variant 2: Patients presenting with criteria A-C as well as D2 and D3, or D4.
- Variant 3: Patients already treated with systemic corticosteroids with or without immunosuppressive agents who have a history of typical appearances of variant 1 or 2 as well as criteria A-C and D5.

TABLE. DIAGNOSTIC CRITERIA FOR VKH DISEASE	
· No history of penetrating ocular trauma or intraocular surgery preceding initial onset of uveitis	
· Bilateral ocular involvement (time interval between the two eyes should be ≤ 2 weeks	
· No evidence of infectious uveitis or accompanying systemic rheumatic diseases or evidence suggestive of other ocular disease entities	
Early-phase VKH disease:	– Signs of diffuse choroiditis and exudative retinal detachment
	– Serous retinal detachment on OCT or B-scan ultrasonography
	– Choroidal thickening on enhanced depth imaging OCT
	– Early punctate staining and late subretinal dye pooling on fluorescein angiography
	– Hyperfluorescence of the optic disc on fluorescein angiography
Late-phase VKH disease:	– Signs of definite sunset glow fundus or retinal pigment epithelium clumping/migration
	– Signs of bilateral recurrent granulomatous anterior uveitis
	– Signs of Dalen-Fuchs nodules or multifocal chorioretinal atrophy
	– Window defects/moth-eaten fluorescence on fluorescein angiography
	– Previous history of characteristic findings corresponding to diagnosis of early-phase VKH disease

Likewise, late phase VKH is divided into three variants.

- Variant 1: Patients presenting with criteria A-C as well as E1 and E2.
- Variant 2: Patients presenting without sunset glow fundus or visible pigment alterations; criteria A-C, E2, and either E3 or E4 must be met.
- Variant 3: Patients presenting with significant media opacity, requiring criteria A-C, E2, and E5.

Stages of VKH

VKH presents in four clinically distinct stages: prodromal, uveitic, convalescent, and chronic recurrent.[1] The prodromal stage occurs during the first 3 to 5 days of the disease process and is characterized by neurologic findings such as tinnitus, neck stiffness, and hearing loss. Examination of cerebrospinal fluid will reveal lymphocytic pleocytosis, which can last several weeks.

The uveitic phase marks the beginning of ocular manifestations. Diffuse choroiditis with multiple locations of exudative retinal detachments and optic disc swelling are common.[1] As the disease progresses to the convalescent stage, integumentary findings, such as poliosis, vitiligo, alopecia, and choroidal depigmentation, described as *sunset-glow fundus*, may present.[1] The chronic recurrent phase is characterized by recurrent granulomatous anterior inflammation.[2] Patients at this stage present with higher rates of sunset-glow fundus, Dalen-Fuchs nodules, cataracts, and ocular hypertension.[2]

Symptom Distribution

A review of 32 patients at a tertiary uveitis clinic in Turkey provided some understanding of symptom distribution for VKH.[7] Sixteen patients (16%) presented with acute uveitic disease, four of whom (25%) experienced recurrent inflammation. Of those with acute uveitic disease, 75% experienced exudative retinal detachment with optic disc edema or hyperemia, and the other 25% presented with only optic disc involvement.[7] Perhaps the most important finding of this study was that only 31.2% of patients experienced all three manifestations of the disease (dermatologic, neurologic, and ocular).

Treatment

Treatment of VKH involves the use of an immunosuppressive agent with steroidal and nonsteroidal therapy. A recent study by Herbort and colleagues found that a therapeutic window of opportunity exists during the initial 2 to 3 weeks of the disease process that may lead to complete remission.[8] They found corticosteroid monotherapy to be inappropriate and ineffective, even when given within the therapeutic window of opportunity. Instead, they recommended a combination of corticosteroids with first-line nonsteroidal immunosuppressive therapies, such as cyclosporine, azathioprine, mycophenolate mofetil, and anti–tumor necrosis factor-alpha agents. Treatment should aim not just at remission of symptoms but also remission of choroidal subclinical disease, as monitored by indocyanine green angiography.[8]

Another study comparing corticotherapy and corticotherapy with immunosuppressive therapy in acute VKH found that the two did not differ significantly in terms of final VA or in development of visually significant complications; however, corticotherapy with immunosuppressive therapy was found to lead to significantly lower rates of recurrence.[6] A larger study in 2018 found that reduced-dose corticosteroids with immunosuppressive agents controlled uveitis in 98% or more of patients, regardless of disease progression.[9]

A report by Budmann, Franco, and Pringe discussed long-term treatment with infliximab (Remicade, Janssen) and methotrexate in a pediatric patient over a 10-year period with no recurrences.[10] However, when discontinuation of infliximab was attempted after 3 years, there was a recurrence of 2+ anterior chamber cells.[10]

Caution should be used when treating ocular pathologies in patients with known VKH. Ranjan and Agarwal reported rebound inflammation in 43-year-old man treated with bevacizumab (Avastin, Genentech) injections

for subfoveal choroidal neovascular membrane.[11] Oral corti-costeroids and immunosuppressants led to a resolution of his rebound exudative retinal detachment and keratic precipitates.

Finally, in contrast with other chronic uveitic conditions, macular edema is not typical in patients with VKH. Our patient had diffuse macular edema OU. Rutzen and colleagues determined that leakage of perifoveal vessels from chronic inflam-mation is the cause in cases such as these. They also found that macular edema in VKH responded well to sub-Tenon triamcino-lone injections, resulting in improvement in VA.[12]

DEALING WITH VKH

VKH disease is an uncommon autoimmune disease with a relatively well-defined clinical course. Clinical symptoms are currently the only way to diagnose VKH. Early diagno-sis and treatment are key for optimal clinical outcomes and potentially complete remission of the disease, but all patients with VKH can benefit from a combination of ste-roidal and immunosuppressive therapies. ∎

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