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A case documenting distinct natural history of multizonal outer retinopathy and retinal pigment epitheliopathy (MORR) with longitudinal multi-modal documentation of progression

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ABSTRACT

Purpose: To describe the clinical and imaging characteristics of the acute progressive phase of a recently proposed clinical entity, Multizonal Outer Retinopathy and Retinal Pigment Epitheliopathy (MORR), a variant of Acute Zonal Occult Outer Retinopathy (AZOOR)
Methods: Single observational case report.
Results: We present the case of a 49-year-old myopic female with progressive outer retinopathy most consistent with a diagnosis of MORR. Through multimodal imaging and longitudinal follow-up, we delineate the clinical course and imaging findings of asymmetrical episodic progressive centrifugal extension of retinal pigment epithelial disturbance in both eyes, highlighting the features of an acute progressive episode not previously described.
Conclusions: Clinicians should be aware of the active clinical and multimodal imaging features of MORR and its distinction from other outer retinopathies due to its sight-threatening distinct clinical course, bilateral involvement with peripapillary lesions, and episodic progression into the macula. Additionally, we describe a "grass-fire" and "spot-fire" progression pattern during acute exacerbation, highlighting the need for vigilant monitoring and early intervention in MORR.

1. Introduction

Acute zonal occult outer retinopathy (AZOOR) was first described by Gass in 1992, who subsequently reported on the natural history of cases with longitudinal follow-up.[1] The majority of cases affect myopic females in their mid-30s but the pathogenesis remains poorly understood.[2]

Using multimodal imaging, the diagnosis and classification of AZOOR has been refined and its clinical features more clearly defined.[2] Recently, Ramtohul et al. described a possible clinical variant of AZOOR with distinct clinical features, imaging characteristics and course, and proposed the term Multizonal Outer Retinopathy and Retinal Pigment Epitheliopathy (MORR) to describe this entity.[3]

The clinical features of MORR were recognized upon retrospective review of cases previously diagnosed as AZOOR and include a stereotypical natural history, bilateral alteration of peripapillary photoreceptors and retinal pigment epithelium initially, with or without a demarcation line of pigmentary change, with progression to involve the far retinal periphery.[3]

A key feature of MORR is episodic progression of the retinal lesions, and Ramtohul et al. documented the changing multimodal imaging appearances over time.[3] In this report we describe the multimodal imaging findings and clinical course of a patient who demonstrates many of the characteristics of MORR, and in whom we observed an episode of acute progression with clinical and imaging findings not reported in the original paper.

The report adheres to the tenets of the Declaration of Helsinki and patient consent was obtained for the report and use of clinical images.

2. Results

A 49-year-old female was referred by her optometrist with progressive pigmentary changes in the left fundus over a 16-month period

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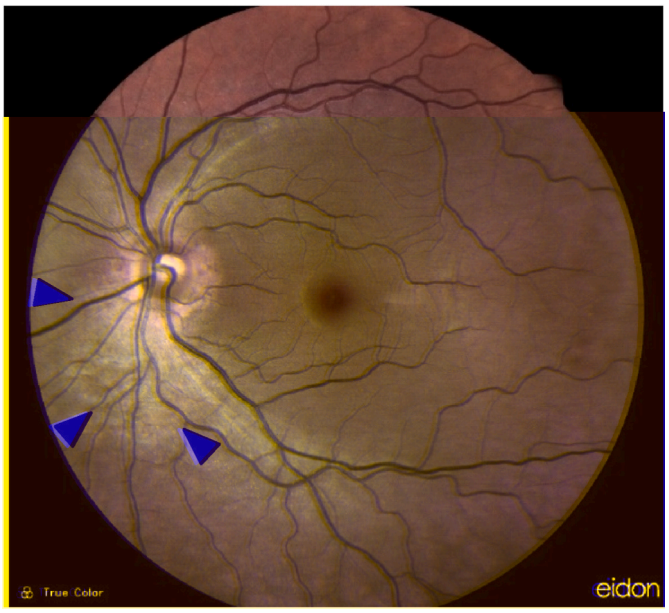


Fig. 1. Left fundus appearance at presentation (July 2021) – an area of pigment disturbance can be seen encircling the optic disc and extending inferiorly between the nasal and temporal inferior arcades.

(Figs. 1and Fig. 2a). She reported visual disturbance affecting the left eye 4 months prior to referral suggestive of a paracentral positive relative scotoma, but this resolved over 2 months and at presentation she was asymptomatic. Past ocular history was of low myopia with a recent small increase in the myopic prescription. There was a medical history of pituitary microadenoma previously treated with oral bromocriptine and now quiescent, a scalp melanoma 9 years prior that was completely excised, and gestational diabetes.

Best corrected visual acuities at baseline were 6/9 right and 6/7.5 left. Anterior segment examination was normal and there was no intraocular inflammation. Dilated funduscopy revealed a bilateral peripapillary lobular pigmentary disturbances, more extensive in the left eye (Fig. 2a and Fig. 2b). There was no optic disc swelling or clinical evidence of retinal vasculitis or choroiditis, and peripheral retinal examination was normal. The images confirm progressive pigmentary changes in the superior fundus of the left eye, radiating from the optic disc in a centrifugal fan-like pattern (Fig. 2A).

Humphrey automated perimetry (Humphrey Instruments, Dublin, CA) was normal with no enlargement of the blind spot in either eye. Fundus Autofluorescence (FAF) imaging showed speckled hypo- and hyper-autofluorescence (Fig. 3).

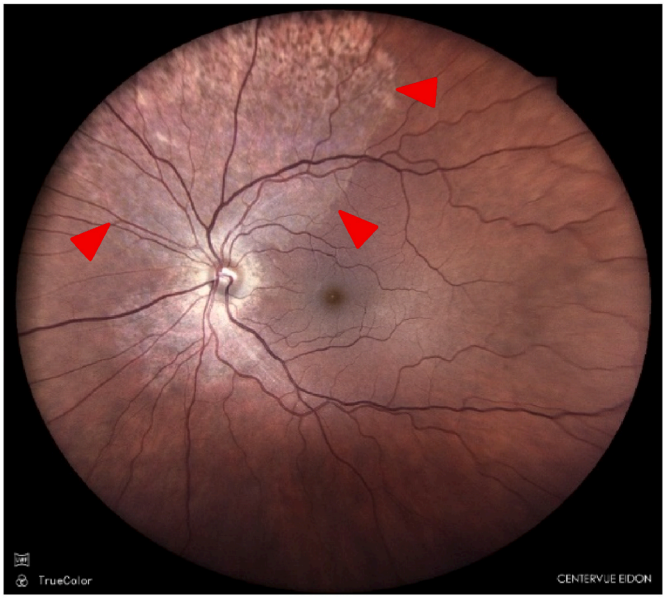
Optical coherence tomography (OCT, Topcon Triton) revealed RPE disruption, with irregularity interspersed with focal RPE atrophy, attenuation of ellipsoid layer and interdigitation zone and thickened choroid (Fig. 4). Fluorescein angiography demonstrated bright speckled hyperfluorescence throughout the peripapillary lesion, but no leakage. There was no disc hyperfluorescence or retinovascular abnormality (Fig. 5).

Electrophysiology testing revealed a normal full-field ERG but slightly reduced signals on multifocal ERG suggesting retinal dysfunction in areas consistent with other imaging abnormalities. There were no ERG features of melanoma-associated retinopathy. Genetic testing was not performed.

Serological investigations were negative for syphilis, tuberculosis, toxoplasmosis and HIV. Angiotensin-converting enzyme (ACE) and antinuclear antibody (ANA) levels were normal. Chest x-ray and MRI brain were normal. Biochemistry was unremarkable with normal fasting glucose. Inflammatory markers were normal.

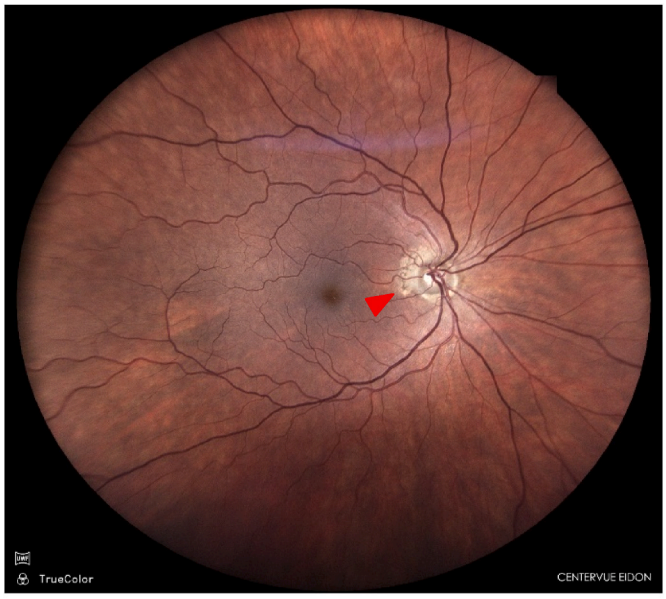
We established a working diagnosis of AZOOR and review over subsequent months showed no new abnormalities or further progression of the fan-shaped RPE disturbance in either eye.

Ten months after her initial referral she reported with deterioration in the vision of the left eye, central photopsiae and temporal scotoma. Her best corrected visual acuities were 6/9 right and 6/15 left. Clinical examination of the right eye was unchanged. The left fundus showed a progressive scalloped area of RPE disturbance inferotemporal to the optic disc approaching the fovea, and a new discontiguous "satellite" lesion in the inferior macula (Fig. 6). The active "leading edge" of the new RPE lesion was marked by a yellow-grey band (Fig. 6B). Widefield fundus imaging was performed and excluded lesions in the far retinal



A

Fig. 2a. Left fundus appearance 16 months after presentation (November 2022) – significant progression of fundus changes superiorly in a fan-like appearance.



B

Fig. 2b. Right fundus appearance 16 months after presentation (Nov 2022) – early changes at the temporal aspect of the optic disc can be seen.

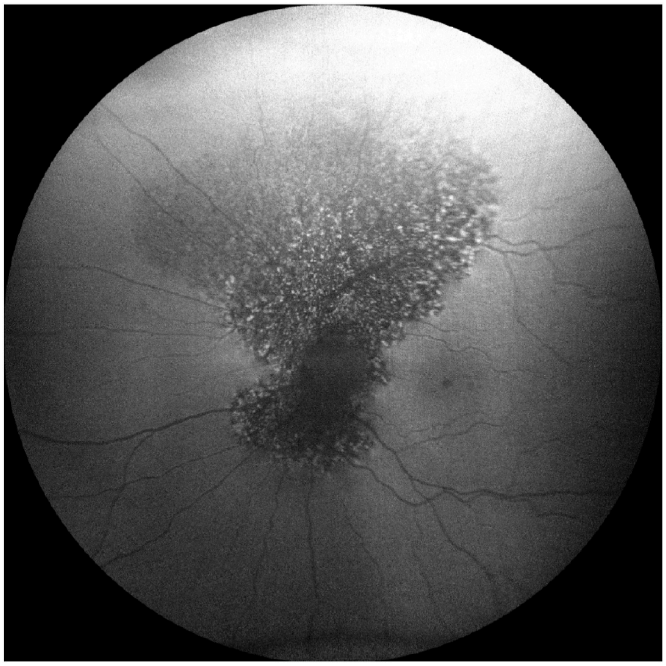


Fig. 3. Fundus Autofluorescence of the left eye at follow-up (Nov 2022) demonstrating hypo- and hyper-autofluorescence with centrifugal progression along the vascular arcades.

periphery.

On OCT imaging this band correlated with hyper-reflectance and elevation of the outer retinal layers (ellipsoid and interdigitation zone) with attenuation of the underlying RPE. The overlying outer nuclear layer and external limiting membrane appeared intact (Figs. 4 and 6G-I). The band was brightly autofluorescent (Fig. 6E).

Because of the acute progression, loss of vision and foveal involvement, the patient was commenced on oral prednisolone at a dose of 1 mg/kg body weight. Despite treatment the yellow-grey band at the active edge progressed temporally through the fovea. Within 4 weeks of the onset of her acute symptoms the band resolved and the RPE lesion stabilized; the satellite lesion in the inferior macula coalesced with the larger lesion (Fig. 6E and I). Oral prednisolone was slowly withdrawn in favor of immunosuppression with oral methotrexate 20 mg weekly. There has been no further change in the clinical appearance of either eye over 7 months of follow-up, and her visual acuities are stable with best corrected visual acuity of 6/7.5 in each eye.

3. Discussion

We have described the clinical features of a 49-year-old myopic female who presented with a bilateral asymmetric retinal pigment epitheliopathy that showed episodic, contiguous centrifugal progression from the optic disc. Our working diagnosis for the patient was AZOOR but following Ramtohul et al.'s paper,[3] we believe that the characteristics of this case are possibly consistent with a diagnosis of MORR.

The classification of AZOOR and other similar outer retinopathies has improved with advances in multimodal imaging and the ability to identify the location and depth of retinal involvement. Higher resolution imaging modalities and careful longer term follow up has allowed clinicians to distinguish the multimodal imaging features of MORR, and another variant of AZOOR known as acute annular outer retinopathy (AAOR), from those of classically described cases of AZOOR.[3,4] However, significant overlapping features and variances in individual clinical cases make differentiation between distinct clinical entities difficult. As such, many cases described as variants of AZOOR, may in fact be part of the same spectrum of disease.

The trizonal pattern of normal retina on FAF, narrow hyperautofluorescent line, followed by hypoautofluorescence of the AZOOR lesion from posterior pole to periphery has become accepted as a defining feature of AZOOR, although the features may be observed in other circumstances such as pattern dystrophies.[5] AZOOR can present with unilateral, asymmetric lesions and a trizonal autoflourescence pattern that delineates normal fundus from the AZOOR lesion. The early or chronic phases of AZOOR can be more variable.[5]

Ramtohul et al. reported a series of patients with bilateral alteration and atrophy of retinal pigment epithelium and outer retina with episodic centrifugal progression from the optic nerve and involvement of the far retinal periphery.[3] These patients had been previously diagnosed as AZOOR by the authors but are now proposed to be a distinct clinical phenotype. Differentiating these phenotypes may benefit the clinician in understanding the pattern of disease, natural history and response to treatment, however conflicting results are documented due to the inclusion of distinct entities into the broader classification of AZOOR. The multizonal pattern and episodic progression of MORR has also been recognized in some of the earliest descriptions of AZOOR.[1] Our patient also demonstrated episodic progressive centrifugal outer retinal and RPE pathology with clinical and multimodal imaging features closely resembling those reported by Ramtohul et al., although she did not have peripheral retinal changes in contradistinction to the reported patients, and this was confirmed on widefield imaging. The presence of concentric peripheral degeneration distinguishes cases of MORR and acute annular outer retinopathy (AAOR) cases from the traditional definitions of AZOOR.

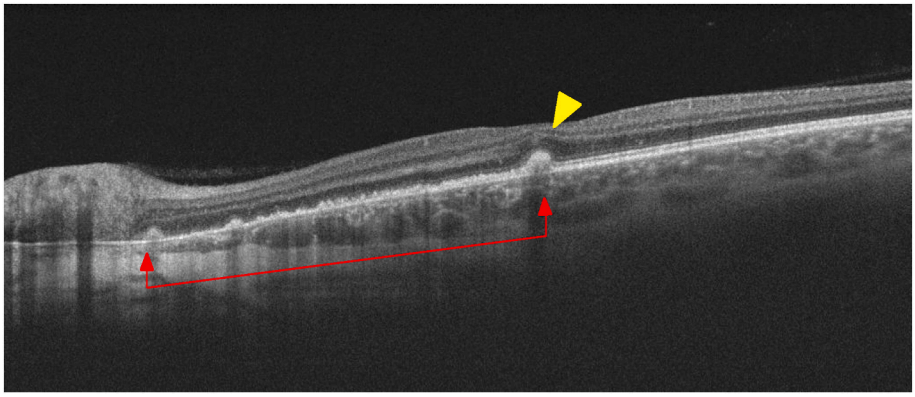


Fig. 4. Close-up OCT B scan of the left eye demonstrating RPE and outer retinal disruption with irregularity and focal atrophy (red arrows). The yellow arrowhead indicates elevation and outer retinal hyperreflectivity corresponding to the yellow-grey line during acute progression; note the involvement of the ellipsoid and interdigitation layers and attenuation of the underlying RPE, but preservation of the overlying external limiting membrane and outer nuclear layer. The subfoveal choroidal thickness was 400 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

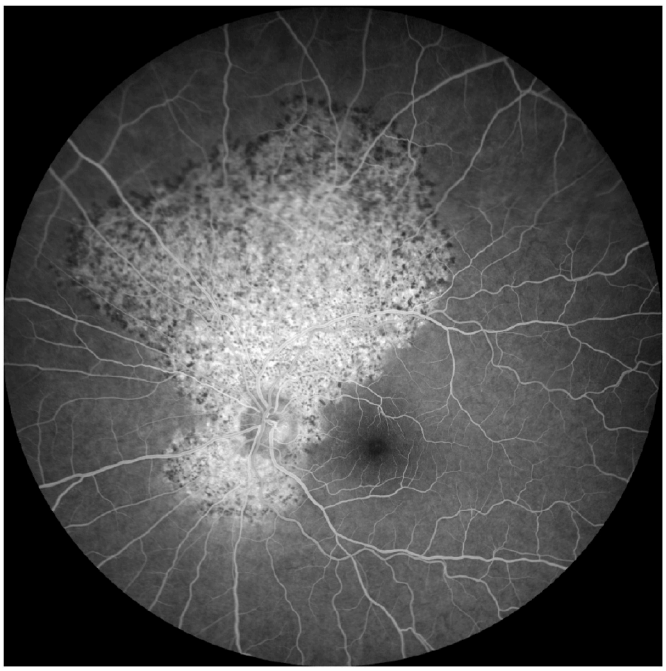


Fig. 5. Fluorescein Angiogram at same time point as Fig. 3, above, in late phase demonstrating bright speckled staining but no leakage within the lesion or optic disc.

Acute annular outer retinopathy (AAOR) is rare variant of AZOOR.[4,6] It is characterized by a peripapillary irregular annular band of deep retinal opacification, associated with a scotoma in most cases.[4] It is usually unilateral, although can present bilaterally, and shows fundus changes early in the disease course, unlike AZOOR.[4,7] There is often a distinguishing grey line between normal and involved retina clinically, similar to that observed in our case during the acute progressive episode.[5] The AAOR lesion progresses symmetrically and centrifugally from the optic disc over several weeks before stabilizing, and there are no reports in the literature of subsequent re-activation or episodic progression.[4,6]

Fundus autofluorescence in our case showed a speckled hypo- and hyperautofluorescent central region surrounded by a thin hyperautofluorescent demarcation line, consistent with lesions in both MORR and AAOR.[3,4] In both MORR and AAOR the OCT is characterized by RPE disruption with variable attenuation of the overlying ellipsoid and interdigitation zones, features that were demonstrated in our patient.[3,4] Gupta described the OCT appearances at the margin of the annular lesion in AAOR as "an abrupt and elevated nodular disruption of the RPE".[4] We believe in our case the OCT of the actively progressing grey-yellow line demonstrated outer retinal involvement with attenuation of the underlying RPE. Although a thickened choroid was present in our case pachychoroid diseases are understood to be distinct from cases of MORR and AZOOR.[3]

The key differentiating features of MORR compared to AAOR and AZOOR include episodic progression, bilateral involvement with peripapillary, far-peripheral lesions, and sometimes mid-peripheral or macular lesions often separate to the peripapillary lesion.[3] Although there is considerable overlap in the clinical features of these entities we believe our patient's presentation demonstrates episodic progression that is more consistent with the features of MORR. She did not have the far peripheral lesions described in other patients, but the episodic centrifugal fan-like progression over time is typical of this condition and has not been reported in AAOR.[3,4,6]

The patients reported by Ramtohul et al. show episodic progression over time, but with prolonged periods of stability, and the authors do not appear to demonstrate the clinical and multimodal imaging features during the acute progressive phase. In our patient we observed an episode of rapid progression which occurred over less than 28 days between August 31 and September 26, 2023. Upon retrospective review of imaging, the FAF shows evidence of a new band of hyperautofluorescence on the activating lesion margin on August 31, but the significance of this was overlooked at the time (Fig. 6D). The patient became symptomatic and 13 days later the active edge had spread centrifugally towards the fovea; the linear distance covered in that time was approximately 1.9 mm, an average of 140 μm/day. The active edge was identified by a distinctive yellow-grey subretinal band, corresponding to the ellipsoid and interdigitation zones on OCT imaging, with associated RPE disturbances affecting the newly involved area (Fig. 4). There was a new discontiguous satellite lesion "ahead" of the advancing active edge. There was further progression of the active edge over the next 13 days and the satellite lesion was "swallowed up" by the main area. The yellow-grey line was no longer apparent either clinically or on OCT imaging, and the autofluorescence of the leading edge was less bright. We interpreted these signs to indicate that the phase of progression was over. This reflects the pattern seen in the previous MORR paper reporting that lesions exhibited an episodic pattern, displaying sporadic episodes of rapid extension, interspersed with periods of relative stability.[3]

We liken the progression of the active edge to a grass fire spreading rapidly outwards from the point of ignition, with a "spot-fire" satellite lesion ahead of the main lesion but which was rapidly overtaken and swallowed up. This clinical and imaging features of this active "grass-fire" progression have not been well documented previously in a case of MORR. The margins of the retinal lesions should be monitored for a line of increasing hyperautofluorescence as this may indicate reactivation of the disease process with a risk of progression, as evidenced by this case.

The pathogenesis of AZOOR and its variants remains unclear. Gass noted that 20 % of patients had an antecedent viral-like illness, and 28 % had a history of various autoimmune diseases.[1] Autoimmune causes are theorized due to the strong female predominance and the susceptibility to develop autoimmune disease in these patients.[8–10]

Recent studies have confirmed that the pathophysiology of AZOOR involves loss of photoreceptor outer segments and subsequent photoreceptor and RPE atrophy and migration.[11–13] It is possible that the pathology described in MORR is similarly in the outer retina, as highlighted in the OCT images of our patient (Fig. 4). It is difficult to be certain of the location of the primary pathology on the basis of the multimodal imaging alone because the outer retinal and RPE changes co-localise.

It is unclear how intervention altered the disease process in our case, however oral steroid did not seem to halt the acute exacerbation, and it may be that other immunosuppression is required. In this case it was felt that the patient responded to methotrexate and lesion progression ceased. Other possible treatments for this condition need to be further elucidated.

In summary, this case describes the clinical and multimodal imaging features of acute rapid progression of a suspected variant of AZOOR, that shares some similarities with cases of MORR recently described. There was an acute onset with episodic progression over time, early fundus changes on multimodal imaging, affecting the outer retina and RPE. The clinical course of MORR, while closely overlapping with AZOOR, describes with intermittent episodes of rapid "grass-fire" progression separated by prolonged periods of clinical stability. We suggest that patients with outer retinopathies, especially those thought to resemble MORR, be counselled carefully to present with any visual symptoms such as worsening vision, enlarging blind spot or scotoma, or photopsiae, and they should be monitored with FAF for early detection of reactivation and progression.

CRediT authorship contribution statement

Alexandra Klejn: Writing – review & editing, Writing – original

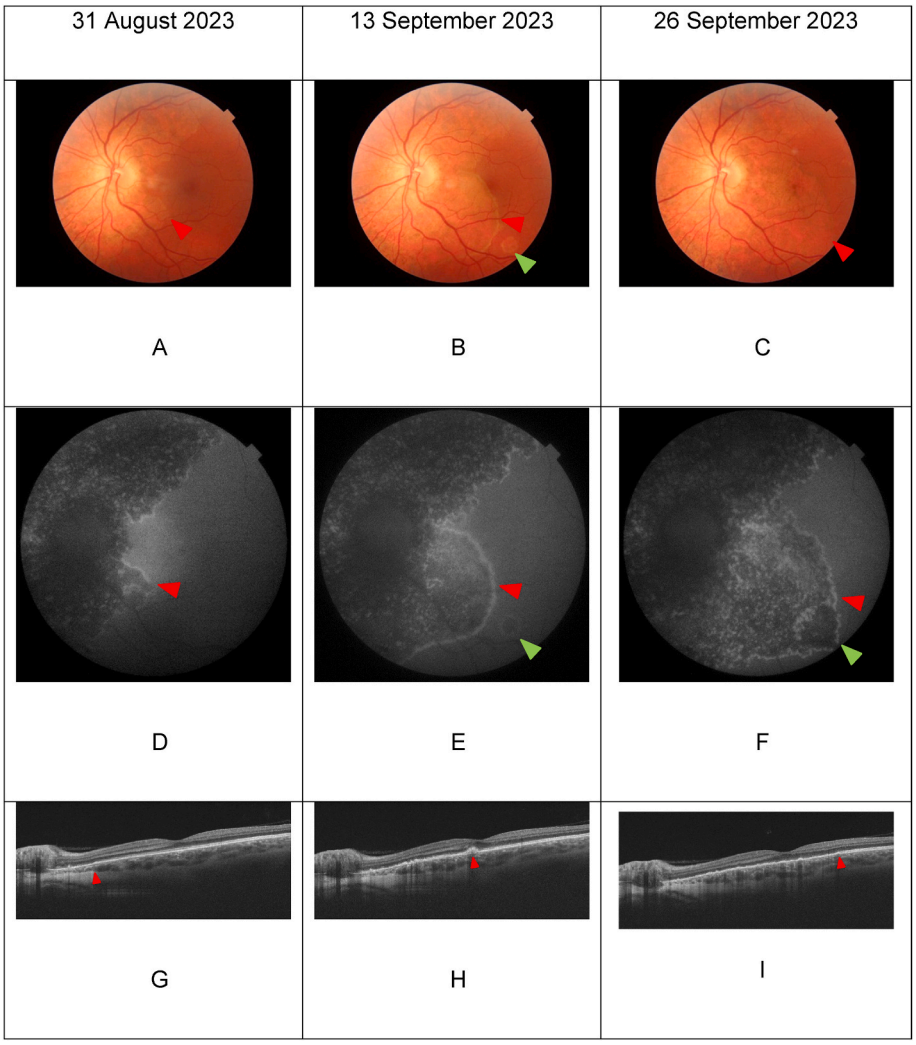


Fig. 6. Multimodal image of acute progression, with a "grass-fire" spread into the macula (red arrowheads) including a new "spot-fire" satellite lesion in the inferior macula developing and then coalesceing with the larger lesion (green arrowheads), showing hyperautofluorescent advancing edge seen as grey-white band on fundus images.
6A-C – Color fundus photos of the left eye demonstrating acute progression of the peripapillary scalloped area of RPE disturbance inferotemporal to and radiating from the optic disc in a centrifugal fan-like pattern. The active "leading edge" of the new RPE lesion is marked by a yellow-grey band, seen best in 6B (red arrow). 6D-F – Fundus autofluorescence of the left eye demonstrating widespread hyper- and hypo-autofluorescence with bright hyperautofluorence at the advancing edge (red arrow in 6E), then meeting with the satellite lesion in the inferior macula (green arrow in 6E and then 6F) 6G-I – Ocular Coherence Tomography of the left eye demonstrating correlation of the band of leading edge of RPE lesion on infra-red imaging with hyper-reflectance and elevation of the outer retinal layers (ellipsoid and interdigitation zone) and attenuation of the underlying RPE. The overlying outer nuclear layer and external limiting membrane appear intact. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Richard Sheard:** Investigation, Formal analysis, Data curation. **John Grigg:** Writing – review & editing, Supervision. **Peter J. McCluskey:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Patient consent

Consent to publish this case report has been obtained from the patient in writing.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors have no conflict of interest.

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