Editorial

Acute Zonal Occult Outer Retinopathy; Revisited

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Acute zonal occult outer retinopathy (AZOOR) was first described by J. Donald M. Gass in 1992[1] as a "syndrome" characterized by sudden onset photopsia and acute scotomas related to loss of sectors of outer retinal function in typically young, otherwise healthy individuals including 10 female and 3 male subjects.[1] Early funduscopic appearance was often normal; however, most patients developed zones of retinal pigment epithelial (RPE) atrophy or pigment clumping in one or both eyes when followed over time.[2] Persistent visual field defects, some corresponding electroretinogram (ERG) changes, retinal arterial narrowing and eventually chorioretinal atrophy were usually observed.[1,2] The pathogenesis of the disease was uncertain, but Gass stated that a virus was the best explanation for the progressive abnormalities in the fundus and no treatment modalities have shown any proven evidence of benefit.

Gass speculated that AZOOR, pathologically and etiologically was related to a spectrum of so called the "AZOOR complex" and included multiple evanescent white dot syndrome (MEWDS), acute idiopathic blind spot enlargement (AIBSE) syndrome, acute macular neuroretinopathy (AMN), presumed ocular histoplasmosis (POHS), punctate inner choroidopathy (PIC), and multifocal choroiditis (MFC).[3] The basis for his speculation was that all of these disorders most commonly occurred in young adult women (similar demographic features) with primary involvement of the outer retina, and that all entities may be associated with inflammation, visual field loss and in some instances, ERG abnormalities.[2] However, the AZOOR complex differs from well-defined AZOOR and should be differentiated in order to assist ophthalmologists in the clinical setting for a particular diagnosis and management.

Since the first description of AZOOR, various aspects of the disease have been evaluated in multiple publications, but this entity was ill-defined and poorly understood because of the absence of histopathology and very little knowledge of its pathogenesis. Nevertheless recently, Mrejen et al[4] have described multimodal imaging including fundus photography, fluorescein angiography (FA), indocyanine green (ICG) angiography, fundus autofluorescence (FAF) imaging, wide-field FAF imaging and spectral-domain optical coherence tomography (SD-OCT), in a relatively large group of patients showing a distinct clinical entity which ideally represents AZOOR. They reassessed their patients who were previously diagnosed as AZOOR cases in order to re-classify this entity more specifically, distinguishing it from other masquerade disorders. They reviewed more than 400 patients and finally chose 30 cases (48 eyes) including 20 female and 10 male subjects who fit their definitions.[4]

Photopsia and scotoma were the initial visual symptoms in each patient. Patient symptoms included frequent photopsias in the area of retinal involvement, distortion of central vision, photophobia and difficulty with night vision. Cases with more advanced conditions reported loss of peripheral vision. Moreover, patients frequently noted a blind spot in their temporal field.

Patients with AZOOR typically were seen with 2 specific clinical appearances: Early (acute) and late (subacute or chronic).[5] Those with acute symptoms and a macular sparing zonal defect often had little visual acuity reduction and a normal-appearing fundus. On FAF imaging, these patients had a diffuse patchy hyperautofluorescent signal which 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. The photopigment loss may increase excitation of the fluorescent signal transmitted through the preserved RPE.[5] SD-OCT in these patients showed diffuse loss of photoreceptors within the zonal defect, usually with relative preservation at the fovea. A white line at the margin of the involved zone was sometimes visualized during this phase on fundus examination.

The majority of patients with AZOOR initially show more advanced clinical manifestations. In this subacute or chronic presentation, visual acuity was only mildly

affected due to relative sparing at the fovea. The AZOOR lesion typically showed a peripapillary area of RPE atrophy, as well as changes in other areas of the fundus. Most eyes had a demarcating (AZOOR) line between the involved and uninvolved retina, which is typically orange and could be continuous, interrupted, or scalloped in appearance. The demarcating line is best seen via FAF imaging, which is markedly hyperautofluorescent initially in a continuous pattern around the zonal area of RPE atrophy.[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 area as well as a smaller peripheral lesion, called "skip lesions".

On SD-OCT, in all cases, the lesion demonstrated abnormalities at the level of the photoreceptors, including disruption of the photoreceptor's ellipsoid zone (EZ) and interdigitation zone (IZ).

FA was usually normal at the onset of a lesion. However, with subsequent degenerative changes at the level of the RPE, early FA hyperfluorescence through 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).[4] Normal FAF imaging, SD-OCT and ICG angiography are observed in the area outside the demarcating line (zone1). Speckled hyperautofluorescence could be seen within the AZOOR lesion related to multifocal material in the subretinal space resembling subretinal drusenoid deposits (SDD) on SD-OCT, showing minimal late extrachoroidal leakage on ICG (zone 2). However, hypoautofluorescence with hypocyanescence, which corresponds to development of photoreceptor, RPE and choriocapillaris atrophy are present in zone 3 [Figure 1]. Advanced cases of AZOOR demonstrate disruption of the inner and outer retina with severe damage or loss of the RPE and choroid.

This trizonal pattern of the AZOOR lesion (with FAF imaging, SD-OCT, and ICG angiography) and "progression" of the lesion are pathognomonic of AZOOR.[4] Progression is defined by an expansion of the demarcating line and enlargement of the lesion size. A persistent line is predictive of progression and when the lesion no longer has an AZOOR line together with stabilized size, progression has halted [Figure 2]. Progressing lesions often extend toward the macula from the posterior pole to the peripheral retina but show relative sparing of the foveal area. Depending on when progression stops, a trizonal pattern could be noted between the normal fundus and the AZOOR lesion.

To differentiate the AZOOR lesion from multifocal choroiditis (MFC) with zonal atrophy it is important

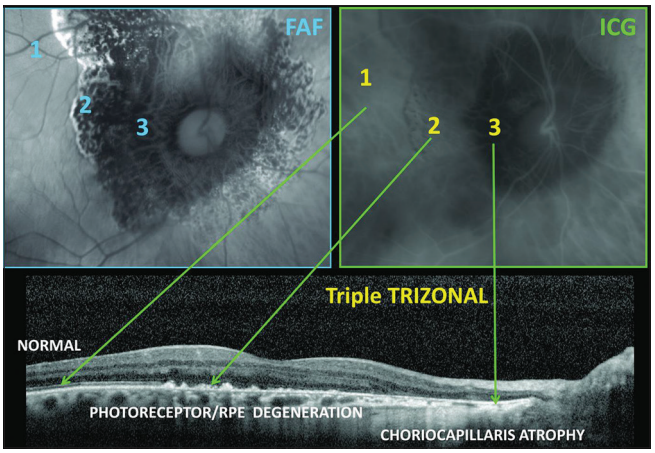

Figure 1. Trizonal degeneration in acute zonal occult outer retinopathy (AZOOR). Upper left image: Fundus autofluorescence (FAF) image reveals normal autofluorescence in the area outside the demarcation line (zone 1), speckled hyperautofluorescence within the AZOOR lesion (zone 2), and hypoautofluorescence corresponding to the development of choroidal atrophy (zone 3). Upper right image: Indocyanine green (ICG) angiography outside the AZOOR lesion is normal (zone 1). Inside the AZOOR line, the subacute area shows minimal late extrachoroidal leakage (zone 2). Hypocyanescence is observed together with the absence of leakage of the ICG molecule into the choroid corresponding to choriocapillaris atrophy (zone 3). Lower image, spectral-domain optical coherence tomography (SD-OCT) findings: SD-OCT is normal outside the AZOOR line (zone 1). Inside the AZOOR line, multifocal material is present in the subretinal space resembling subretinal drusenoid deposits (zone 2). Photoreceptor, retinal pigment epithelium and choroidal atrophy is evident in the more advanced or long-standing area of the lesion (zone 3).

to note that no patient with MFC and zonal atrophy develops a demarcating line or a trizonal pattern of abnormalities as described herein, and using multimodal imaging, AZOOR can be clearly differentiated from AZOOR complex.[4]

Gass and Stern[6] also described acute annular outer retinopathy (AAOR), in which they noted a distinguishing gray line between the normal and involved retina. It is believed 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.[4]

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 may manifest as unilateral and asymmetric lesions. Characteristic symptoms corresponding to visual dysfunction and progressive clinical and imaging findings form a constellation of findings which are highly specific as described herein. The sequential outer retinal, RPE and choroidal zonal lesions, and the trizonal features on SD-OCT, FAF

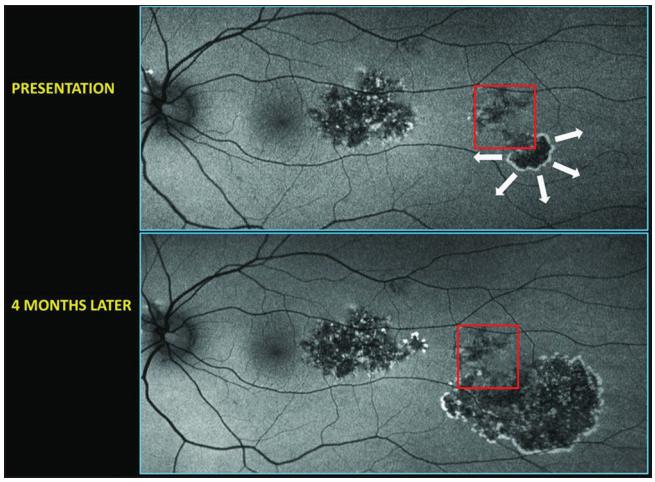

Figure 2. Progression of acute zonal occult outer retinopathy (AZOOR) over 4 months. Progression is defined by expansion of the demarcating line and enlargement of lesion size (white arrows). When the lesion no longer has an AZOOR line with stabilized size, progression is stopped (red squares).

imaging and ICG angiography with demarcating line alongside the progression of lesion are unique in diagnosing AZOOR.

In summary, the diagnosis of AZOOR should be considered when a young patient, often female, develops photopsia in a localized area of the visual field. These visual symptoms correspond to an area with loss of function on visual field testing. Imaging (SD-OCT, FAF, and FA) and ICG angiography demonstrate abnormalities at the level of the photoreceptors such as 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 outer retina is initially involved, visual field loss can be documented, ERG 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 the second eye often becomes involved during follow-up. With time, many of the eyes stabilize; however, diffuse retinal degeneration is occasionally observed.

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