Acute Zonal Occult Outer Retinopathy
A Classification Based on Multimodal Imaging

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IMPORTANCE We describe the multimodal imaging in a group of patients showing a distinct clinical entity that best represents acute zonal occult outer retinopathy (AZOOR).

OBJECTIVE To propose a classification of AZOOR based on clinical fundus and multimodal imaging.

DESIGN, SETTING AND PARTICIPANTS A retrospective review of patients diagnosed as having AZOOR at 2 centers. After reviewing more than 400 cases diagnosed or referred to us as AZOOR or AZOOR complex, we assembled 30 cases that fit our current definition; (48 eyes) with a median age at diagnosis of 47 years (age range, 17-86 years) and a mean follow-up period of 39 months. Twenty patients were female. Eighteen patients had initially been seen with bilateral lesions, mostly asymmetric (4 cases were symmetric). Most patients had no remarkable medical or ocular history. The median visual acuity at the time of presentation was 20/25 (range, 20/20 to 20/400).

MAIN OUTCOMES AND MEASURES Multimodal imaging, including fundus photography, fluorescein and indocyanine green angiography, fundus autofluorescence imaging, and corresponding eye-tracked spectral-domain coherence tomography imaging.

RESULTS Each patient was initially seen with visual symptoms of photopsia and scotoma, and most had a detectable lesion in the fundus evident clinically or detected on multimodal imaging. The clinical appearance of the AZOOR lesions varied depending on their duration and location, but some features were characteristic, including a demarcating line of the progression at the level of the outer retina and a trizonal pattern of sequential involvement of the outer retina, retinal pigment epithelium, and choroid, as well as frequent zonal progression. Advanced cases of AZOOR demonstrated disruption of the inner and outer retina and severe damage or loss of the retinal pigment epithelium and the choroid.

CONCLUSIONS AND RELEVANCE A specific definition of AZOOR based on multimodal imaging is proposed to help physicians distinguish it from other diseases of the posterior fundus, including white spot syndromes and autoimmune, hereditary, paraneoplastic, toxic, and other inflammatory retinopathies.
In 1992, Gass described 13 patients who were seen with photopsias, a disturbance in central vision, a normal fundus examination at the onset of visual symptoms, and initially or subsequently 1 or more geographic areas of atrophic and pigmentary degeneration. The patients were typically young, often female, and otherwise healthy. Involvement in the fundus was unilateral or bilateral. Zonal field loss was observed and, in some of them, corresponding nonspecific electroretinographic abnormalities. During the follow-up period, many developed retinal arterial attenuation, pigmentary changes in the fundus, and eventually retinal and choroidal atrophy. Mild vitreous inflammation was seen in a few of these patients, and one had peripheral phlebitis followed by retinal pigment epithelium (RPE) degeneration. Based on their clinical presentation and the development and progression of zonal areas of chorioretinal degeneration, Gass believed that the initial manifestations involved the outer retina. He named the condition acute zonal occult outer retinopathy (AZOOR), and his publication was followed by other reports of this novel outer retinopathy. The pathogenesis of the disease was uncertain, but Gass speculated that a virus, entering the retina through the peripapillary area, was the best explanation for the progressive abnormalities in the fundus. Further considerations included its viral hypothesis, an immune-mediated process or toxic retinopathy, or fungal infections. Numerous therapies, including immunosuppressive agents, anti-inflammatory drugs, and antiviral therapy, used singularly and in combination have shown no proven evidence of benefit.

Since the original report by Gass, the described spectrum of changes in the fundus in numerous studies has varied from a normal appearance to a severely damaged retina. Nonspecific chorioretinal signs of inflammation and the unknown etiology of the condition have led to difficulties in distinguishing AZOOR from other entities such as optic neuropathies, paraneoplastic diseases, autoimmune retinopathies, toxic degenerations, and infectious diseases, including diffuse unilateral subacute neuroretinitis, lymphoma, and a myriad of hereditary chorioretinal diseases (eg, retinitis pigmentosa). Perhaps the most difficult disorders simulating AZOOR were the so-called white spot syndromes such as multiple evanescent white spot syndrome, multifocal choroiditis (MFC), and acute macular neuroretinopathy, previously classified by Gass as part of an AZOOR complex. This group of idiopathic diseases shared similarities to AZOOR with regard to its demographic features, inflammatory nature, and primary involvement of the outer retina. In particular, the disease course in patients having MFC with zonal chorioretinal atrophy, a distinct variant of MFC, resembled AZOOR. As the description of AZOOR complex diseases appeared in the ophthalmic literature, confusion was apparent in the understanding of the original AZOOR entity. Articles that described AZOOR were clearly reporting a heterogeneous group of disorders, including studies using electrophysiology and, recently, adaptive optics. Therefore, AZOOR became a general diagnostic term for chorioretinal diseases with visual loss of uncertain origin. However, the advent of modern multimodal imaging has allowed us to reassess our patients previously diagnosed as having AZOOR to classify this entity more specifically, distinguishing it from other masquerading disorders. Herein, we describe the multimodal imaging in a group of patients showing a distinct clinical entity that best represents AZOOR.

Methods

The study was approved by institutional review boards at the Northwestern University Feinberg School of Medicine and Vitreous Retina Macula Consultants of New York (New York City), and it complied with the Health Insurance Portability and Accountability Act of 1996. Oral informed consent was obtained from the participants. We performed a retrospective review of cases that we believed had been appropriately categorized as AZOOR at the Northwestern University Feinberg School of Medicine and at Vitreous Retina Macula Consultants of New York. Three of the patients seen in New York were consultations by mail; the rest of the patients were examined by 2 of us (L.M.J. and L.A.Y.). Seven of the patients seen in New York and one from Chicago have been included in previously published studies.

Most patients had multimodal imaging, including fundus photography, fluorescein angiography (FA) and indocyanine green (ICG) angiography, fundus autofluorescence (FAF) imaging, wide-field FAF imaging, and spectral-domain optical coherence tomography (SD-OCT), performed at the initial visit or at subsequent follow-up visits. Eleven patients did not have complete multimodal imaging because they had been evaluated before the advent of SD-OCT, FAF imaging, and wide-field FAF imaging. The SD-OCT had been performed using a confocal or scanning laser ophthalmoscope and eye-tracked SD-OCT (Spectralis; Heidelberg Engineering). Color photographs, FA, and ICG angiography were obtained using a fundus camera (TRC 501; Topcon Medical Systems). Fundus autofluorescence imaging had been performed with a bandpass filter for the excitation light centered at 550 nm and a matched barrier filter centered at 665 nm. In some patients, wide-field FAF imaging had been performed using a system imaging 200° of the retina (200Tx; Optos plc).

Results

After reviewing more than 400 cases diagnosed in our records or referred to us as AZOOR, including patients with AZOOR complex, we assembled 30 cases that fit our current definition. Each patient had initially been seen with visual symptoms of photopsia and scotoma, and most had a detectable lesion in the fundus evident clinically or detected on multimodal imaging.

Patient presentation included frequent photopias in the area of retinal involvement, distortion of central vision, photophobia, and difficulty with night vision. Those with more advanced cases reported loss of peripheral vision. Patients frequently noted a blind spot in their temporal field. Five eyes were asymptomatic (representing contralateral eyes, whereby
the opposite eye was symptomatic). The median visual acuity at the time of presentation was 20/25 (range, 20/20 to 20/400). Eighteen patients had been initially seen with bilateral lesions (4 symmetric and 14 asymmetric). Twelve patients had a unilateral presentation.

**Demographics**

Forty-eight eyes of 30 patients were included in this study. Twenty patients were female, and 10 patients were male. The median age at diagnosis was 47 years (age range, 17-86 years). Patients were followed up for a mean of 39 months (range, 1-156 months). No repetitive systemic medical history was elicited, although there was a history of 1 patient each with fibromyalgia, migraine, multiple sclerosis, rheumatoid arthritis, type 2 diabetes mellitus, and type 1 diabetes mellitus, as well as 4 patients with thyroid disease, 3 patients with systemic hypertension and asthma, and 2 patients with elevated lipid levels. One patient had a history of prostate adenocarcinoma and renal carcinoma, both treated 7 years before retinal symptoms, without any recur-
Most patients had no remarkable medical history. Ocular history was also unremarkable except for 1 patient with Fuchs heterochromic iridocyclitis, 1 patient with optic neuritis, 1 patient with a history of branch retinal vein occlusion, 1 patient with herpetic keratitis, and 2 patients with bilateral nonproliferative diabetic retinopathy.

The AZOOR Lesion
The clinical appearance in the fundus depended on the duration of symptoms, the size and stage of the zonal AZOOR lesions, and the presence or absence of involvement of the central macula (eTable in the Supplement). Patients with AZOOR typically were seen with 2 specific clinical appearances. Those with a recent onset of symptoms and a zonal defect eccentric to the central macula often had little visual acuity reduction and a normal-appearing fundus (Figure 1 and Figure 2). On FAF imaging, these patients had a diffuse hyperautofluorescence signal that sometimes progressed over time. At this early stage, the RPE may still be intact clinically, but hyperautofluorescence could be related to outer retinal disruption with subsequent photopigment loss (Figure 1). The photopigment loss can increase the excitation of the fluorescent signal emitted from the preserved RPE. The SD-OCT in these patients showed diffuse loss of photoreceptors within the zonal defect, usually with relative preservation at the fovea (Figures 1 and 2). A white line at the margin of the involved zone was sometimes visualized during this phase on fundoscopic examination (Figure 2); the white line disappeared during a pe-
Acute Zonal Occult Outer Retinopathy

Acute Zonal Occult Outer Retinopathy (AZOOR) is a rare retinal condition characterized by a demarcating line between the involved and uninvolved retina. This article presents various clinical variations of the demarcating line in patients with AZOOR.

**Figure 3. Clinical Variations of the Demarcating Line in Patients With Acute Zonal Occult Outer Retinopathy (AZOOR)**

A. Right eye of a 70-year-old white man with myopia (−4.75 diopters [D]) reporting vision loss and photopsia in the right eye for 2 weeks. The best-corrected visual acuity (BCVA) was reduced to 20/50 OD. A gray outer retinal demarcating line (arrowheads) is visualized along the superotemporal edge of the peripapillary zonal lesion but not the inferior and nasal borders.

B. Right eye of a 47-year-old white woman with moderate myopia (−2.5 D) reporting photopsia in the right eye for 3 weeks. The BCVA was 20/30 OD. The peripapillary zonal lesion is bordered completely by an interrupted yellow-orange line with a beaded appearance (arrowheads).

C. Left eye of a 65-year-old white man with hyperopia (+1.5 D) reporting distortion, central scotoma, and photopsia in the left eye for 10 days. The BCVA was 20/100 OS. The peripapillary zonal lesion is bordered completely by a continuous yellow-orange demarcating line (arrowheads). Note the foveal sparing.

D. Left eye of a 32-year-old white woman reporting visual loss and photopsia for 1 year. The BCVA was 20/400 OS. Note the orange continuous outer retinal line (arrowheads) partially bordering the temporal border of a peripapillary zonal depigmented lesion.

E. Montage of the right eye of a 32-year-old woman reporting distortion. Visual acuity was 20/40 OD. Note the continuous white demarcating line (arrowheads) bordering the retinal area involved.

F. Left eye of a 34-year-old white woman with myopia (−3.00 D) reporting photopsia. The BCVA was 20/20 OS. Note the brownish pigmented demarcating line (arrowhead) bordering the lesion in the temporal midperiphery.

G. Montage of a 34-year-old white woman reporting distortion. Visual acuity was 20/400 OS. Note the orange continuous outer retinal line (arrowheads) partially bordering the temporal border of a peripapillary zonal depigmented lesion.

**Figure 4**

As an AZOOR lesion progressed, the AZOOR line assumed an incomplete or interrupted pattern, commonly in a beaded appearance.

The location of the AZOOR lesions varied. One or more zonal areas were present in each patient, with the peripapillary region being the most frequently involved. One patient had a large peripapillary lesion and a smaller peripheral lesion, called skip lesions. Another 2 patients had a peripapillary lesion and a paramacular lesion. On SD-OCT, the lesion demonstrated abnormalities at the level of the photoreceptors in all cases, including disruption of the photoreceptor’s ellipsoid line (formerly known as the inner and outer segment junction) and the interdigitation line (formerly known as cone outer segment tips). Fluorescein angiography was usually normal at the onset of a lesion. However, with subsequent degenerative changes at the level of the RPE, early FA hyperfluorescence from depigmentation of the RPE with perfusion of the choriocapillaris produced a window defect.

Subacute or chronic AZOOR lesions demonstrated a trizonal pattern of abnormalities on multimodal imaging (FAF, SD-OCT, and ICG angiography). The trizonal appearance of a
The typical lesion manifested changes on FAF imaging, SD-OCT, and ICG angiography (eFigures 1, 4, 5, and 6 in the Supplement).

**FAF Imaging**
Normal autofluorescence was observed in the area outside of the delineating line (zone 1), speckled hyperautofluorescence could be seen within the AZOOR lesion (zone 2), and hypofluorescence was present, which corresponded to the development of choroidal atrophy (zone 3). The speckled hyperautofluorescence was usually seen in subacute lesions, and the hypofluorescence corresponded to choroidal atrophy. The photoreceptor outer segments and RPE were also atrophic at this stage.

**Spectral-Domain Optical Coherence Tomography**
A similar trizonal appearance was seen on SD-OCT. The SD-OCT was normal outside of the AZOOR line (zone 1). Inside the AZOOR line, multifocal material was present in the subretinal space resembling subretinal drusenoid deposits (zone 2). Photoreceptor, RPE, and choroidal atrophy was evident in the more advanced or long-standing area of the lesion (zone 3).

**ICG Angiography**
Late-stage AZOOR lesions showed a trizonal pattern. Outside of the AZOOR lesion was a normal zone (zone 1). Inside the AZOOR line, the subacute area showed minimal late extrachoroidal leakage (zone 2). Hypofluorescence was observed with the absence of leakage of the ICG molecule into the choroid corresponding to choriocapillaris atrophy (zone 3).
Chronic Form of AZOOR
The chronic form of AZOOR showed lesion progression. Loss of visual function was documented by visual field testing, which revealed a deficit corresponding to the lesion. This trizonal pattern of the AZOOR lesion (with FAF imaging, SD-OCT, and ICG angiography) and the progression of the lesion are pathognomonic of AZOOR. The progression was defined by an expansion of the demarcating line and enlargement of the lesion size. A persistent line was predictive of the progression (Figure 5 and eFigure 3 and eFigure 7 in the Supplement). Progressing lesions often extended toward the macula but curiously showed a relative sparing of the foveal cones (Figures 1 and 2 and eFigure 7 and eFigure 8 in the Supplement). Extension of the lesion was also often observed from the posterior pole toward the peripheral fundus. Three patients developed lesions in the periphery that progressed toward the posterior pole (eFigures 2 and 7 in the Supplement). Two patients showed relentless progression encompassing almost all of the fundus (eFigure 7 in the Supplement). Some lesions remained stable for long periods, while others permanently stopped. In general, when the lesion no longer had an AZOOR line and the lesion size stabilized, the progression halted (Figure 5 and eFigure 3 in the Supplement). Advanced cases of AZOOR demonstrated disruption of the inner and outer retina and severe damage or loss of the RPE and the choroid. Bone spicule pigmentation with intraretinal migration of pigment was seen in 3 patients (eFigure 9 in the Supplement). Depending on when the progression stopped, a trizonal pattern could be noted between normal fundus and the AZOOR lesion (eFigures 1, 4, 5, and 6 in the Supplement).

Differentiating an AZOOR Lesion From MFC With Zonal Atrophy
It is challenging in some cases to differentiate the AZOOR lesion from MFC with zonal atrophy.27 These cases of idiopathic MFC with zonal atrophy may demonstrate a mild vitreous cellular reaction. Jung et al27 evaluated 10 patients with idiopathic MFC with zonal atrophy, and one of them developed choroidal neovascularization (CNV) adjacent to an MFC lesion. No patient with MFC and zonal atrophy developed a demarcating line or a trizonal pattern of abnormalities as described herein. Three of our study patients with AZOOR demonstrated a mild vitreous cellular reaction. No choriretinal scars characteristic of MFC were observed; however, in 3 patients, a few small discrete AZOOR lesions were seen in the midperiphery detected as hypocyanescent spots on ICG angiography or as scattered hypofluorescent lesions on FAF imaging (eFigures 2 and 8 in the Supplement) that progressed and coalesced into a more typical AZOOR lesion over time. Four patients developed CNV within or adjacent to the AZOOR lesion.35 Initial hemorrhage was seen, followed by subretinal fibrous scarring. Two patients having CNV were treated with anti–vascular endothelial growth factor (VEGF) injections, with resulting consolidation and regression of CNV as well as resolution of serosanguineous complications. One patient was treated with full-fluence verteporfin photodynamic therapy, with resulting consolidation of CNV. However, this anti–VEGF treatment and the photodynamic therapy did not interrupt the progression of the AZOOR lesion. At various stages, virtually all patients were treated with corticosteroids or immunosuppressive agents, without clear benefit. Many also received antiviral agents, also without clinically evident benefit.

Discussion
Although AZOOR was first described more than 20 years ago,1 its etiology and treatment remain unclear. After reviewing all the cases diagnosed in our records as AZOOR, we observed a lack of consistency in the ophthalmic community on the definition of this disease. No clear classification delineated the initial or progressive clinical manifestations, including the angio-graphic changes and the visual function as measured by electro-physiology. Some of the confusion in the ophthalmic literature can be traced to the original classification of AZOOR by Gass.40 Based on his keen observations, Gass hypothesized that AZOOR manifestations originated in the outer retina, but he could not show such changes without modern multimodal imaging. He classified an early stage of AZOOR as occult cases with a normal fundus.40 The SD-OCT now shows clearly that such cases have loss of photoreceptor outer segments, beginning with abnormalities in the ellipsoid line.18,41-49 However, even today, rare cases diagnosed as AZOOR, including case 13 in the original series by Gass,1 maintain a virtually normal fundus, with little or no chorioretinal abnormalities. We believe that these cases represent a separate entity, which we will describe in a future study. A principal source of confusion in the diagnosis of AZOOR is the variant termed AZOOR complex by Gass.40 He originally created this AZOOR category because of similarities with the white spot syndromes, including the demographic features, clinical findings, and even the presence of systemic autoimmune diseases. Most described cases in the ophthalmic literature represent AZOOR complex15,24,35 and not AZOOR as we describe it. However, some reports of AZOOR seem to be consistent with our classification.37,50

In this era of multimodal imaging, AZOOR can be clearly differentiated from multiple evanescent white spot syndrome, MFC or punctate inner choroidopathy, acute macular neuroretinopathy, and other white spot diseases. The trizonal pattern of FAF imaging is a defining feature of AZOOR, particularly the hyperautofluorescent line demarcating the normal retina from the AZOOR lesion. With ICG angiography, a trizonal pattern is observed as well. The trizonal pattern seen on SD-OCT showing disruption of both the ellipsoid and the interdigitation lines is characteristic (Figure 3 and eFigures 2 and 3 in the Supplement). However, review of our cases revealed a rare but distinguishable set of variables that we believe represents a strict definition of AZOOR. This new definition allowed us to identify 30 bona fide cases of AZOOR from scrutinizing 400 records at 2 world-renowned referral centers for retinal diseases, which emphasizes the rarity of the disease.

In particular, AZOOR complex diseases have commonly been confused as AZOOR as we define it. Some patients with MFC may also develop zonal, multizonal, or diffuse chorioretinal atrophy. Although these cases have been considered AZOOR in the ophthalmic literature, we believe that they rep-
resent a distinct clinical entity. The patients initially or subsequently develop multifocal chorioretinal scars, and the zonal areas of atrophy do not precisely resemble AZOOR lesions in their morphologic and imaging characteristics.

What is distinct about AZOOR to help physicians distinguish it from other diseases of the posterior fundus? Unlike hereditary diseases, autoimmune and cancer-associated retinopathies, and toxic chorioretinal disorders, AZOOR can manifest as unilateral and asymmetric lesions. Characteristic symptoms corresponding to visual dysfunction and progressive clinical and imaging findings form a constellation of findings that are highly specific as described herein. The sequential outer retinal, RPE, and choroidal zonal lesions and the trizonal features on SD-OCT, FAF imaging, and ICG angiography are unique in diagnosing AZOOR in these patients. Furthermore, no known genetic predisposition or serum antibodies implicate hereditary or other inflammatory diseases.

Other simulating diseases have no delineating line to segregate the normal fundus from the AZOOR lesion. The trizonal imaging changes are also reinforced by the progression of the lesion, a development that is not characteristic of hereditary, paraneoplastic, toxic, or other inflammatory and infectious diseases of the fundus.

Gass and Stern\(^5\) also described acute annular occult retinopathy (AAOR), in which they noted a distinguishing gray line between the normal and involved retina. Additional studies\(^5\) reinforced this finding in AAOR. We believe that AAOR represents cases of AZOOR in which the delineation is acutely apparent ophthalmoscopically as a white or gray line. This white line fades but can be replaced by a delineating orange line.

Our classification of AZOOR strives to be specific and adherent to clinical and imaging guidelines, including the narrow hyperautofluorescent demarcating line between the involved and uninvolved retina, the trizonal pattern of chorioretinal degeneration, and the frequent zonal progression described. However, we believe that the disease expresses variability, and 3 of our patients did not show these specific findings but rather diffuse hyperautofluorescence in the areas of involvement, with subsequent development of surrounding speckled hypofluorescence, as shown in Figures 1 and 2. In our series, these 3 cases represented earlier stages of the disease (lasting from weeks to months), but one of them progressed to diffuse hypofluorescence over time. We suspect that some AZOOR cases may evolve toward more generalized areas of hypofluorescence rather than the typical trizonal pattern of chorioretinal degeneration, demonstrating the clinical variability of AZOOR in its progression as well.

Our study has distinct limitations. We report only 30 cases, and some lack a full analysis by all imaging modalities at the initial examination and during the course of the disorder. Furthermore, no histopathological correlations exist to clarify the nature of the observed clinical manifestations. The precise nature of the AZOOR line and the speckled hyperautofluorescence in the subacute AZOOR lesion is unknown. Lipofuscin may have a role because the demarcating line is orange and hypofluorescent with FA. An alternative explanation may be inflammatory debris in conjunction with accumulated photoreceptors, which contain chromophores.

**Conclusions**

In summary, the diagnosis of AZOOR should be considered when a young patient, often female, develops the onset of photopsia in a localized area of the visual field. These visual symptoms correspond to an area of loss of function on visual field testing. Imaging (eg, SD-OCT, FAF, and FA) and ICG angiography demonstrate abnormalities at the level of the photoreceptors, including involvement of the ellipsoid zone. Sequential involvement of the RPE and choroid is seen. As the RPE degenerates, FA will show a window defect. Typical trizonal patterns evolve on SD-OCT, FAF imaging, and ICG angiography. Characteristically, the retina is initially involved, visual field loss can be documented, electoretinography is abnormal, and sequential RPE degeneration and choroidal atrophy occur. The progression or stabilization of the area of visual impairment can be seen with or without the development of new zonal areas of visual impairment. The disease may be unilateral, but often the second eye becomes involved during the follow-up period. With time, many of the eyes stabilize, but diffuse retinal degeneration is sometimes seen.
Acute Zonal Occult Outer Retinopathy


OPHTHALMIC IMAGES

Vitelliform Macular Dystrophy
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Fundus photographs of the right eye in the vitelliform stage with a “fried egg” appearance due to the accumulation of lipofuscin in retinal pigment epithelial cells (A), the left eye in the vitelliform stage with a “fried egg” appearance and pseudohypopyon (B), the right eye in the “scrambled egg” stage with choroidal neovascularization (C), and the left eye in the “scrambled egg” stage (D).