BILATERAL SUBRETINAL FLUID IN A 66-YEAR-OLD WOMAN

Findings on multimodal imaging led to a diagnosis of autosomal recessive bestrophinopathy.

BY TIMOTHY T. XU, MD; JUSTIN C. MUSTE, MD; AND SIDRA ZAFAR, MD

A 66-year-old Asian woman was referred to our clinic for evaluation of bilateral subretinal fluid. The referring physician had raised concern for chronic central serous chorioretinopathy (CSCR). The patient reported chronic bilateral progressive vision loss since early adulthood but denied acute visual changes and nyctalopia. Her ocular history was notable for hyperopia and mild cataract, and her medical history included diet-controlled type 2 diabetes and hyperlipidemia. She denied all pertinent medications associated with retinal toxicity and had no known family history of vision loss.

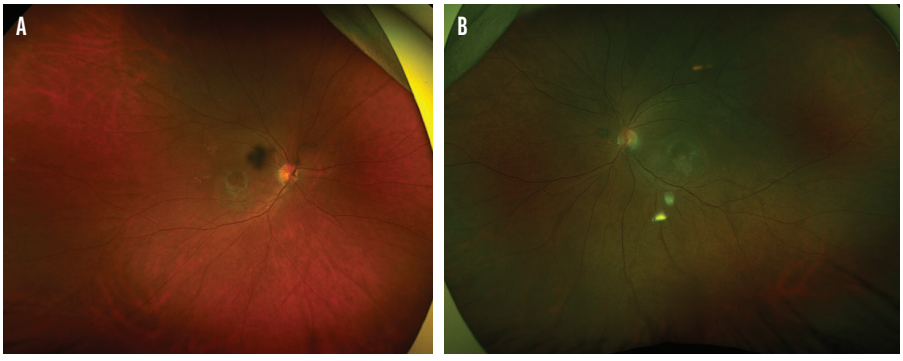

Figure 1. Ultra-widefield fundus photography of the right (A) and left (B) eye demonstrated bilateral perifoveal circular hypopigmentation with temporal vitelliform punctate lesions in the temporal macula.

On examination, her VA was 20/200 OU, and manifest refraction revealed mild hyperopia (+0.75 spherical equivalent OU). Examination of the anterior segment was unremarkable, other than 1+ nuclear sclerosis cataract in each eye. Vitreous cell and vitreous haze were not present. Dilated fundus examination demonstrated bilateral perifoveal circular hypopigmentation with temporal vitelliform punctate lesions in the temporal macula (Figure 1).

IMAGING AND WORKUP

Autofluorescence demonstrated corresponding hypoautofluorescent foveal changes with a surrounding hyperautofluorescent rim (Figure 2). OCT showed bilateral subretinal fluid and disruption of the outer retinal layers (ie, interdigitation zone, ellipsoid zone) with notable pachyvessels. Fluorescein angiography showed corresponding late macular hyperfluorescence without smokestack appearance or expansile dot (Figures 3 and 4). The combination of subretinal fluid, temporal vitelliform punctate lesions, and foveal outer retinal abnormalities prompted consideration of a broad differential diagnosis, including pachychoroid spectrum disease, infectious/inflammatory etiologies (eg, syphilis, tuberculosis, sarcoidosis, Vogt-Koyanagi-Harada disease, posterior scleritis), drug-induced retinopathies (eg, hydroxychloroquine, pentosan polysulfate sodium, tamoxifen), and inherited retinal disease (IRD; eg, Stargardt disease, *PRPH2*-associated pattern dystrophy, bestrophinopathies, cone-rod dystrophy, Sorsby macular dystrophy).

Complete blood count, comprehensive metabolic panel, syphilis serologies, QuantiFERON-TB Gold, angiotensin-converting enzyme level, and chest radiography were each unrevealing. Genetic testing was obtained, which demonstrated two compound heterozygous pathogenic variants in the *BEST1* gene in trans configuration (eg, located on opposite alleles), confirming a diagnosis of autosomal recessive bestrophinopathy (ARB).

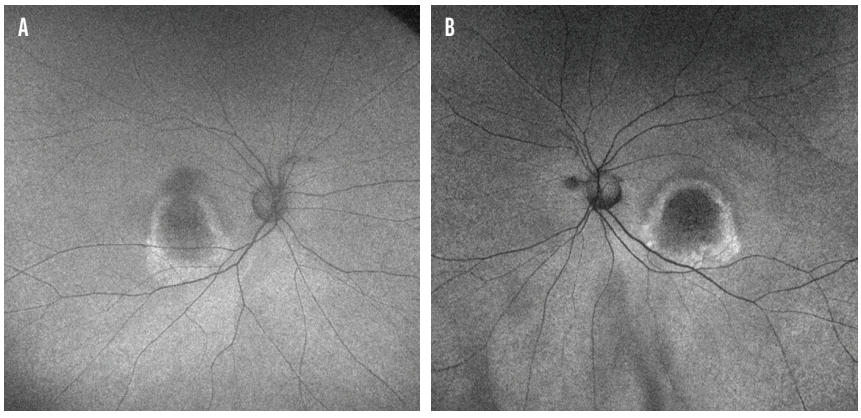

Figure 2. Fundus autofluorescence of the right (A) and left (B) eye demonstrated corresponding hypoautofluorescent foveal changes with a surrounding hyperautofluorescent rim.

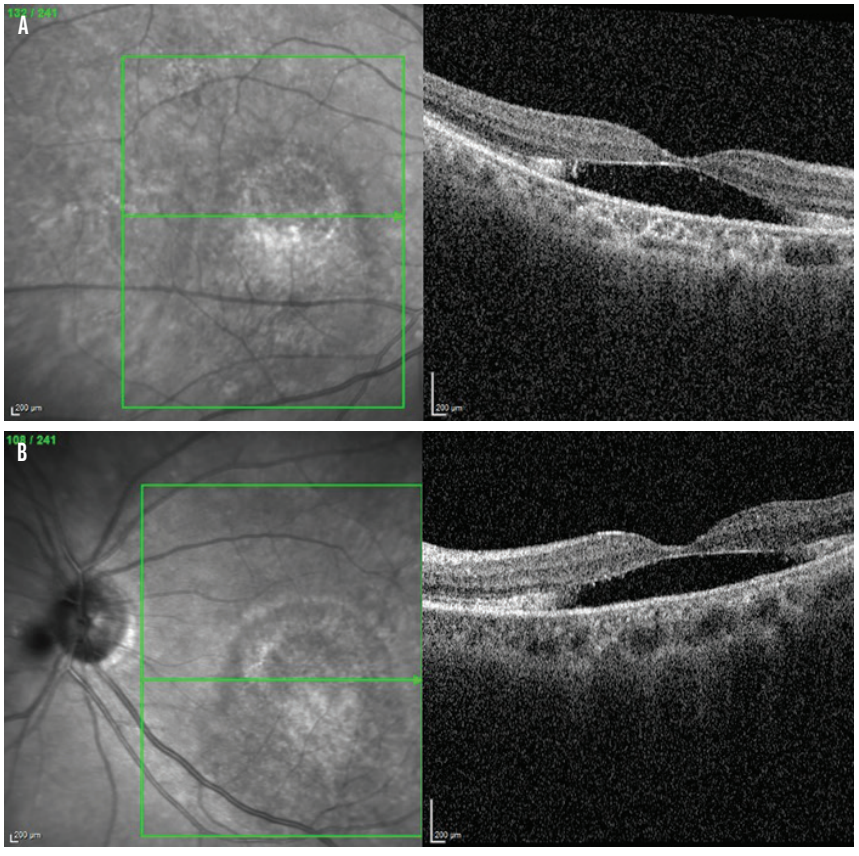

Figure 3. OCT of the right (A) and left (B) eye demonstrated bilateral subretinal fluid and disruption of the outer retinal layers.

ABOUT ARB

The *BEST1* gene encodes bestrophin-1, a calcium-sensitive chloride channel expressed in the retinal pigment epithelium.[1] Pathogenic variants in *BEST1* give rise to a spectrum of IRDs collectively known as bestrophinopathies. These disorders demonstrate substantial phenotypic variability including Best vitelliform macular dystrophy, adult-onset foveomacular vitelliform dystrophy, autosomal dominant vitreoretinochoroidopathy, and ARB. Electrooculogram abnormalities are a classic feature of bestrophinopathies.

ARB is a rare phenotype associated with biallelic *BEST1* pathogenic variants.[2] It often presents with multifocal vitelliform deposits, diffuse retinal pigment epithelium abnormalities, intraretinal and subretinal fluid, and widespread retinal dysfunction.[3,4] The phenotype can be highly variable. Reported findings include punctate subretinal fleck deposits extending beyond the vascular arcades, confluent yellow lesions extending into the midperiphery, macular atrophy or fibrosis, vitelliruptive lesions, and exudative retinal detachments. Our patient demonstrated several ARB features, including bilateral subretinal fluid, diffuse fleck-like subretinal deposits, chronic visual decline, and outer retinal abnormalities.

There is currently no definitive treatment for ARB. Management focuses on accurate diagnosis, avoiding unnecessary interventions (eg, intravitreal injections, lasers), low vision support, genetic counseling, and monitoring for complications. At the 1-year follow-up, our patient demonstrated no significant change in symptoms, visual acuity, or OCT findings.

As gene therapy advances, establishing an accurate molecular diagnosis may become increasingly important for future clinical trial eligibility and targeted therapies.

DIAGNOSTIC CHALLENGES WITH IRDS

Accurately diagnosing ARB and other IRDs presents several challenges. First, ARB can masquerade as more common retinal conditions, particularly chronic CSCR or inflammatory disease. Bilateral subretinal fluid frequently prompts evaluation for pachychoroid spectrum disease.

Second, IRDs may present later in life than expected. Although the patient described decreased vision since early

(Continued on page 52)

KEY TAKEAWAYS

- The authors present a case of a 66-year-old Asian woman who was referred for evaluation of bilateral subretinal fluid and was ultimately diagnosed with autosomal recessive bestrophinopathy (ARB) following genetic testing.
- Accurately diagnosing ARB and other inherited retinal diseases is challenging because they may present later in life than expected and their appearance can overlap with more common retinal dystrophies and toxic retinopathies.
- As gene therapies continue to advance, establishing an accurate molecular diagnosis may become increasingly important for future clinical trial eligibility and targeted therapies.

(Continued from page 48)

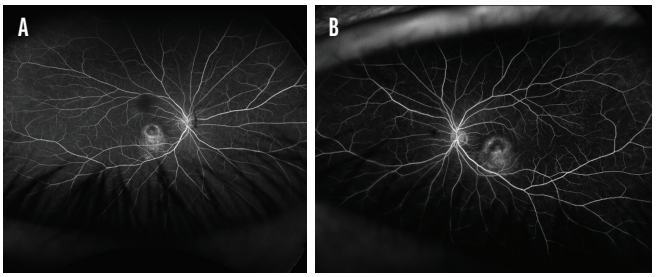

Figure 4. Ultra-widefield fluorescein angiography of the right (A) and left (B) eye demonstrated corresponding late-phase macular hyperfluorescence.

adulthood, she did not receive a definitive diagnosis until her sixth decade of life. Slowly progressive IRDs may remain unrecognized for decades, especially when patients present without a known family history. Lastly, the vitelliform deposits and/or flecked appearance of ARB can overlap with various retinal dystrophies and toxic retinopathies.

Careful attention to the distribution of lesions, presence of subretinal fluid, angiographic findings, and clinical history is critical.

MAINTAIN SUSPICION FOR IRD REGARDLESS OF PATIENT AGE

ARB is a rare IRD that can mimic chronic CSCR, inflammatory disease, and other retinal degenerations. Bilateral, chronic, refractory subretinal fluid accompanied by diffuse vitelliform or fleck-like deposits should prompt consideration of a bestrophinopathy. Multimodal imaging and genetic testing can help differentiate ARB. This case demonstrates the importance of a broad differential diagnosis and how IRD can remain undiagnosed well into adulthood. ■

1. Pontikos N, Georgiou M, Webster AR, et al. Autosomal recessive bestrophinopathy: clinical features, natural history, and genetic findings in preparation for clinical trials. *Ophthalmology*. 2021;128(5):706-718.
2. Querques G, Forte R, Querques L, Massamba N, Souied EH. Natural course of adult-onset foveomacular vitelliform dystrophy: a spectral-domain optical coherence tomography analysis. *Am J Ophthalmol*. 2011;152(2):304-313.
3. da Palma MM, Vargas ME, Burr A, et al. Variable expressivity of *BEST1*-associated autosomal dominant vitreoretinochoroidopathy (ADVIRC) in a three-generation pedigree. *BMJ Open Ophthalmology*. 2021;6:e000813.
4. Shi J, Tian L, Sun TY, et al. Bestrophinopathies: clinical characteristics, natural history, and genetic landscape. *Ophthalmol Retina*. 2026; 10(4):452-464.

TIMOTHY T. XU, MD
- Vitreoretinal Surgery Fellow, Mid Atlantic Retina, Wills Eye Hospital, Philadelphia
- txu@midatlanticretina.com
- Financial disclosure: None

JUSTIN C. MUSTE, MD
- Vitreoretinal Surgery Fellow, Mid Atlantic Retina, Wills Eye Hospital, Philadelphia
- jmuste@midatlanticretina.com
- Financial disclosure: None

SIDRA ZAFAR, MD
- Vitreoretinal Surgery Fellow, Mid Atlantic Retina, Wills Eye Hospital, Philadelphia
- sidrazafariqbal@gmail.com
- Financial disclosure: None