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Multimodality Diagnostic Imaging in Unilateral Acute Idiopathic Maculopathy

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Abstract

Objective—To describe the clinical features and imaging characteristics in unilateral acute idiopathic maculopathy (UAIM).

Methods—This is a retrospective review of four patients diagnosed with UAIM. Clinical characteristics (age, symptoms, Snellen visual acuity (VA), and funduscopy features) and images from spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), fluorescein (FA), and indocyanine green (ICG) angiography were analyzed.

Results—The median age at presentation was 31 years (range 27–52 years). The median interval between symptom onset and presentation was four weeks (range 1–20 weeks). Associated systemic findings included a viral prodrome (50%), orchitis (50%), hand-foot-mouth disease (25%), and positive Coxsackie virus titers (50%). The median presenting VA was 20/400 (range 20/70–1/400), which improved to 20/30 (range 20/20–20/60) at final follow-up. The median follow-up time was 6 weeks (range 0–8 weeks). Early in the disease course, the central macula developed irregular, circular areas of white-grey discoloration. Following recovery, the macula had a stippled retinal pigment epithelium characterized by rarefaction and hyperplasia. FA demonstrated irregular early hyperfluorescence and late subretinal hyperfluorescence. SD-OCT showed a partially reversible disruption of the outer photoreceptor layer. FAF initially revealed stippled autofluorescence that eventually became more hypoautofluorescent. ICG showed “moth-eaten” appearing choroidal vasculature, suggestive of choroidal inflammation.

Conclusions—The imaging characteristics highlight the structural changes during the active and resolution phases of UAIM. The visual recovery correlates with structural changes and suggests that the pathogenesis involves inflammation of the inner choroid, retinal pigment epithelium, and outer photoreceptor complex that is partially reversible.

Unilateral acute idiopathic maculopathy (UAIM) is a rare cause of unilateral, sudden, painless vision loss in young healthy adults. It was originally described by Yannuzzi et al in

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a series of nine patients in 1991.¹ A viral prodrome is common and nearly all patients experience spontaneous visual recovery.^{1,2} Initially, patients characteristically have unilateral, irregular, pigmentary changes and some have a neurosensory retinal detachment involving the macula.² Several studies report the fluorescein angiographic findings of an irregular hyperfluorescence and hypofluorescence that originates at the level of the retinal pigment epithelium (RPE). Following resolution of the disease process, most maculae have a bull's eye pattern of pigmentary disturbance with late staining on fluorescein angiography (FA).^{1,2} Because this condition is rare and the spectrum of disease is variable, the diagnostic criteria still remain somewhat ill-defined.²⁻⁵

With evolving imaging technologies, specific anatomic characteristics of UAIM may help us to better understand the disease process and involved tissues. Prior studies have documented this condition using conventional fundus photography, time domain optical coherence tomography (TD-OCT), and FA. Recently, Day and colleagues described the fundus appearance of a UAIM patient using fundus autofluorescence (FAF), indocyanine green angiography (ICG), and electrophysiology.³ Newer imaging modalities, such as FAF and spectral-domain optical coherence tomography (SD-OCT) are non-invasive methods of evaluating the retinal pigment epithelium (RPE) and specific layers of the retina.^{6,7} FAF provides topographic mapping of various fluorophores in the RPE, largely lipofuscin and has been used for the evaluation of age-related macular degeneration, inflammatory maculopathies, and retinal dystrophies.⁸ The axial resolution of most SD-OCT technology is approximately 5 μm , and allows for detailed assessment of the integrity of specific retinal layers and provides insight into pathogenic processes during disease progression and recovery.⁹ The purpose of this study was to further characterize the features of UAIM using multimodality imaging techniques and to correlate the ultrastructural choroidal, RPE, and retinal changes during the acute and convalescent phases of the disease with the recovery of visual function.

Methods

The Institutional Review Board of Emory University approved this study. We reviewed the medical records of consecutive patients who were diagnosed with UAIM between January 1, 2009 and December 31, 2010. Four patients with clinical features of UAIM were included for analysis. The demographic information, age at presentation, month of presentation, visual and systemic symptoms, past ocular and medical history, family history, and a detailed medication history were recorded for each patient. Snellen visual acuity, funduscopy features, electroretinography findings, and the results of clinical diagnostic imaging (SD-OCT, FAF, FA, and ICG) were also reviewed.

Retinal photography of the macula and fluorescein angiography was performed using a Topcon TRC 50DX retinal camera (Topcon America Corporation; Oakland, New Jersey). Time-domain OCT was performed using the Stratus OCT and SD-OCT images were taken on the Cirrus-HD OCT4000 instrument (Carl Zeiss Meditec; Dublin, CA). High-speed ICG and FAF images were recorded using a modified confocal scanning laser ophthalmoscope (HRA2; Heidelberg Engineering; Dossenheim, Germany). Full-field electroretinography was used in one patient, and results were recorded in accordance with the International

Society for Clinical Electrophysiology and Vision (ISCEV) protocol on a Nicolet Bravo system (Madison, Wisconsin).¹⁰

Results

Patient characteristics

The clinical characteristics of the four study patients are included in Table 1. All patients were healthy, except patient 4 who had controlled hypertension. The median age at presentation was 31 years (range 27 – 52 years). All patients presented with a complaint of acute-onset, unilateral, painless vision loss. Three patients (75%), all of whom presented shortly after symptom onset, presented during the late summer months (June through September). Patient 4 had amblyopia in the involved eye and presented five months after his initial visual disturbance.

Two patients (50%) described a viral prodrome (patients 1 and 2), and one patient (patient 1) described the clinical signs and symptoms of hand-foot-mouth disease. Two patients concomitantly developed orchitis or epididymitis (patients 2 and 3) around the time of vision loss. Additionally, two patients (patients 1 and 3) had positive titers for Coxsackie virus around the time of presentation.

The median visual acuity at presentation to our institution was 20/400 (range 20/70 to 1/400), which improved to 20/30 (range 20/20 to 20/30) at final follow-up. The median followup time was 8 weeks (range 0 to 13 weeks).

Funduscopy features

Most patients initially presented with irregular, circular areas of mild white-grey discoloration of the central macula. Patient 1 initially had a subfoveal exudative neurosensory retinal detachment (Figure 1) that resolved one week after symptom onset. Over the initial two to three weeks, the macula developed well-circumscribed areas of RPE atrophy and hyperplasia. Despite the abnormal funduscopy appearance during the disease process, the visual acuity improved dramatically. Figure 2 shows the funduscopy appearance and imaging characteristics one week after symptom onset for patient 1. Most patients showed increased retinal pigment hyperplasia as time progressed (Figure 3).

Optical coherence tomography

TD-OCT was performed in patients 1, 3, and 4. One patient had subfoveal subretinal fluid documented with TD-OCT shortly after symptom onset. Retinal thinning and irregularity of the outer photoreceptor layer was the most prominent finding in the TD-OCT images from later in the disease course.

SD-OCT was performed in patients 1 and 2. Both had disruption and irregularity of the outer photoreceptor layer early after disease onset. The external limiting membrane was well preserved in each case. Later in the course of this condition, the outer photoreceptor layer appeared to be normalizing (Figure 3).

Fundus autofluorescence imaging

Patients 1, 2, and 4 underwent FAF imaging. The alteration in autofluorescence corresponded to the clinically significant lesion on funduscopic exam. Earlier in the course of the disease, the demarcation line between hypo- and hyper-autofluorescence was distinct. The lesions showed a complex, mixed pattern of hypo- and hyper-autofluorescence, typically involving the fovea or peripapillary region. Later in the disease course, the affected areas displayed decreased hyper-autofluorescence and became more hypo-autofluorescent (Figure 3), suggesting loss of the RPE. The shift from hyper- to hypo-autofluorescence paralleled the visual acuity improvement.

Fluorescein and indocyanine green angiography

All four patients underwent fluorescein angiography and patient 1 had an ICG angiogram. Patient 1, who presented very early in the disease course, showed subretinal fluid leakage with pooling in the central macula that resolved one week later. In the subacute and chronic phases of the disease, the macula from each patient showed a well-demarcated, speckled pattern of subretinal fluorescein staining (Figures 4 and 5). Patient 1 underwent ICG angiography approximately 2 weeks after symptom onset with an irregular “moth-eaten” appearance of the choroidal vasculature throughout the involved area (Figure 2). There were no areas of abnormal hyperfluorescence or definite leakage.

Electroretinography

The full-field electroretinogram (ERG) performed on patient 1, approximately two weeks after symptom onset, showed mildly diminished 30 Hz flicker amplitudes, suggesting mild cone dysfunction, and was otherwise unremarkable.

Discussion

In this series of UAIM patients, we found that multimodality diagnostic imaging was helpful in identifying the structural changes that occur and evolve during the early phases of this disease process. These findings provide insight related to the pathogenesis of this rare maculopathy. FAF signal, which is primarily derived from lipofuscin deposition within the RPE,⁸ was particularly revealing. Specifically, the abnormal stippled hyper-autofluorescent pattern observed in the acute phase of UAIM evolved into a more stellate pattern in the late phase of the disease while concomitant loss of the surrounding of background autofluorescence suggested a fibrotic process with loss of normal RPE cells in the foveal and perifoveal region. In some cases, the changes follow along the distribution of the papillomacular bundle. High-speed ICG angiography demonstrating dilated choroidal vessels and neighboring “moth-eaten” vessels were suggestive of active choroidal inflammation and disturbance of the RPE layer. The absence of retinal vascular and optic disc hyperfluorescence suggests that disease activity appeared localized at the inner choroid, RPE and outer retina. However, we do note that papillitis has been previously reported.²

Early in the disease process, OCT imaging confirmed the presence of a subfoveal neurosensory detachment, possibly resulting from underlying choroidal vasculitis or choroidal congestion and resultant RPE injury. SD-OCT demonstrated that outer segment

photoreceptor disruption and injury occurs during the acute phase of UAIM. Interestingly, the anatomic disruption in this layer appears to be at least partially reversible. The photoreceptor layer was partially restored in patients 1 and 2; however, anatomic improvement lagged behind the visual recovery. Furthermore, each case seems to have a hyperreflective material during the acute phase of UAIM, which may represent photoreceptor outer segments. Multimodal imaging later in the disease course demonstrates at least partial resolution of this material.

The integrity of the outer photoreceptor layer, specifically studying the inner segment /outer segment (IS/OS) junction, has been a topic of increasing interest with the evolution of more sophisticated imaging modalities. Inoue and colleagues showed that the persistent disruption of the IS/OS junction correlated to poor visual outcome in patients who had epiretinal membrane (ERM) surgery.¹² The authors speculated that postoperative inflammation may lead to reversible damage to the photoreceptors in some patients. Several other studies also suggest a similar correlation between IS/OS junction disruption and visual potential.^{13,14} In patients with diabetic macular edema, Maheshwary et al. reported that the integrity of the IS/OS junction is an important predictor of visual acuity.¹⁵ In the current study, the IS/OS junction was significantly disrupted during the acute phase of the illness, yet there was partial restoration of the photoreceptor integrity two to three months after symptom onset in some patients. The relatively good visual recovery and OCT findings in these UAIM patients suggest that the outer photoreceptor layer injury is partially reversible. Preservation of the external limiting membrane (ELM) may indicate that the inner retina, cell nuclei, and cellular structures necessary for outer segment regeneration remain intact. Furthermore, it is possible that restoration of RPE pump function occurs following resolution of the acute inner choroidal inflammatory process with secondary resolution of the subretinal fluid and photoreceptor debris. The inflammation may be either directly or indirectly related to coxsackievirus infection.

The precise mechanism of coxsackievirus tissue injury in UAIM is still unclear. Multiple reports have documented the association of Hand-Foot-Mouth Disease (HFMD) with UAIM.^{2,5} HFMD, originally described by Robinson in 1958, occurred as an outbreak of vesicular and ulcerative stomatitis associated with a maculopapular rash and vesicles on the hands and feet.^{21,22} HFMD is usually a self-limited, benign condition in children under 10 years of age, but adults may also be affected.²² HFMD is most frequently associated with coxsackievirus serotype A16 or enterovirus 71, but multiple serotypes including A2, A5, A7, A9, A10, B1, B2, B3, B4, B6 have been reported in association with HFMD.^{5, 23–25} In this study, one patient had clinical signs of HFMD and developed vision loss in temporal proximity with the evolution of the skin rash and also had an elevated coxsackie A9 viral titer. While HFMD associated with coxsackievirus A16 has a more benign course, outbreaks of enterovirus 71 have been associated with serious clinical findings including encephalitis, fatal pulmonary edema and myocarditis.²⁴ In addition to HFMD, the Coxsackie virus has been associated with orchitis, epididymitis, as well as other ophthalmic pathologies.^{5, 25–33}

Uveitis associated with coxsackie virus has been reported in several cases.^{25–29} One patient with a serotype B4 infection developed iridocyclitis and an occlusive retinal vasculitis.²⁸ Additionally, Coxsackie virus B3 and B4 serotypes have been implicated in posterior

segment inflammatory conditions with lesions similar to those seen in UAIM.^{26–29} Coxsackievirus A16 and B6 antibodies were also found to be elevated in a case report of a 30 year old woman with UAIM.⁵ Among the positive serotypes found in our patients (A9, B2, B5), none had previously been reported in the English literature to be associated with ocular inflammation.

In this series, a viral prodrome was reported in the majority of UAIM patients. A comprehensive medical history and review of systems was especially helpful in raising our clinical suspicion of UAIM. Specifically, two patients reported viral prodromes and two had positive coxsackievirus antibodies. One patient was diagnosed with HFMD and two developed orchitis or epididymitis prior to the visual loss. Interestingly, three of our four patients (75%) presented during the late summer to early fall months. Given that coxsackievirus transmission is highest during these months, it is feasible that patients with UAIM may present more frequently during this season.

The strong association of UAIM with coxsackievirus, viral prodromal illness and systemic comorbidities including orchitis and epididymitis, suggests that two broad categories of disease mechanism may be involved. First, UAIM may result from direct viral infection. Second, UAIM may also be due to an autoimmune response in the setting of the viral infection. Indeed, coxsackievirus B3 is capable of infecting RPE cells *in vitro*, and it is possible that hematogenous spread to the RPE may occur during coxsackievirus-associated viremia.³⁴ Another category of disease mechanism relates to immune-mediated damage, as typified by coxsackievirus-associated myocarditis.³⁵ Specifically, molecular mimicry from coxsackievirus proteins may lead to activation of the host immune response and the failure of autoreactive Tcells to distinguish between non-self (i.e. coxsackievirus) and self-antigen (e.g. choroidal, RPE or outer retina). These processes may subsequently result in local tissue inflammation and structural damage. Although the role of local or systemic immunosuppression has not been explored, the majority of patients with UAIM experience improvement in vision and spontaneous resolution of serous retinal detachments. The role of corticosteroids in this condition could potentially expedite visual recovery by limiting tissue damage. However, with the potential to worsen a direct viral-mediated process, we do not currently recommend corticosteroid use in this setting.

In summary, we have described the clinical features of UAIM using multimodality clinical imaging, highlighting disease evolution its ultra-structural characteristics. Abnormalities on FA, ICG angiography and FAF suggest the critical role of inflammation at the level of the inner choroid, RPE, and outer retinal layers. SD-OCT was especially valuable in highlighting the partially reversible disruption of the outer photoreceptor layer. Specifically, the disruption of IS/OS junction during acute illness was correlated with visual loss, while its partial restoration during the convalescent phase of illness corresponded to visual recovery. Although the majority of patients experience a spontaneous improvement in visual acuity, a better understanding of the precise relationship between viral infection and inflammation is needed to target therapies that minimize tissue damage in patients with UAIM.

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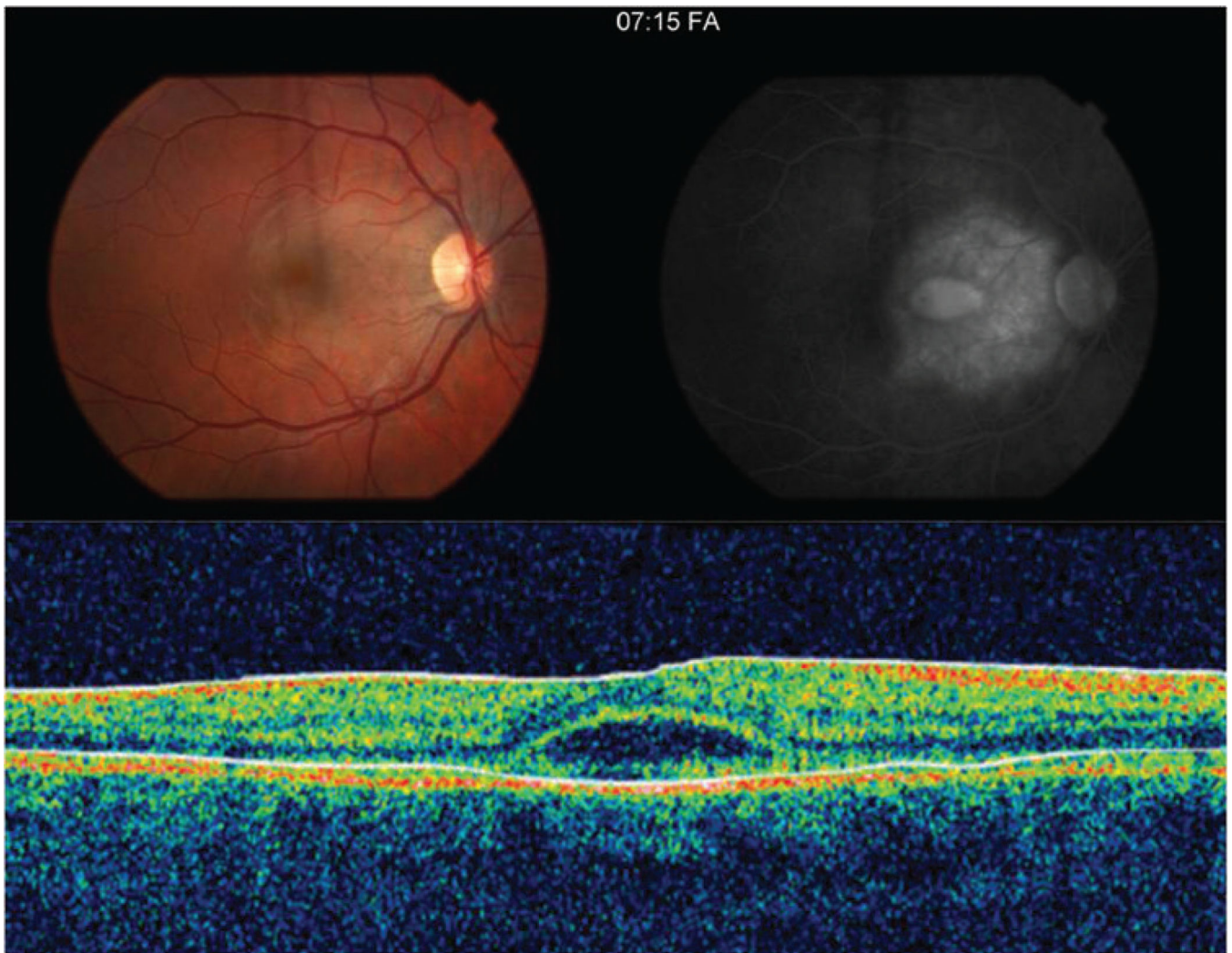


Figure 1.

The color fundus photograph of the affected right eye (A) one day after symptom onset demonstrates an irregular, circular area of grey-white discoloration in the macula. (B) Late-phase fluorescein angiogram image shows a large area of intense subretinal hyperfluorescence consistent with leakage and a smaller central area of pooling coinciding with an exudative detachment of the neurosensory retina. (C) TD-OCT shows a small subfoveal neurosensory detachment with hyperreflective debris at the apical side of the retinal pigment epithelium.

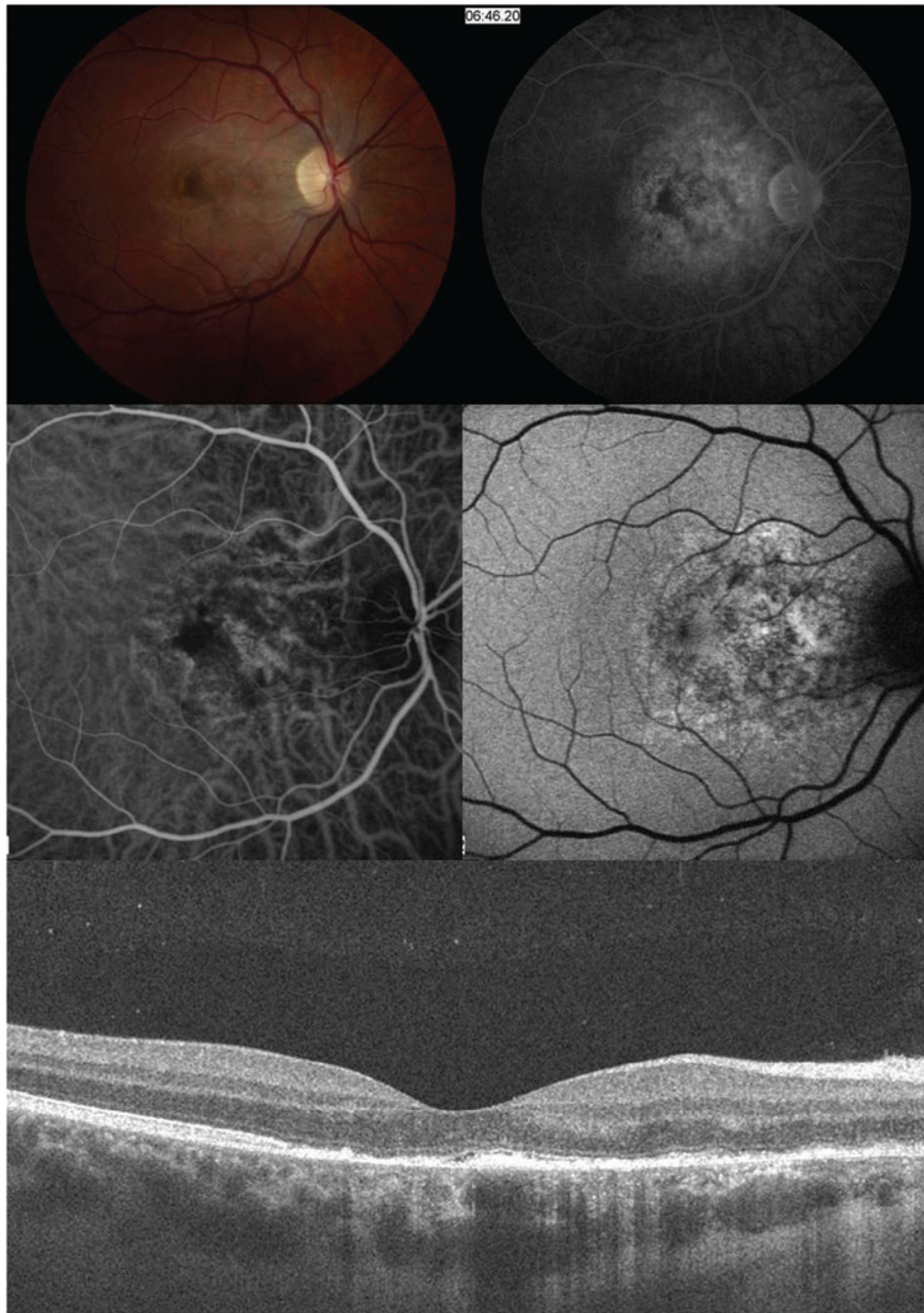


Figure 2.

(A) Fundus photography in patient 1 one week after symptom onset showing granular hyperpigmentation of the retina and retinal pigment epithelium. (B) Fluorescein angiography demonstrates late staining and less leakage in the nasal macula compared to the patient's prior angiogram. (C) ICG angiography shows irregular "moth-eaten" choroidal vascular appearance with dilated choroidal vessels underlying the perifoveal region. (D) FAF shows a stippled autofluorescence in the macula areas extending to the optic nerve. (E) SD-OCT reveals disruption and irregularity of the photoreceptor layer, subtle hyporeflectivity at the

foveal outer segment area, and hyper-reflective material on the apical side of the retinal pigment epithelium.

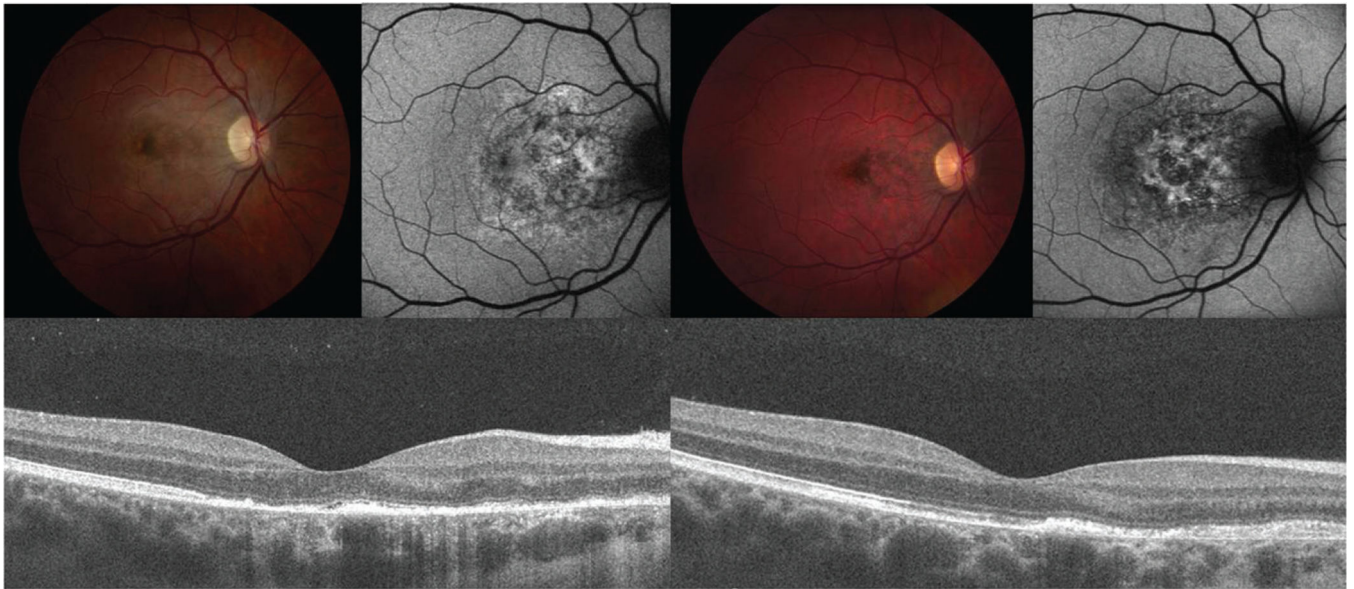


Figure 3.

Color fundus photograph, FAF, and SD-OCT findings in patient 1 at one week (A) and two months (B) after symptom onset. There is a loss of the grey-white discoloration and an increase in retinal pigment hyperplasia later in the disease course. The FAF shows less stippled autofluorescent areas (A, upper right) that evolve to a more stellate shaped autofluorescence with loss of background autofluorescence (B, upper right). SD-OCT shows hyporeflectivity of the outer photoreceptor layer (A, arrows), that are partially restored (B, arrowheads) at the twomonth follow-up visit. Note that the external limiting membrane remains intact in both A and B, yet the apical debris on the RPE has diminished.

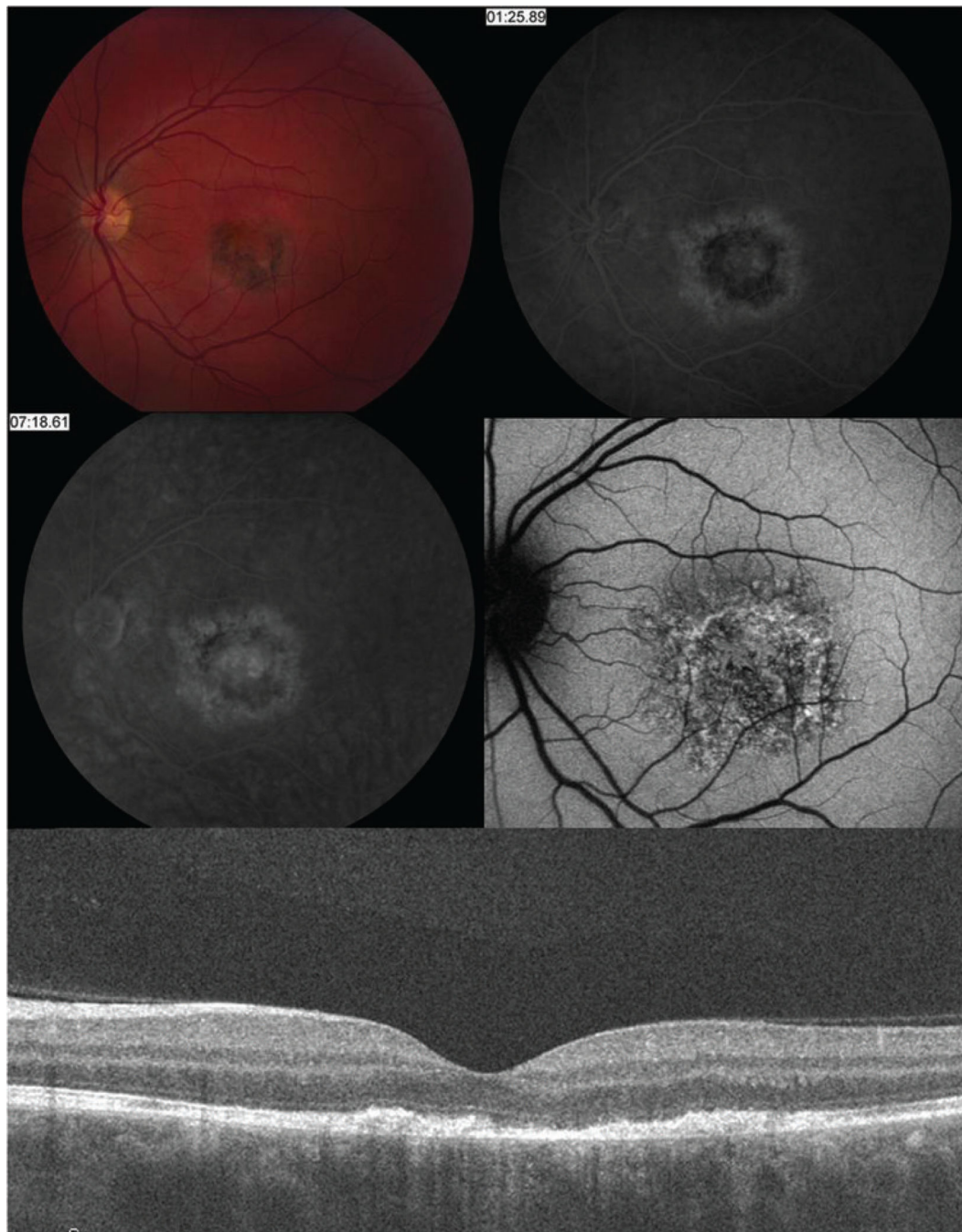


Figure 4. Six weeks after symptom onset in patient 2, there is increased retinal pigment hyperplasia (A) and late subretinal staining on FA (B and C). FAF (D) shows a stippled pattern of autofluorescence, as well as loss of background autofluorescence. The SD-OCT (E) reveals disruption and irregularity of the outer photoreceptors and debris on the apical side of the RPE.



Figure 5. Fundus imaging in patient 3 one week after symptom onset reveals a grayish discoloration of the retina within the macula (A) and subretinal staining on FA (B). Seven weeks after symptom onset, there is increased retinal pigment hyperplasia (C).

Table 1

Clinical characteristics of the study patients with UAIM.

Patient No./Sex/ Age	Month of Onset	Systemic Findings	FA *	OCT		FAF		ICG	Initial V/A	Final V/A	Total follow-up (weeks)
				Initial*	Final*	Initial*	Final*				
1/F/27	Sept.	HFMD; Positive Cocksackie virus A9	Day 1: Irregular subretinal leakage / central pooling with neurosensory detachment. Week 1: Irregular stippled subretinal staining/ leakage	Small subfoveal neurosensory detachment. Week 1: PRL present with preservation of external limiting membrane	Partial restoration of PRL	Stippled HOAF and HRAF	Largely HOAF with granular HRAF	"Moth-eaten" chorooidal vasculature	1/400	20/20	8
2/M/30	Aug.	Viral prodrome; Orchitis	Week 7: Outer circular ring of subretinal staining, middle ring of blockage and central ring of subretinal staining	PRL disruption with preservation of external limiting membrane	Partial restoration of PRL	Mixed HOAF and HRAF	Largely HOAF with granular HRAF	-	20/70	20/30	8
3/M/31	July	Orchitis; Positive Cocksackie virus B2/B5	Week 1: Outer circular ring of subretinal staining, middle ring of blockage and central ring of subretinal staining	Mildly noncystic edema of neurosensory retina	-	-	-	-	2/200	20/60	13
4/M/52	Oct.	None	Month 5: Granular area of subretinal staining and blockage	Atrophic retina	-	Well demarcated HRAF with specks of HOAF	-	-	20/400	-	-

* Dates indicate time after onset of symptoms

HOAF: hypoa autofluorescence, HRAF: hypera autofluorescence, PRL: photoreceptor layer