• Letter to the Editor •

# Acute zonal occult outer retinopathy complex and angioid streaks: a case report

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**Dear Editor,**

We present a case of acute zonal occult outer retinopathy (AZOOR) complex in a myopic patient with angioid streaks (ASs). A 19-year-old female has been experiencing visual field defects in her left eye for more than 3y. She was diagnosed with ASs and choroiditis at a local hospital. She has a seven-year history of bilateral high myopia. A fundus examination confirmed the presence of ASs and myopic fundus changes in both eyes. Multimodal imaging revealed an AZOOR complex in the left eye. The lesion in the left eye was inactive at the time of the visit, so no special treatment was administered. We encountered a rare case of AZOOR complex in a patient with high myopia and ASs. We hypothesize that these conditions significantly contribute to the development of the AZOOR complex. Multiple causes, including inflammatory and autoimmune factors, played a role in the subsequent development of choroidal neovascularization (CNV) in this young patient.

**Ethical Approval** This case report was conducted in accordance with the Declaration of Helsinki. The study was exempt from formal ethics approval by the Ethics Committee of Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, as it involves retrospective analysis of routine clinical data. Written informed consent was obtained from the patient(s) and legal guardians for the publication of this case report.

ASs are a type of fundus disorder where the site of the lesion was identified at the Bruch's membrane in 1917. Nearly half of the patients with ASs also have systemic diseases like pseudoxanthoma elasticum (PXE)[1]. This is due to a mutation in the *ABCC6* gene, causing patients with PXE to experience calcification of the elastic tissue and progressive degeneration of collagen. The ocular of this mutation makes the Bruch's membrane fragile and prone to rupture. This results in a dehiscence of the fundus, which appears similar to a vessel.

AZOOR complex is a syndrome that consists of fundus diseases with similar symptoms and signs, such as AZOOR and multiple evanescent white dot syndrome (MEWDS)[2]. It primarily occurs in young women and can coexist with autoimmune diseases, thus suggesting a possible autoimmune or inflammatory etiology.

In previous reports of ASs or AZOOR complex, only a few young patients developed CNV[3]. We hypothesize that high myopia and inflammatory factors significantly contribute to the development of CNV in the patient.

A 19-year-old female patient came to the clinic due to repeated progression of visual field defects in the left eye for more than 3y. She was diagnosed with bilateral ASs and choroiditis and had received 8 intravitreal injections of anti-vascular endothelial growth factor (VEGF) in the left eye. The patient had suffered from high myopia in both eyes for 7y. The best corrected visual acuity was 20/13 with -8.00 diopter sphere (DS) in the right eye and 20/22 with -9.50 DS-1.50 diopter cylinder (DC)×180° in the left eye. The intraocular pressure was 19 mm Hg (1 mm Hg=0.133 kPa) in both eyes. The fundus examination revealed myopic changes and ASs around the optic disc, with multiple yellow-white spots noted at the posterior pole of both eyes.

The color fundus photography (CR-2 AF automatic no-dilatation fundus camera, CANON, Japan) revealed a neovascular membrane in the macular area of the left eye (Figure 1A-1B). The streaks appear as dark, well-demarcated cracks on infrared rays (IR; Heidelberg SPETRALIS HRA+OCT, Heidelberg, Germany; Figure 1C-1D). In the fundus autofluorescence (Heidelberg SPETRALIS HRA+OCT,

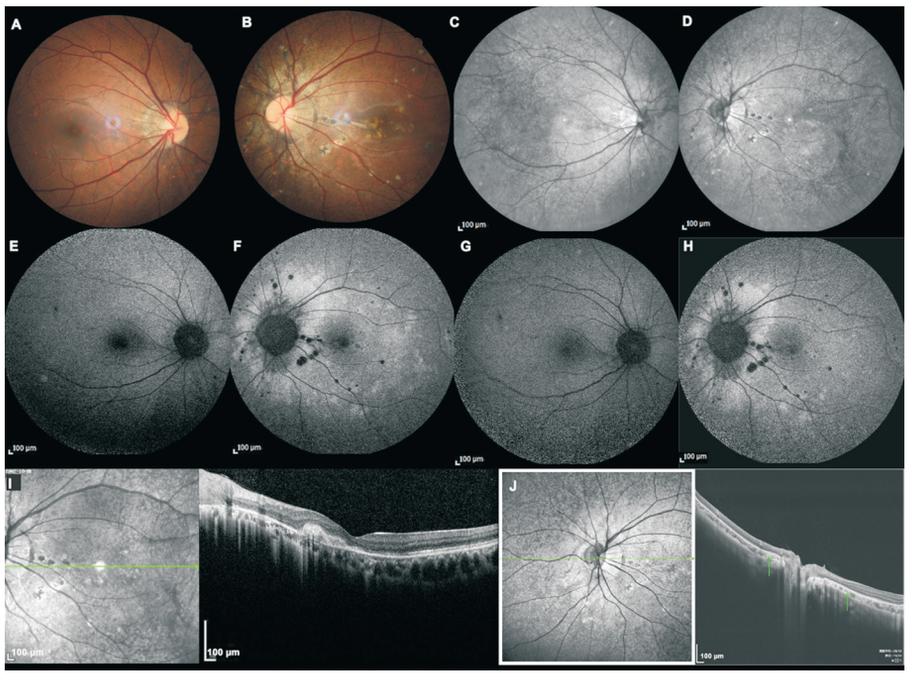


**Figure 1 Multimodal imaging of the patient** A-B: Color fundus photography showed bilateral fundus tessellation, Peau d'orange appearance, and temporal parapapillary atrophy. The brown ASs radiated from the optic disc (towards the peripheral retina), tapering, and the ends of ASs were bent and branched. Speckled pigmented atrophy can be seen near ASs. Multiple yellow-white spots were noted at the posterior pole of both eyes, especially the left. The neovascular membrane can be seen in the macular area of the left eye. C-D: ASs appeared as crack-like, well-demarcated dehiscences on IR. E-F: Hypoautofluorescence was noted in the area of the ASs and scattered quasi-circular hypoautofluorescent lesions were found in both eyes. Sheet-like hyperautofluorescence was noted at the posterior pole in the left eye without the involvement of the macular region (F). G-H. Fundus autofluorescence was reviewed two months later and the hyperautofluorescence in the left eye partially resolved (H). I: OCT demonstrated that the retina in the macular area of the left eye had a localized bulge with uneven signal. There were hyperreflective lesions under the left retina. Bruch's membrane disruption occurred with no remarkable edema of the peripheral retina. J: SS-OCT showed the continuous lack of outer retina around the optic disc and the atrophy of retinal pigment epithelium and choroid in the left eye. Arrow: The boundary of the lack of outer retina, corresponds to the hyperautofluorescence in Figure 1H. AS: Angioid streak; IR: Infrared rays; SS: Swept source; OCT: Optical coherence tomography.

Heidelberg, Germany), we noted hypoautofluorescence in the area of the streaks and found scattered quasi-circular hypoautofluorescent lesions in both eyes. There was also sheet-like hyperautofluorescence at the posterior pole in the left eye (Figure 1E-1H). Spectral-domain optical coherence tomography (Heidelberg SPETRALIS HRA+OCT, Heidelberg, Germany) showed the macular CNV of the left eye (Figure 1I). Additionally, swept source-OCT (SS-OCT; VG100; SVision Imaging, Ltd., Luoyang, China) showed the absence of outer retina around the optic disc and atrophy of retinal pigment epithelial (RPE) and choroid in the left eye (Figure 1J).

Fundus fluorescein angiography (FFA; Heidelberg SPETRALIS HRA+OCT, Heidelberg, Germany) showed dotted hyperfluorescence scattered at the posterior pole of both eyes and the hyperfluorescent strips within the vascular arcade of the left eye, which involved the macula. The streaks appeared as radial strips of hypofluorescence around the optic disc on late-indocyanine green angiography (ICGA; Heidelberg SPETRALIS HRA+OCT, Heidelberg, Germany). The area corresponding to the hyperautofluorescence showed hyperfluorescence on late ICGA in the left eye (Figure 2A-2D).

B-scan ultrasonography showed the axial length was 26.78 mm in the right eye and 26.22 mm in the left eye. Whole-exome sequencing identified variants of ABCC6 (c.4404-1, G>A) and ROM1 (c.342_362delCCTGGTCGTCGGCCTCGGGCT), both of which were inherited from her mother and are heterozygous variants. On the basis of all these findings, a diagnosis of bilateral ASs and choroiditis coincident with left AZOOR complex and secondary CNV was established.

Since there was no active inflammation in the left eye and CNV was stable, the patients were advised to have regular check-ups, and no special treatment was necessary.

Gliem *et al*[4] reported a MEWDS-like reaction in 9 patients with PXE. This reaction, occurring in about 5% of PXE patients, is characterized by temporary evanescent yellow-white spots of the outer retina. This phenomenon, similar to MEWDS, is identified as a secondary pathology following the disruption of RPE-Bruch's membrane-choriocapillaris

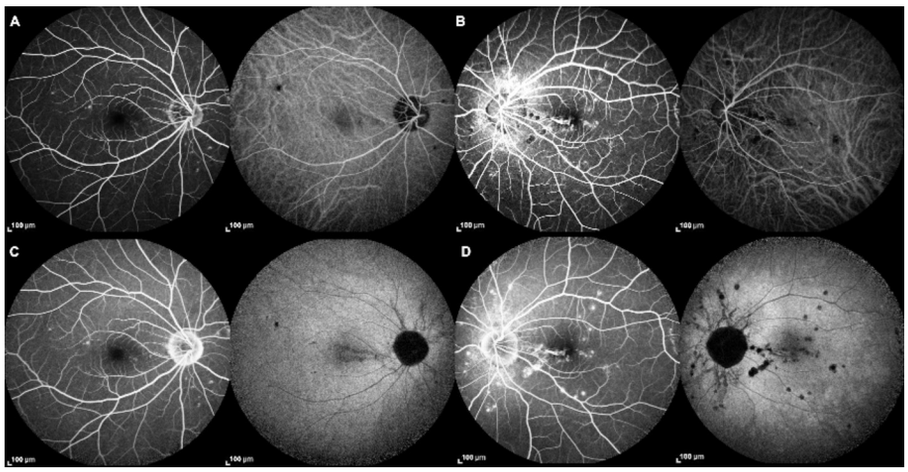


**Figure 2 Bilateral early (A-B) and late (C-D) FFA/ICGA** In FFA, there were scattered dots of hyperfluorescence at the posterior pole, especially in the left eye. FFA of the left eye showed circular and radial hyperfluorescence around the optic disc which changed with the background fluorescence. The large choroidal vessels can be seen through the quasi-circular hypofluorescence around the disc, and there was banded hyperfluorescence in the macular area of the left eye, which was gradually stained. The dots shown in FFA were partially stained without leakage, corresponding to hypocyanescence on late-ICGA. The ASs showed radial hypocyanescence on late-ICGA. The area corresponding to hyper autofluorescence at the posterior pole of the left eye showed hypercyanescence on late-ICGA. FFA: Fundus fluorescein angiography; ICGA: Indocyanine green angiography; AS: Angioid streak.

complex (RPE-BM-CC)[5]. Gliem *et al*[4] and Abdelhakim *et al*[6] proposed potential mechanisms. Damage to the RPE-BM-CC, caused by pathological or iatrogenic factors, compromises the posterior blood-retinal barrier, leading to a loss of immune privilege of the outer retina. The exposure of retinal antigens triggers a temporary inflammatory response[4]. The MEWDS-like reaction generally resolves without any permanent structural damage[4]. But in the case of this patient, the hyperautofluorescence did not fully disappear over two months. The condition resembled AZOOR, with regional continuous hyperautofluorescence of the posterior pole and corresponding peri-disc chorioretinal atrophy. So it's possible that there are pathological changes similar to AZOOR. In addition, there were atrophic choroiditis lesions. Yellow-white dots were visible in posterior pole, with staining on FFA and hypofluorescent on late-ICGA.

The latest study categorizes all the mentioned diseases under the AZOOR complex[7]. AZOOR complex consists of several fundus diseases with similar etiological and demographic characteristics[2]. Its pathogenesis remains unknown, but it is believed to be related to autoimmunity and inflammation. There have been reports of Myopia or ASs patients also having the AZOOR complex[8]. In this patient, the changes in the RPE-BM-CC caused by myopia and ASs could trigger autoimmune and inflammatory reactions, increasing susceptibility to various AZOOR complex diseases. Furthermore, different types of AZOOR complex diseases could develop simultaneously in the same patient, especially in young women. This supports the theory of immune and inflammatory factors across different AZOOR complex diseases.

CNV is the leading cause of vision loss in patients with ASs. Most patients with ASs-related CNV are over 40 years old, making this patient, who is younger, an outlier[9]. For instance, a study in 2024 reported a case suffered CNV to ASs with PXE in a 46-year-old patients[10]. A Beta Thalassemia patient was diagnosed with CNV secondary to ASs, who was treated with a monthly loading dose of intravitreal ranibizumab followed by a treat-and-extend regimen up to 16-week intervals with visual acuity improvement[11]. Therefore, the patient's history of high myopia played a significant role. Bruch's membrane functions as a barrier between the outer retina and choroid, limiting fluid flow and aiding in material transport to maintain the function of the retina and choroid. ASs and myopia cause damage to Bruch's membrane, leading to a disruption in the diffusion of oxygen and nutrients. As a result, the RPE and outer retina may become hypoxic, further damaging photoreceptor cells and producing VEGF, which promotes the development of CNV. Moreover, the disruption of RPE-BM-CC exposes relevant antigens and breaks the preexisting immune privilege, inducing an autoimmune reaction. This damage to the retinal barrier enhances the transport of inflammatory factors and the development of immune responses. These factors could explain why the patient developed CNV at a younger age.

CNV appears in the left eye, despite its axial length being shorter than the right eye. This further substantiates the role of inflammation in CNV production. As Burke *et al*[12] proposed, an inflammatory environment can lead to CNV and concurrent AZOOR complex disease. Lee *et al*[13] found that

CNV is more likely to occur in the presence of myopia and choroiditis, especially in patients with posterior inflammation and progressing myopia.

In conclusion, we have presented a case of AZOOR complex in a patient with high myopia and ASs. The pathogenesis involved both inflammatory and autoimmune factors. The structural changes in the fundus due to high myopia and ASs increase the patient's susceptibility to RPE-BM-CC-related complications, which lead to CNV in this young patient.

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