Acute Zonal Occult Outer Retinopathy in Patients With Multiple Evanescent White Dot Syndrome

Howard F. Fine, MD, MHSc; Richard F. Spaide, MD; Edwin H. Ryan Jr, MD; Yoko Matsumoto, MD; Lawrence A. Yannuzzi, MD

Objective: To describe cases of acute zonal occult outer retinopathy (AZOOR) in patients previously diagnosed as having multiple evanescent white dot syndrome (MEWDS).

Methods: In a retrospective case series, we studied fundus photographs, fundus autofluorescence images, optical coherence tomographic scans, fluorescein and indocyanine green angiograms, visual fields, and results of electroretinography.

Results: Three patients diagnosed as having MEWDS developed clinical, angiographic, autofluorescence, visual field, and/or electrophysiologic evidence of AZOOR. Spectral domain optical coherence tomographic findings disclosed attenuation of the photoreceptor inner segment–outer segment junction in areas of AZOOR involvement. In 1 patient, hyperautofluorescence on fundus autofluorescence images during the MEWDS episode coincided with the area of involvement of AZOOR.

Conclusions: Development of AZOOR may occur in patients with MEWDS, suggesting that the conditions may share a common genetic susceptibility and/or pathogenic factor. Although the typical visual prognosis after MEWDS is excellent, subsequent diagnosis of AZOOR may portend a worse outcome.


CUTÉ ZONAL OCCULT OUTER retinopathy (AZOOR) has been reported to occur in eyes previously diagnosed as having white spot syndromes, including punctate inner choroidopathy1 and multifocal choroiditis.2 In addition, overlap between various white spot syndromes has been described, such as the progression of multiple evanescent white dot syndrome (MEWDS) to multifocal choroiditis and vice versa.3 However, the intersection of MEWDS and AZOOR has not been well documented clinically.

Jampol and associates4 originally described MEWDS, which is characterized by numerous yellow-white spots at the level of the retinal pigment epithelium (RPE) or deep retina. The outcome of MEWDS is associated with a rapid recovery over weeks, often with resultant foveal granularity, and it typically has an excellent prognosis with nearly complete visual recovery.5 However, patients can rarely develop recurrences,6 permanent chorioretinal scarring,7 and/or choroidal neovascularization.8

Gass,9 who first described AZOOR, noted minimal to no fundus or fluorescein angiographic changes, loss of zones of outer retinal function, irreversible electroretinographic abnormalities, and permanent visual field loss. Continued field loss may occur months or years after onset. Late in the disease course, atrophy of photoreceptors and RPE can be accompanied by narrowing of arterioles and pigment migration in a bone-spicule pattern.10

The etiologies of both MEWDS and AZOOR remain unknown. We review 3 clinical cases of patients diagnosed as having MEWDS who subsequently demonstrated clinical, angiographic, autofluorescence, visual field, and/or electrophysiologic characteristics diagnostic of AZOOR.

REPORT OF CASES

CASE 1

A healthy 29-year-old white woman sought care for blurry vision in the right eye and periorbital pain. Results of review of systems were negative, although the patient noted having had a purified protein derivative antigen skin test 2 days earlier. Vi-
Visual acuity was 20/100 OD and 20/20 OS. The anterior segments were normal bilaterally. Fundus examination disclosed small punctuate white lesions scattered about the posterior pole in the right eye. Larger white spots demonstrated central clearing. Autofluorescence imaging showed subtle hyperautofluorescence encompassing the same location in the right eye showing subtle hyperautofluorescence encompassing the area affected by the white spots in A (arrowheads). C, Color fundus photograph of the same location in the right eye approximately 3 weeks later, demonstrating resolution of the white dots. D, Humphrey 24-2 visual field of the right eye during the initial episode of MEWDS in A and B, demonstrating blind spot enlargement. E, Color fundus photograph montage of the right eye 14 months after the diagnosis of MEWDS, demonstrating atrophy of the RPE in a peripapillary zone that spares the fovea (arrowheads). F, Autofluorescence montage corresponding to E, demonstrating a zone of hypofluorescence (arrowheads) that coincides with the distribution in E. G, Late indocyanine green montage of the right eye, with a distribution of hypofluorescence (arrowheads) again corresponding to E. Staining of retinal vessels is also present. H, Humphrey 24-2 visual field demonstrating temporal field loss corresponding to the atrophy seen clinically with a diagnosis of AZOOR.

Within 14 months of follow-up, the patient complained of progressive visual field loss in the right eye. Autofluorescence imaging demonstrated diffuse atrophy of the RPE in a zone surrounding the optic nerve head to the nasal half of the macula, sparing the fovea. This atrophy was also evident on indocyanine green angiography. Goldberg and Humphrey visual fields disclosed a marked right temporal visual field loss (Figure 1). Visual evoked potentials reflected gross optic nerve dysfunction, and a full-field electroretinogram showed diminished rod and cone function in the right eye only. These findings were characteristic of AZOOR.

The patient was offered systemic immunosuppression because of the proximity of RPE atrophy to the fovea. She agreed to treatment and was begun on a regimen of prednisone and mycophenolate mofetil. A switch to azathioprine was prompted by an allergic reaction to mycophenolate. Twenty-six months after the initial examination, the visual acuity was 20/20 in both eyes.

CASE 2

A healthy 51-year-old white man experienced photopsias, headache, and an enlarged blind spot in the right eye after a flu-like illness with fevers, chills, night sweats, and diarrhea. Examination disclosed a visual acuity of counting fingers OD and 20/20 OS with a right relative afferent pupillary defect. The anterior segments were normal. The right eye had trace vitritis, mild disc swelling, and multiple white spots at the level of the outer retina in a posterior polar distribution (Figure 2). Results of left fundus examination were unremarkable. There was no family history of retinal or autoimmune disease. A diagnosis of MEWDS was made. During the course of 1 month, the white spots faded clinically (Figure 2).

However, visual acuity did not improve and an extensive medical workup was initiated. Diagnostic evaluation showed a normal complete blood cell count with differential and normal electrolyte levels, results of liver function tests, angiotensin-converting enzyme level, purified protein derivative result, chest radiograph, and magnetic resonance image of the brain. Serologic tests were negative for antinuclear antibody, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, syphilis, Lyme disease, human immunodeficiency virus, toxoplasmosis, and Bartonella henselae. Lumbar puncture yielded normal glu-
Figure 2. Photographs, autofluorescence images, and optical coherence tomographic images of a 51-year-old man with multiple evanescent white dot syndrome (MEWDS) and acute zonal occult outer retinopathy (patient 2). A, Red-free photograph of the right eye during the acute episode of MEWDS. Typical dots and spots are seen surrounding the posterior pole. B, Autofluorescence montage of the right eye 11 months after the acute episode of MEWDS, demonstrating diffuse hypoautofluorescence surrounding the optic nerve head and extending along both superior and inferior arcades, with macular stippling. C, Optical coherence tomographic images of the right (top image) and left (bottom image) eyes. Note the attenuation of the inner segment–outer segment junction in the right compared with the left eye.

A healthy 35-year-old white woman complained of photopsias, a temporal blind spot, and headache. Her visual acuity was 20/20 OU. Examination disclosed normal anterior segments and a right fundus with numerous yellow-white dots and spots (Figure 3) about the posterior pole without vitritis. Her symptoms abated and the fundus appearance normalized, except for minimal foveal granularity, within approximately 1 month. A visual field test was not performed. There was no family history of retinal or autoimmune disease. A diagnosis of MEWDS was made.

Fifteen months after the initial episode, the patient returned complaining of further temporal field loss in the right eye. Examination disclosed 20/20 visual acuity, no evidence of anterior segment inflammation or vitritis, and a well-demarcated zone of RPE atrophy circumscribing the optic nerve but sparing the fovea. A fluorescein angiogram showed a window defect in the area corresponding to the RPE atrophy. A Humphrey visual field demonstrated temporal field loss in the right eye that mirrored the area of atrophy seen clinically (Figure 3). These findings are characteristic of AZOOR.

This report describes 3 patients with MEWDS who were subsequently diagnosed as having AZOOR. The presence of these 2 entities in the same eye implies a common environmental or genetic susceptibility, or that the syndromes share a common etiopathogenesis; otherwise, the probability of a chance concurrence of 2 rare conditions would be infinitesimally small. Although the typical visual prognosis after MEWDS is excellent, the development of subsequent multifocal choroiditis may portend a worse outcome. Similarly, patients who are diagnosed as having AZOOR after MEWDS can experience foveal involvement and/or significant visual field loss.

There were several unique features in the cases examined. The area of involvement of AZOOR in the first case surrounded the optic nerve head and extended out to the nasal half of the macula, sparing the fovea. This area tightly correlated with the hypofluorescence on indocyanine green imaging, with the hypoautofluorescence on autofluorescence imaging, and with the visual field defect. This same zone coincided with a subtle area of hyperautofluorescence during the MEWDS episode that appeared to encompass all of the MEWDS spots, before there was angiographic or clinical evidence of AZOOR.

The pathogenesis of both MEWDS and AZOOR is not yet understood. Therefore, it is difficult to determine whether the clinical appearance of MEWDS merely preceded AZOOR, triggered AZOOR, or even coincided with the onset of AZOOR. In the first and third cases, the patients were asymptomatic after the MEWDS episode but later developed complaints of field loss, suggesting that AZOOR followed MEWDS. However, the second patient never regained normal central visual acuity, atypical of MEWDS, suggesting possible early AZOOR involvement. AZOOR may initially exhibit minimal or no
fundus or angiographic changes, only later causing photoreceptor and RPE cell loss. Spaide previously published autofluorescence imaging findings in a patient with AZOOR demonstrating central hypoautofluorescence, corresponding to RPE atrophy, with a hyperautofluorescent border that he concluded represented lipofuscin accumulation. The contiguous geographic nature of AZOOR does not appear to follow retinal or choroidal vascular patterns or the nerve fiber layer. This suggests that the insult in AZOOR may involve direct cell-to-cell communication.

Gass et al described the long-term follow-up of 51 patients with a diagnosis of AZOOR and noted that several patients who showed blind spot enlargement and normal fundi on initial examination may have previously experienced MEWDS, presumably with fading of the spots before referral. However, direct observation of the MEWDS episodes was lacking.

Our review of the literature failed to identify other convincing cases of AZOOR following MEWDS. Francis and colleagues reviewed the electrophysiologic findings of 28 patients with a diagnosis of AZOOR. Their series included 13 individuals with a history of a white dot syndrome. The authors did not note how many of these 13 were diagnosed as having MEWDS before AZOOR, nor are clinical vignettes or fundus photographs included. Many patients were likely referred after initial examination.

Jampol and Becker noted in 2003 that no cases of MEWDS had yet been observed to overlap with or progress to AZOOR. They argued that each white spot syndrome has a characteristic appearance and prognosis and that the syndromes do not represent manifestations of a single disease complex. They conjectured that genetic factors could, however, predispose a single patient to more than 1 disease entity.

Immunosuppression is often a successful therapy for autoimmune conditions, as well as for diseases with misdirected immunity. However, corticosteroids and other forms of immunosuppression have not been shown to alter the natural course of AZOOR. Unfortunately, convincing evidence supporting a treatment for AZOOR remains elusive.

The cases reviewed herein demonstrate the development of AZOOR in patients diagnosed as having MEWDS. In 1 patient, the area of hyperautofluorescence during MEWDS coincided with the area of involvement of AZOOR. Spectral domain optical coherence tomograms may reflect inner segment–outer segment attenuation in areas of AZOOR involvement. Although the typical vi-
sual prognosis after MEWDS is excellent, a subsequent diagnosis of AZOOR may portend a worse outcome.

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Correspondence: Howard F. Fine, MD, MHSc, Gerstner Clinical Research Center, Edward S. Harkness Eye Institute, Department of Ophthalmology, Columbia University Medical Center, 635 W 165th St, New York, NY 10032 (hffine@gmail.com).
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