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

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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.


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 derivate 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 in a zone encompassing the spots. The patient complained of an enlarged blind spot, which was confirmed with automated perimetry (Figure 1). Laboratory workup demonstrated negative results of serologic tests for Lyme disease and syphilis. Computed tomographic scans of the chest and magnetic resonance images of the brain were within normal limits. There was no family history of retinal or autoimmune disease. A diagnosis of MEWDS was made. Within 3 weeks, the acuity had improved to 20/20 and the retinal spots had faded clinically.

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. Goldmann 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 flulike 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 eye, 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 fundus 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-

Figure 3. Fundus photographs, fluorescein angiogram, and visual field of a 35-year-old woman with multiple evanescent white dot syndrome (MEWDS) and acute zonal occult outer retinopathy (patient 3). A, Color fundus photograph of the right eye exhibiting yellow-white dots inferior to the optic nerve, characteristic of MEWDS. B, Color fundus photograph of the right eye taken 15 months after the initial episode of MEWDS, after the patient complained of blind spot enlargement. Note the peripapillary zone of retinal pigment epithelium (RPE) atrophy that spares the fovea. C, Recirculation-phase fluorescein angiogram demonstrating hyperfluorescence due to window defect from RPE atrophy in a peripapillary distribution sparing the fovea, corresponding to B. D, Humphrey 24-2 visual field of the right eye confirming blind spot enlargement in a distribution reflective of the zone of atrophy seen clinically.
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REFERENCES


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