• Clinical Research •

Clinical manifestation and multimodal images of Chinese acute zonal occult outer retinopathy patients

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Abstract

● **AIM:** To comprehensively examine the clinical presentations, multimodal images, and long-term follow-up of Chinese patients with acute zonal occult outer retinopathy (AZOOR), a rare inflammatory disorder.

● **METHODS:** This was a retrospective study. A total of 20 patients (32 eyes) were included. The medical records and multimodal imaging, including wide-field fundus photography, wide-field fundus autofluorescence (FAF), and swept-source optical coherence tomography (SS-OCT) were analyzed.

● **RESULTS:** The study included 20 patients with a mean age of 38.2±10.9y, and females accounted for 60%. Lesions could involve peripapillary areas, macular region, and peripheral retina. The mean best-corrected visual acuity (BCVA) at presentation was 0.38±0.60 logMAR, with no significant difference in visual acuity between acute cases (within 6mo of onset) and chronic cases (beyond 6mo of onset; *P*=0.390). There was no statistically significant difference in visual acuity between eyes of acute case (within 6mo of onset) and the chronic case (beyond 6mo of onset). In some chronic case, FAF examination revealed the presence of a hyperautofluorescent (hyperAF) ring around the macular area (6/18), a phenomenon not observed in the acute case (*P*=0.024). A higher proportion of chronic cases showed predominantly hypoautofluorescent (hypoAF) lesions compared to the acute case (13/18 *vs* 2/14, *P*=0.0016). SS-OCT examination showed that both acute and chronic cases exhibited hyperreflective dots above the retinal pigment epithelium (RPE), and ellipsoid zone (EZ) and RPE damage. In the chronic case, eyes with hyperreflective dots above the RPE were more likely to exhibit EZ and RPE damage in the macular region compared to those without these dots.

● **CONCLUSION:** Multimodal imaging plays a crucial role in the follow-up of patients with AZOOR. In chronic cases of AZOOR, the presence of hyperreflective dots above the RPE indicates a higher likelihood of outer retinal involvement in the macular region. This study provides critical insights into the complex presentation and progression of AZOOR.

● **KEYWORDS:** acute zonal occult outer retinopathy; fundus autofluorescence; optical coherence tomography; hyperreflective dots

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INTRODUCTION

Acute zonal occult outer retinopathy (AZOOR) is acknowledged an inflammatory disorder affecting the outer retina, characterized by sudden unilateral onset with symptoms such as photopsias and visual field loss. Typically, the affected eye may exhibit a transient contiguous scotoma near the optic nerve. AZOOR can affect one or both eyes, and it usually stabilizes within six months of symptom onset, though some cases may continue to progress. In most cases, central vision remains unaffected[1-2]. A classification based on multimodal imaging was proposed, emphasizing the identification of a trizonal pattern involving a zone with normal autofluorescence (AF), a hyperautofluorescent (hyperAF) zone and a hypoautofluorescent (hypoAF) zone[3]. Systemic corticosteroids are subsequently used as mainstay therapy, while the use of periocular triamcinolone acetonide injections, intravitreal steroid injections, and combinations of non-corticosteroid systemic immunosuppressive drugs with steroids has been reported in isolated cases[4-6]. However, significant heterogeneity persisted within AZOOR, as clinical appearance,

disease progression, and response to treatment varied among the included cases[3]. To enhance our comprehension of AZOOR and elucidate the substantial variability among patients, we conducted a comprehensive analysis of clinical presentations and long-term follow-up of AZOOR cases.

PARTICIPANTS AND METHODS

Ethical Approval The Institutional Review Board of Peking Union Medical College Hospital granted approval for the study (No.S-K2033), written informed consent was obtained from the subjects and the research was carried out in accordance with the principles outlined in the Declaration of Helsinki.

This was an observational, longitudinal, retrospective study, focusing on a single center case series. The research included new patients diagnosed with AZOOR, who were examined by one author (Chen YX) from January 2018 to June 2023. AZOOR diagnosis was based on: 1) characteristic symptoms (photopsia/scotoma); 2) multimodal imaging evidence of tri-zonal patterns [outer retina, retinal pigment epithelium (RPE), choroid] and demarcating lines; 3) lesion progression on follow-up[3]. All patients underwent wide-field fundus photography, spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF); indocyanine green angiography (ICGA)/fluorescein fundus angiography (FFA) was performed in select cases. Exclusion workup: Patients were screened for mimics *via* medical/family history, biochemical tests, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, antineutrophil cytoplasmic antibody, syphilis serology, tuberculosis testing, serum tumor markers and chest computed tomography scans. The treatments for these patients included peribulbar injections of triamcinolone acetonide, oral corticosteroids, and oral immunosuppressants. In Gass *et al*'s[7] long term follow-up study, 78% of eyes achieved stability of visual symptoms within 6mo of presentation. Therefore, based on disease duration, involving eyes were categorized into acute (within 6mo of onset) and chronic (beyond 6mo of onset) stages.

Data Collection All participants underwent a comprehensive ophthalmologic examination at both baseline and subsequent follow-up visits. This assessment included measurements of decimal best-corrected visual acuity (BCVA), slit-lamp, and indirect fundus ophthalmoscopy. Additionally, data from multimodal imaging techniques were utilized, including ultra-wide-field scanning laser ophthalmoscopy (UWF-SLO) (Daytona P200T, Optos PLC, Dunfermline, United Kingdom), Zeiss Clarus 500 (Carl Zeiss AG), ultra-wide-field FAF (UWF-FAF) imaging (Daytona P200T, Optos PLC, Dunfermline, United Kingdom), FAF (Carl Zeiss AG), SS-OCT (VG200; SVision Imaging, Ltd., Luoyang, China).

Statistical Analysis Continuous data were presented as mean ±standard deviation (SD). The BCVA measured with a Snellen chart was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Data was analyzed using SPSS 20.0 statistical software. The independent two-sample *t*-test and Mann-Whitney tests were used to compare age and BCVA. Fisher's exact tests were used to compare the number of patients with certain characteristics. The level of significance adopted in our study was less than 0.05.

RESULTS

Basic Characteristics of the AZOOR Patients The study included a total of 20 subjects (32 affected eyes) with 12 women and 8 men (Table 1). The mean age of the subjects was 38.2±10.9y (range: 21-57y). Presenting symptoms included scotomata and photopsia, with 12 patients (60.0%) having bilateral involvement. Fourteen (70.0%) patients had myopia. Vitreous cells were observed in 8 out of 32 eyes (25.0%). None of the patients displayed systemic symptoms. The past ocular history was unremarkable for all included eyes. Biochemical tests, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, antineutrophil cytoplasmic antibody, syphilis serology, tuberculosis testing, serum tumor markers and chest computed tomography scans were unremarkable. Symptom duration at presentation varied from 2wk to 4y. The median follow-up duration was 27.0mo [interquartile range (IQR) 22.0–56.0]. Based on disease duration, involving eyes were categorized into acute (within 6mo of onset) and chronic (beyond 6mo of onset) stages. The BCVA at presentation was 0.38±0.60 (logMAR, mean±SD). For acute-stage eyes (n=14), the logMAR vision was 0.26±0.33, and for chronic-stage eyes (n=18), it was 0.45±0.72 at presentation, with no statistically significant difference between the two groups (P=0.390). At the last follow-up, there was no significant difference in BCVA compared to baseline for both acute and chronic-stage eyes. Analysis of gender-related differences revealed no statistically significant disparities in visual outcomes: Baseline BCVA (female: 0.39±0.65 *vs* male: 0.35±0.51, P=0.872), final BCVA (0.34±0.62 *vs* 0.29±0.48, P=0.825), and BCVA change (-0.05±0.33 *vs* -0.06±0.29, P=0.926) showed comparable trends between genders.

Multimodal Images of AZOOR Patients All eyes included in the study underwent wide-field SLO/fundus photography, wide-field FAF, and SS-OCT at every visit.

Wide-field SLO/fundus photography Seventeen affected eyes displayed well-demarcated RPE atrophy with hyperpigmentary changes, ranging from subtle RPE stippling to granular RPE clumping, and increased visibility of the choroidal vasculature (Figure 1). These changes were observed in peripapillary areas surrounding the optic disc or at far-peripheral locations (Figure 1). Among them, 6 eyes were at acute stage, and 11 eyes at chronic stage. Some cases showed no retinal abnormalities on SLO (Figure 1).

Table 1 Management and prognosis of 20 patients (32 eyes) with AZOOR

Patients	Unilateral/ bilateral	Sex	Age (y)	Acute/ chronic	Disease duration at baseline (mo)	Baseline BCVA (logMAR)	Treatment	Final follow-up BCVA (logMAR)
1	Unilateral	Male	23	Acute	0.5	0.4	1	0.4
2	Unilateral	Female	25	Acute	3	0.82	1	0.82
3	Unilateral	Female	34	Acute	6	0	1	0
4	Bilateral	Female	25	Acute	3	OD 0	1	0
					3	OS 0	1	0
5	Unilateral	Female	30	Acute	2	0	1	0
6	Unilateral	Female	21	Acute	2	0.22	1+2+4	0.22
7	Bilateral	Female	46	Acute	6	OD 0.3	1+2	0.3
					6	OS 0.4	1+2	0.4
8	Unilateral	Female	32	Acute	3	0	1	0
9	Bilateral	Male	57	Acute	2	OD 0.92	1+2	0.7
					1	OS 0	1+2	0
10	Bilateral	Male	51	Acute	1	OD 0.22	1	0.22
					1	OS 0.7	1	0.7
11	Bilateral	Male	44	Chronic	36	OD -0.08	1+2	-0.08
					36	OS 0	1+2	0
12	Bilateral	Male	44	Chronic	12	OD 0.7	1+2+4	1
					12	OS 0	1+2+4	0
13	Bilateral	Male	52	Chronic	12	OD 0.22	1+2+4	0.1
					12	OS 0.3	1+2+4	0.3
14	Unilateral	Female	52	Chronic	12	0	1	0.22
15	Unilateral	Female	40	Chronic	12	2	1	1.4
16	Bilateral	Female	31	Chronic	8	OD 1.3	1+2+4	1.3
					8	OS 1.3	1+2+4	1.3
17	Bilateral	Female	42	Chronic	24	OD 0	1+2+3+4	0
					24	OS 0	1+2+3+4	0
18	Bilateral	Female	30	Chronic	24	OD 0	1+2	0
					24	OS 0	1+2	0
19	Bilateral	Male	48	Chronic	24	OD 2.3	1+2+4	2.3
					24	OS 0	1+2+4	0
20	Bilateral	Male	37	Chronic	48	OD 0	1	0
					48	OS 0	1	0

Treatment 1: Triamcinolone acetonide periocular injection; Treatment 2: Intravitreal steroid injection; Treatment 3: Systemic steroids; Treatment 4: Immunosuppressants. BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; AZOOR: Acute zonal occult outer retinopathy.

Wide-field fundus autofluorescence While some cases (4 acute stage eyes and 12 chronic stage eyes) showed the typical trizone presentation, with a hypoAF core surrounded by a hyperAF ring (Figure 2). There were also some variations in FAF, which included a contiguous zone of hyperAF with a prominent hyperAF ring (Figure 2), a hyperAF ring around the macula (Figure 2), multiple hypeAF satellite lesions (Figure 2) and perivascular satellite lesions (Figure 3). AZOOR lesions were also be found in peripheral area in 4 patients (Figure 2). Table 2 presents the FAF manifestations in AZOOR patients during the acute and chronic stages. In chronic AZOOR patients, the proportion of those with a hyperAF ring around the macular region is significantly higher compared to acute patients (33.3% *vs* 0, P=0.024). Additionally, a greater proportion of chronic AZOOR patients had hypoAF lesions (72.2% *vs* 14.3%, P=0.0016). In 61.1% chronic cases, there were also persistent hyperAF lesions present during extended follow-up.

Table 2 FAF presentations of acute and chronic stage AZOOR patients

n (eyes)

FAF pattern	Acute (*n*=14)	Chronic (*n*=18)	*P* (only <0.05 were shown)
Typical trizonal pattern	4	12	
HyperAF ring around the macula	0	6	0.024
HyperAF satellite lesions	4	6	
Majority of lesion was hypoAF	2	13	0.0016
Peripheral lesion	1	3	
Perivascular hyperAF	1	3	

HyperAF: Hyperautofluorescent; HypoAF: Hypoautofluorescent; FAF: Fundus autofluorescence; AZOOR: Acute zonal occult outer retinopathy.

Presentation of AZOOR in SS-OCT SS-OCT findings in AZOOR during both acute and chronic stages are summarized in Table 3. Typical OCT changes in AZOOR included loss or irregularity of the ellipsoid zone (EZ) and interdigitation zone (IZ), hyperreflective dots between RPE and the EZ, disruption

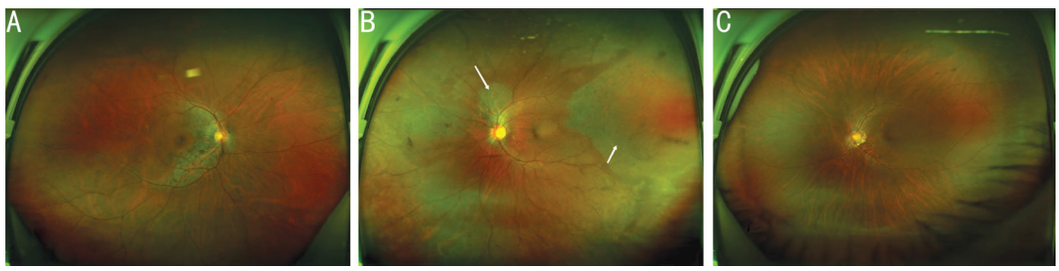

Figure 1 Different wide-field SLO patterns in AZOOR patients A: Patient 13, with a disease onset of 1y in the right eye. The SLO shows peripapillary RPE atrophy with hyperpigmentary changes; B: Patient 19, with a disease onset of 2y in the left eye. Peripapillary retinal atrophy with pigmentary disturbances is visible, as well as in the mid-peripheral and peripheral regions of the temporal side of the retina (areas indicated by white arrows); C: Patient 4, with a disease onset of 3mo in the left eye. Apart from myopic fundus changes, no retinal abnormalities associated with AZOOR were detected. AZOOR: Acute zonal occult outer retinopathy; SLO: Scanning laser ophthalmoscopy.

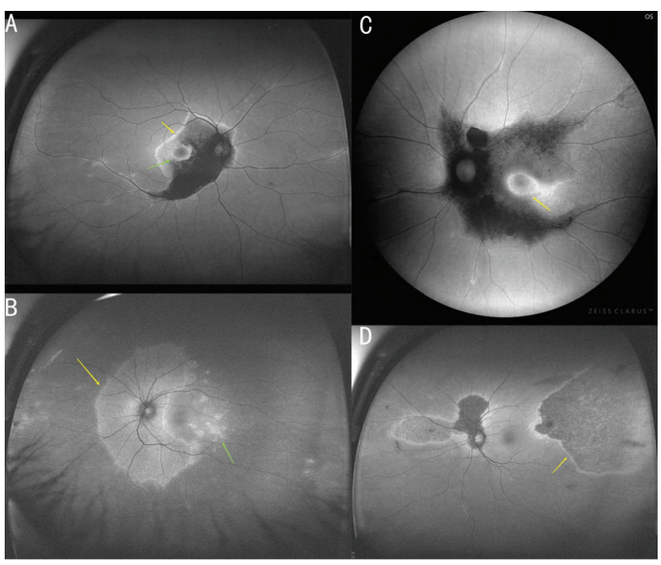

Figure 2 Different wide-field FAF patterns in AZOOR patients A: Patient 13, with a disease onset of 1y, exhibits a typical trizonal presentation, with a hypoautofluorescent (hypoAF) core surrounded by a hyperautofluorescent (hyperAF) ring (yellow arrow). The macular area is surrounded by a hyperAF ring (green arrow); B: Patient 7, with a disease onset of 6mo, shows a contiguous zone of hyperAF core surrounded by a prominent hyperAF ring (yellow arrow), and multiple hyperAF satellite lesions (green arrow); C: Patient 20, with a disease onset of 4y, exhibits a typical trizonal presentation, with a hyperAF ring around the macula (yellow arrow); D: Patient 19, with a disease onset of 2y, exhibits lesions surrounding the optic disc in the posterior pole, most of which are hypoAF, with a hyperAF ring visible around the lesions. HypoAF lesion are also present in the peripheral retina on the temporal side, with hyperAF ring visible around the lesion (yellow arrow). FAF: Fundus autofluorescence; AZOOR: Acute zonal occult outer retinopathy.

of RPE, and thinning of the outer nuclear layer (ONL), resulting in decreased overall retinal thickness (Figures 3 and 4). These hyperreflective dots have different sizes and locations (Figures 3 and 4). These mentioned presentations were observed in both acute and chronic stage cases, with no significant differences. During follow-up, 23 affected eyes

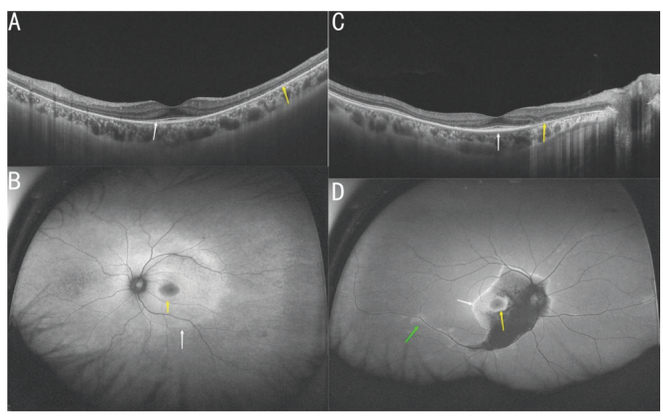

Figure 3 Different swept source optical coherence tomography (SS-OCT) and hyperAF ring in the wide-field fundus autofluorescence image in acute zonal occult outer retinopathy (AZOOR) patients A, B: Patient 17 has had a disease in the left eye for 2y. A: Aside from the foveal region, the EZ across the rest of the retina has disappeared. The outer layers of the retina at the fovea are disorganized (white arrow). RPE deposits are visible at the location indicated by yellow arrows. B: Despite 2y of disease progression, the lesions around the optic disc and in the posterior pole still exhibit hyperAF, with a hyperAF ring visible around the lesions (white arrows) and a hyperAF ring around the macular area (yellow arrow). C, D: Patient 13 has had a disease in the right eye for 1y. C: Extensive loss of the EZ is visible, with RPE deposits evident at the location indicated by yellow arrows. The outer structure of the fovea is disorganized (white arrows). D: Within the lesion area surrounding the optic disc and posterior pole, a large portion of the area has become hypoautofluorescent, indicating severe damage to the RPE. The lesion areas in the temporal side of the macula still exhibit hyperautofluorescence. A hyperAF ring is visible around the lesions (white arrow) and around the macular area (yellow arrow). Hyperautofluorescence scatter lesions adjacent to blood vessels are indicated by green arrow. EZ: Ellipsoid zone; RPE: Retinal pigment epithelium.

showed no significant OCT changes, while we also noted recovery in the EZ and IZ in 3 cases. Four affected eyes exhibited definitive OCT progression, with increased extent of EZ and IZ disruption.

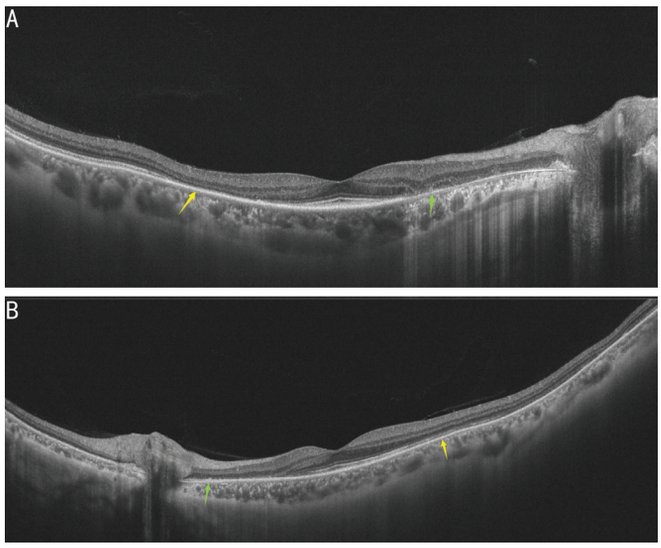

Figure 4 Different swept source optical coherence tomography (SS-OCT) changes in acute zonal occult outer retinopathy (AZOOR) patients A: Patient 13, with a disease onset of 1y in the right eye, exhibits extensive loss of the EZ, damage to the RPE, and retinal thinning (yellow arrow). The thinning of the retina enhances the scleral reflectance beneath it. Hyperreflective dots are visible at the location indicated by green arrow; B: Patient 9, with a disease onset of 1mo, OCT imaging reveals smaller hyperreflective RPE deposits at the location indicated by green arrow. There is partial loss of the EZ and retinal thinning (yellow arrow). EZ: Ellipsoid zone.

Table 3 The presentation of acute and chronic stage AZOOR patients in SS-OCT *n* (eyes)

SS-OCT pattern	Acute (*n*=14)	Chronic (*n*=18)
Hyperreflective dots above RPE	6	10
Hyperreflective dots above RPE in the macula	4	4
RPE atrophy	6	10
RPE atrophy in the macula	4	4
EZ and IZ loss or irregularity	13	17
EZ and IZ loss or irregularity in macula	5	6

SS-OCT: Swept-source optical coherence tomography; RPE: Retinal pigment epithelium; EZ: Ellipsoid zone; IZ: Interdigitation zone; AZOOR: Acute zonal occult outer retinopathy.

Detailed examination using SS-OCT scans indicated that within the hyperAF ring, there was a reduction of EZ and external limiting membrane (ELM), along with thinning of the ONL. Inside the ring, all retinal layers were observable, but there was a decrease of the EZ, ONL, and IZ as they neared the inner boundary of the ring (Figure 5).

When classifying AZOOR patients based on the presence or absence of RPE deposits, we observed significant differences in the incidence of macular damage among chronic AZOOR patients (Table 4). In acute-phase patients, the proportion of macular damage on OCT was not significantly different regardless of the presence of RPE deposits. However, among

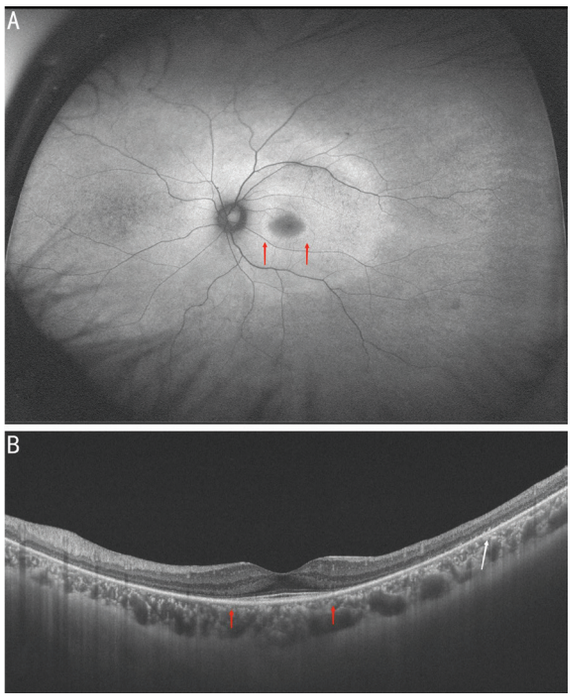

Figure 5 The detailed structure of hyperautofluorescent ring in the wide field fundus autofluorescence image of acute zonal occult outer retinopathy (AZOOR) patient In Patient 17, who has been experiencing symptoms in the left eye for two years, SS-OCT revealed detailed structural characteristics of the hyperAF ring (A). Within this hyperAF ring, a noticeable reduction in the EZ and ELM was observed, accompanied by thinning of the ONL. Progressing inward towards the ring's boundary, there was a gradual decrease in the integrity of the EZ, ONL, and IZ, as indicated by the red arrow. Additionally, RPE deposits were visible at the location marked by the white arrow (B). EZ: Ellipsoid zone; ELM: External limiting membrane; ONL: Outer nuclear layer; RPE: Retinal pigment epithelium; IZ: interdigitation zone; HyperAF: Hyperautofluorescent.

chronic-phase AZOOR patients, those with RPE deposits were more likely to exhibit EZ and IZ loss or irregularity in the macular area (6/10 *vs* 0/8, *P*=0.0128).

DISCUSSION

Due to the rarity of AZOOR, prior studies have not adequately elucidated the nature of this disease[3,7-9]. Our study included a relatively large number of cases and employed multimodal imaging techniques such as FAF and SS-OCT to comprehensively characterize Chinese AZOOR patients. To our knowledge, this is the first report to find that in chronic AZOOR, the presence of hyperreflective dots above the RPE is more likely to be associated with macular abnormalities on OCT. In addition to the classical trizonal presentation, our study has identified a broader range of imaging manifestations in FAF.

While female predominance (65%) aligns with epidemiological reports[3], our patient-level analysis revealed no significant gender differences in visual outcomes. This suggests that sex

Table 4 Multimodal imaging and visual prognosis in AZOOR patients with or without RPE deposits *n* (eyes)

SS-OCT presentations	Acute (*n*=14)			Chronic (*n*=18)		
	RPE deposits (*n*=8)	w/RPE deposits (*n*=6)	*P* (only <0.05 were shown)	RPE deposits (*n*=10)	w/RPE deposits (*n*=8)	*P* (only <0.05 were shown)
RPE atrophy	3	3		6	4	
RPE atrophy in the macula	4	0		4	0	
EZ and IZ loss or irregularity	6	6		10	7	
EZ and IZ loss or irregularity in the macular	3	2		6	0	0.0128
HyperAF ring at macula	0	0		3	3	

SS-OCT: Swept-source optical coherence tomography; EZ: Ellipsoid zone; IZ: interdigitation zone; HyperAF: Hyperautofluorescent; AZOOR: Acute zonal occult outer retinopathy; w/RPE deposits: without Retinal pigment epithelium deposits.

may influence disease susceptibility rather than progression patterns. In our study, no notable disparity in visual acuity was evident between acute and chronic AZOOR cases, both at baseline and during the final visit. This implies that for the majority of AZOOR patients, central vision can be well preserved, even over extended disease duration[8,10-11].

In this study, we found hyperreflective dots above the RPE on OCT in some AZOOR patients. Chronic AZOOR patients with hyperreflective dots above the RPE showed increased susceptibility to damage in the EZ and RPE at the fovea. Hyperreflective dots above the RPE observed on OCT can be found in many diseases. Such as age-related macular degeneration (AMD), pseudoxanthoma elasticum[12], Sorsby's dystrophy[13], IgA nephropathy[14], vitamin A deficiency[15], fundus albipunctatus[16] and adult-onset foveomacular dystrophy[17]. The hyperreflective dots extended into the photoreceptor outer segment and inner nuclear layers. These were associated with photoreceptor disruption, photoreceptor loss, localized Müller cell gliosis, and RPE alterations[18-20]. Similarly, in our study of AZOOR, the presence of these dots above RPE was associated with significant RPE and EZ damage. The specific pathological features of hyperreflective dots in patients with AZOOR remain unclear, thus making it challenging to confirm their consistency with the hyperreflective dots described in previous literature. Zhang *et al*[21] reported dynamic changes in hyperreflective dots among AMD patients over a 12-month follow-up period, with 11% resolving, indicating the potential of regression. Emerging evidence suggests the involvement of microglia in the regression process of hyperreflective dots[19]. In our study, we also observed the disappearance of hyperreflective dots during the follow-up period. Further research is necessary to uncover the underlying mechanisms and potential shared pathophysiology between these conditions.

In our investigation, hyperAF and hypoAF lesions can be found in AZOOR patients by FAF. The predominant FAF characteristic of retinal lesions in chronic cases was hypoAF, indicating extensive RPE damage in those areas. The presence of hypoAF regions was relatively more straightforward to interpret, however, the precise mechanism underlying the occurrence of hyperAF in affected retinal zones in AZOOR is still unclear. Earlier research proposed that in acute cases, this phenomenon might result from inflammation affecting the photoreceptor outer segments, causing photopigment loss and a subsequent relative increase in AF emanating from the underlying RPE. The inflammation of photoreceptor or infiltration of leukocytes may also lead to elevated autofluorophore production, which could potentially contribute to this observation[9]. Conversely, in chronic cases where photoreceptors were already compromised, the heightened AF might result from elevated production and/or diminished clearance of lipofuscin by the RPE[22]. In our study, two chronic cases presented with hyper AF lesion on UWF-FAF and corresponding disruption of EZ in SS-OCT, indicating that the heightened AF possibly resulted from a relatively higher AF transmission from the RPE.

In AZOOR, it is currently unclear whether RPE damage is the primary pathological manifestation or a consequence of photoreceptor damage. Mrejen *et al*[3] describe the trizonal pattern of AZOOR on FAF. However, the classic trizonal pattern was observed in half of cases in this study. Previous research also indicated that not all patients exhibited this trizonal pattern[9]. Shifera *et al*[9] found that the acute stage of AZOOR manifests with diffuse hyperAF, while chronic cases exhibit hypoAF lesions on FAF. However, our study identified some different cases. Two acute cases showed hypoAF lesions, implying rapid progression and accelerated RPE atrophy. Furthermore, 61.1% chronic cases displayed persistent hyperAF lesions during extended follow-up. These cases indicate that the incidence of RPE atrophy/choroidal atrophy progression is not exceedingly high, or it advances gradually, requiring several years of observation to detect.

The presence of a hyperAF ring around the macula was exclusive to chronic patients. However, whether the hyperAF ring signifies disease activity in AZOOR remains unclear. In autoimmune retinopathy, a hyperAF ring appeared in the parafoveal area, accompanied by EZ loss and ONL thinning detected through OCT, aligning with our study's findings[23].

However, not all disruption in EZ resulted in hyperAF ring in our study. The pathogenesis of the hyperAF ring in AZOOR remains unclear. In some patients with retinitis pigmentosa, there is also a hyperAF ring around the macula[24], possibly due to an unusually high rate of photoreceptor phagocytosis. We speculate that the hyperAF ring in AZOOR has a similar mechanism to that in retinitis pigmentosa. This increased photoreceptor apoptosis ultimately leads to an elevated metabolic load on the RPE[22].

We also identified 4 AZOOR cases with periphery lesions. Similarly, Prithvi Ramtohul recently identified a new subset of AZOOR patients who exhibit centrifugal and centripetal progression of peripapillary and far-peripheral lesions, respectively, over the follow-up period. This progression results in areas of complete outer retinal and RPE atrophy[25]. These findings suggest that AZOOR can initiate peripherally. These new pieces of evidence suggest that not all patients with AZOOR exhibit the peripapillary trizonal pattern traditionally. According to Gass *et al*'s[7] hypothesis, the inciting agent of AZOOR may not only infiltrate the retina through the optic nerve, but also the ora serrata. These areas are less isolated from the systemic circulation. This may explain the peripheral lesions observed in AZOOR patients.

Gass *et al*[7] also suggested that the retina involvement in AZOOR results from the transmission of an infectious agent among photoreceptors, followed by a delayed immune response. This theory can explain the contiguous zone in some AZOOR cases. However, our study revealed that, besides contiguous lesions, 31.3% of patients had satellite lesions, and some of these lesions were distant from the contiguous lesion. Totally 12.5% of patients had perivascular satellite lesions. We speculate that certain inflammatory mediators, rather than cell-to-cell spread, may be responsible for this phenomenon.

Despite the typical OCT manifestations showing disruptions in the outer retina for AZOOR patients[26-27], we also noted recovery in the EZ and IZ in 3 cases through SS-OCT images. Özyol *et al*[28] also demonstrates a significant recovery of the outer retinal layer on OCT in an AZOOR patient after treatment. Due to the rarity of AZOOR, therapeutic trials have yet to be conducted, rendering treatment approaches largely empirical. Notably, spontaneous remission of AZOOR has been documented[29]. A Japanese study encompassing 52 eyes, reported a favorable outcome without any treatment in 60% of cases, while systemic corticosteroids were beneficial for another 40% of the eyes[30]. The efficacy of corticosteroids has been observed with various administration routes, including systemic[5], pulse intravenous corticosteroid therapy or intravitreal administration. Additionally, nonsteroidal immunosuppressive treatments have been explored[4,31-32]. Biologic agents have resulted in mixed results. Predicting the disease's evolution and response to treatments remains challenging.

This study has several limitations. First, the retrospective nature of the study and relatively small sample size limit the generalizability of our findings and may introduce bias. AZOOR is a rare condition, making it challenging to obtain a large sample and conduct prospective study. Additionally, the follow-up period varied among patients, ranging from 12.5 to 84.5mo, potentially affecting the observed disease progression and outcomes. Furthermore, treatment regimens in AZOOR are not standardized due to the lack of well-established treatment guidelines. Further research, including histopathological studies, is essential to deepen our understanding of AZOOR at a cellular and molecular level.

In this study, we conducted a comprehensive analysis of Chinese AZOOR utilizing multimodal imaging techniques. We have conducted preliminary exploration of the influence of hyperreflective dots above the RPE on disease progression. Additionally, the mechanism of hyperAF ring was also investigated. Future investigations to delve deeper into the intricate nature of AZOOR are necessary.

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