

# Multimodality Diagnostic Imaging in Unilateral Acute Idiopathic Maculopathy

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**Objective:** To describe the clinical features and imaging characteristics in unilateral acute idiopathic maculopathy.

**Methods:** Retrospective review of 4 patients with a diagnosis of unilateral acute idiopathic maculopathy. Clinical characteristics (age, symptoms, Snellen visual acuity, and funduscopic features) and images from spectral-domain optical coherence tomography, fundus autofluorescence, fluorescein angiography, and indocyanine green angiography were analyzed.

**Results:** The median (range) age at presentation was 31 (27-52) years. The median (range) interval between symptom onset and presentation was 4 (1-20) weeks. Associated systemic findings included a viral prodrome (50%), orchitis (50%), hand-foot-mouth disease (25%), and positive coxsackievirus titers (50%). The median (range) visual acuity at initial examination was 20/400 (20/70 to 1/400), which improved to 20/30 (20/20 to 20/60) at final follow-up. The median (range) follow-up time was 8 (8-13) weeks. Early in the disease course, the central macula developed irregular, circular areas of white-gray

discoloration. Following recovery, the macula had a stippled retinal pigment epithelium characterized by rarefaction and hyperplasia. Fluorescein angiography demonstrated irregular early hyperfluorescence and late subretinal hyperfluorescence. Spectral-domain optical coherence tomography showed a partially reversible disruption of the outer photoreceptor layer. Fundus autofluorescence initially revealed stippled autofluorescence that eventually became more hypoautofluorescent. Indocyanine green angiography 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 unilateral acute idiopathic maculopathy. 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.

*Arch Ophthalmol.* 2012;130(1):50-56

**U**NILATERAL 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<sup>1</sup> in a series of 9 patients in 1991. A viral prodrome is common, and nearly all patients experience spontaneous visual recovery.<sup>1,2</sup> Initially, patients characteristically have unilateral, irregular pigmentary changes, and some have a neurosensory retinal detachment involving the macula.<sup>2</sup> Several studies report the fluorescein angiographic findings of an irregular hyperfluorescence and hypofluorescence that originate 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.<sup>1,2</sup> Be-

cause this condition is rare and the spectrum of disease is variable, the diagnostic criteria still remain somewhat ill-defined.<sup>2-5</sup>

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 (OCT), and fluorescein angiography. Recently, Day and colleagues<sup>3</sup> described the fundus appearance of a patient with UAIM using fundus autofluorescence (FAF), indocyanine green (ICG) angiography, and electrophysiology. Newer imaging modalities, such as FAF and spectral-domain OCT, are noninvasive methods of evaluating the RPE and specific layers of the retina.<sup>6,7</sup> Fundus autofluorescence provides topographic mapping of various fluorophores in the RPE, largely

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lipofuscin, and has been used for the evaluation of age-related macular degeneration, inflammatory maculopathies, and retinal dystrophies.<sup>8</sup> The axial resolution of most spectral-domain OCT technology is approximately 5  $\mu$ m, which allows for detailed assessment of the integrity of specific retinal layers and provides insight into pathogenic processes during disease progression and recovery.<sup>9</sup> 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. All work pertaining to this project maintained compliance with the Health Insurance Portability and Accountability Act. We reviewed the medical records of consecutive patients who were given a diagnosis of UAIM from January 1, 2009, through 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, ocular and medical history, family history, and detailed medication history were recorded for each patient. Snellen visual acuity, funduscopy features, electroretinography findings, and the results of clinical diagnostic imaging (spectral-domain OCT, FAF, fluorescein angiography, and ICG angiography) were also reviewed.

Retinal photography of the macula and fluorescein angiography were performed using a Topcon TRC 50DX retinal camera (Topcon America Corporation). Time-domain OCT was performed using the Stratus OCT (Carl Zeiss Meditec, Inc), and spectral-domain OCT images were taken on the Cirrus-HD OCT4000 instrument (Carl Zeiss Meditec, Inc). High-speed ICG angiography and FAF images were recorded using a modified confocal scanning laser ophthalmoscope (model HRA2; Heidelberg Engineering). Full-field electroretinography was used in 1 patient, and results were recorded in accordance with the International Society for Clinical Electrophysiology and Vision protocol on a Nicolet Bravo system.<sup>10</sup>

## RESULTS

### PATIENT CHARACTERISTICS

The clinical characteristics of the 4 study patients are included in the **Table**. All patients were healthy except patient 4, who had controlled hypertension. The median (range) age at presentation was 31 (27-52) years. All patients were seen with a complaint of acute-onset, unilateral, painless vision loss. Three patients (75%), all of whom sought care shortly after symptom onset, were seen during the late summer months (June through September). Patient 4 had amblyopia in the involved eye and sought care 5 months after his initial visual disturbance.

Two patients (patients 1 and 2) described a viral prodrome and 1 patient (patient 1) described the clinical signs and symptoms of hand-foot-mouth disease (HFMD). Two patients (patients 2 and 3) concomi-

tantly developed orchitis or epididymitis around the time of vision loss. In addition, 2 patients (patients 1 and 3) had positive titers for coxsackievirus around the time of presentation.

The median (range) visual acuity at presentation to our institution was 20/400 (20/70 to 1/400), which improved to 20/30 (20/20 to 20/60) at final follow-up. The median (range) follow-up time was 8 (8-13) weeks.

### FUNDUSCOPIC FEATURES

Most patients initially manifested irregular, circular areas of mild white-gray discoloration of the central macula. Patient 1 initially had a subfoveal exudative neurosensory retinal detachment (**Figure 1**) that resolved 1 week after symptom onset. During the initial 2 to 3 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 1 week after symptom onset for patient 1. Most patients showed increased retinal pigment hyperplasia as time progressed (**Figure 3**).

### OPTICAL COHERENCE TOMOGRAPHY

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

Spectral-domain 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).

### FAF IMAGING

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

### FLUORESCEIN AND ICG ANGIOGRAPHY

All 4 patients underwent fluorescein angiography, and patient 1 had an ICG angiogram. Patient 1, who sought care very early in the disease course, showed subretinal

**Table. Clinical Characteristics of Study Patients With UAIM<sup>a</sup>**

Patient No./Sex/ Age, y	Onset	Systemic Findings	FA	OCT		FAF		ICG	VA		Follow-up, wks
				Initial	Final	Initial	Final		Initial	Final	
1/F/27	Sept	HFMD; positive coxsackievirus 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 disruption presentation with preservation of external limiting membrane	Partial restoration of PRL	Stippled HOAF and HRAF	Largely HOAF with granular HRAF	"Moth-eaten" choroidal 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 coxsackievirus 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	...	...

Abbreviations: FA, fluorescein angiography; FAF, fundus autofluorescence; HFMD, hand-foot-mouth disease; HOAF, hypoautofluorescence; HRAF, hyperautofluorescence; ICG, indocyanine green angiography; OCT, optical coherence tomography; PRL, photoreceptor layer; UAIM, unilateral acute idiopathic maculopathy; VA, visual acuity.

<sup>a</sup>Dates indicate time after onset of symptoms.

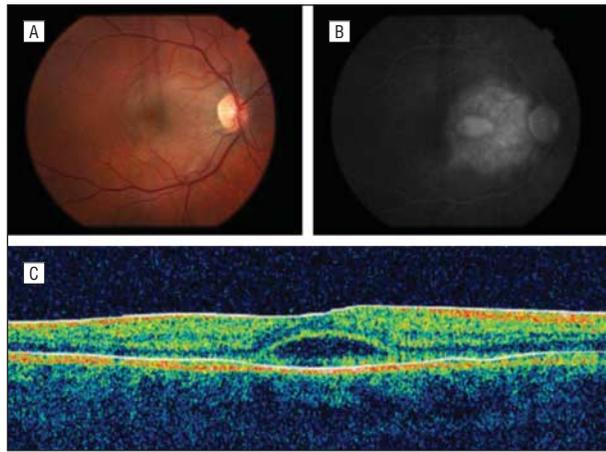
fluid leakage with pooling in the central macula that resolved 1 week later. In the subacute and chronic phases of the disease, the macula from each patient showed a well-demarcated, speckled pattern of subretinal fluorescein staining (**Figure 4** and **Figure 5**). Patient 1 underwent ICG angiography 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 was performed on patient 1 approximately 2 weeks after symptom onset. The result showed mildly diminished 30-Hz flicker amplitudes, suggesting mild cone dysfunction, and was otherwise unremarkable.

#### COMMENT

In this series of patients with UAIM, 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. The FAF signal, which is primarily derived from lipofuscin deposition within the RPE,<sup>8</sup> was particularly revealing. Specifically, the abnormal stippled hyperautofluorescent 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 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 an-

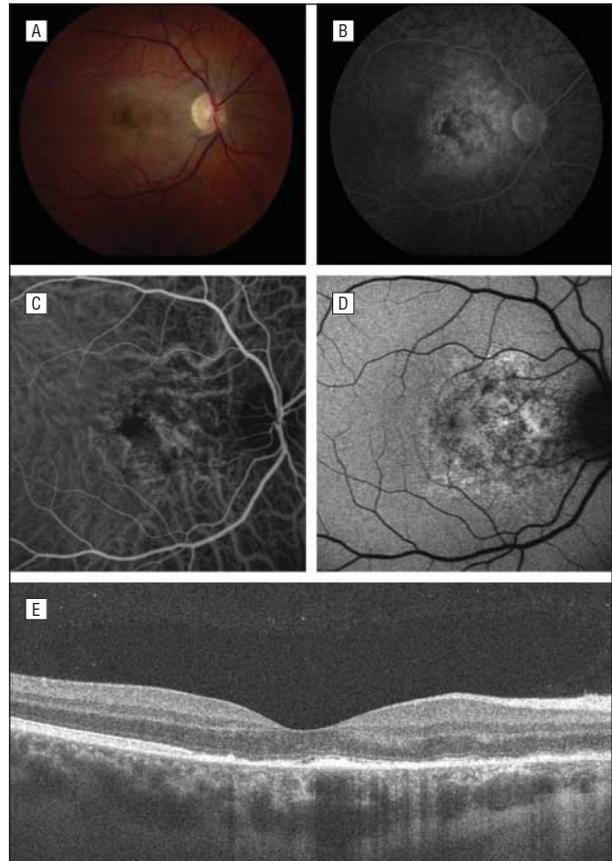


**Figure 1.** The color fundus photograph of the affected right eye (A) 1 day after symptom onset demonstrates an irregular, circular area of gray-white discoloration in the macula. B, Late-phase fluorescein angiogram image shows a large area of intense subretinal hyperfluorescence consistent with leakage and a smaller central area of pooling coinciding with an exudative detachment of the neurosensory retina. C, Time-domain optical coherence tomography shows a small subfoveal neurosensory detachment with hyperreflective debris at the apical side of the retinal pigment epithelium.

giography 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 was localized at the inner choroid, RPE, and outer retina. However, we do note that papillitis has been previously reported.<sup>2</sup>

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. Spectral-domain 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.

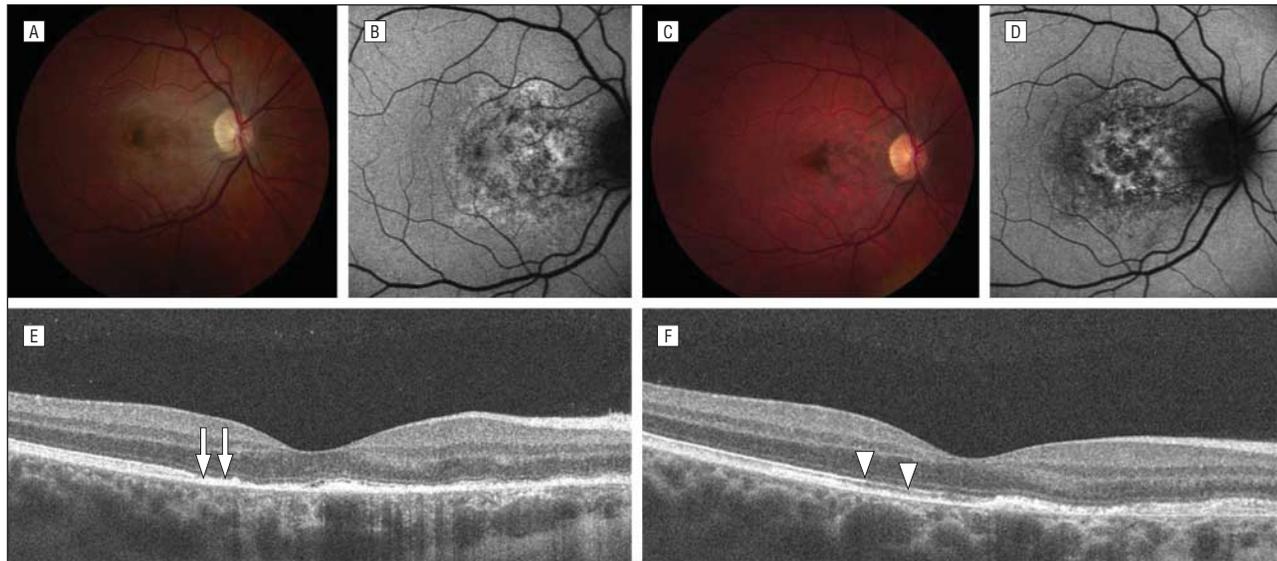
The integrity of the outer photoreceptor layer, specifically the inner segment/outer segment (IS/OS) junction, has been a topic of increasing interest with the evolution of more sophisticated imaging modalities. Inoue and colleagues<sup>11</sup> showed that the persistent disruption of the IS/OS junction correlated with poor visual outcome in patients who had epiretinal membrane surgery. The authors speculated that postoperative inflammation may lead to reversible damage to the photoreceptors in some patients. Several other studies<sup>12,13</sup> also suggest a similar correlation between IS/OS junction disruption and visual potential. In patients with diabetic macular edema, Maheshwary et al<sup>14</sup> reported that the integrity of the IS/OS junction is an important predictor of visual acuity. In the current study, the IS/OS



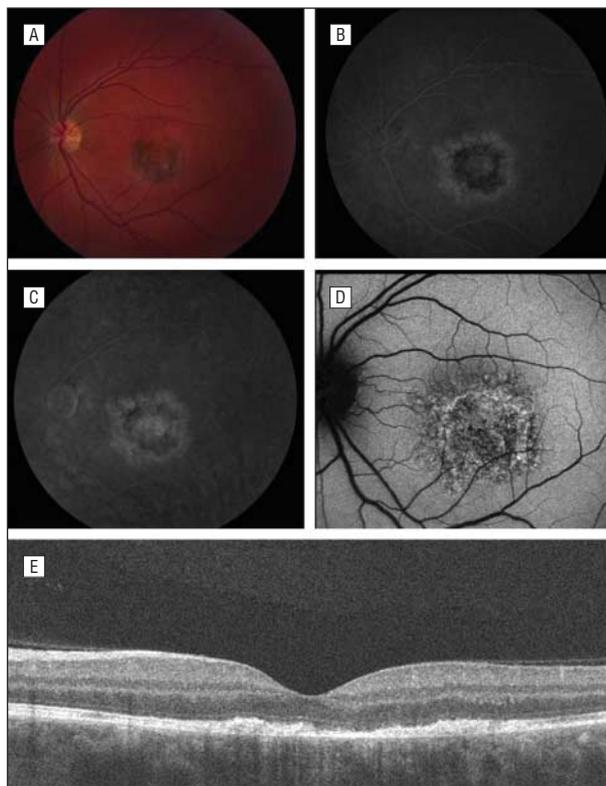
**Figure 2.** Diagnostic imaging of patient 1 at 1-week follow-up. A, Fundus photography 1 week after symptom onset showing granular hyperpigmentation of the retina and retinal pigment epithelium. B, Fluorescein angiography demonstrates late staining and less leakage in the nasal macula compared with the patient’s prior angiogram. C, Indocyanine green angiography shows irregular “moth-eaten” choroidal vascular appearance with dilated choroidal vessels underlying the perifoveal region. D, Fundus autofluorescence shows a stippled autofluorescence in the macula areas extending to the optic nerve. E, Spectral-domain optical coherence tomography reveals disruption and irregularity of the photoreceptor layer, subtle hyporeflectivity at the foveal outer segment area, and hyperreflective material on the apical side of the retinal pigment epithelium.

junction was significantly disrupted during the acute phase of the illness, yet there was partial restoration of the photoreceptor integrity 2 to 3 months after symptom onset in some patients. The relatively good visual recovery and OCT findings in these patients with UAIM suggest that the outer photoreceptor layer injury is partially reversible. Preservation of the external limiting membrane 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 HFMD with UAIM.<sup>2,5</sup> Originally described by Robinson et al<sup>15</sup> in 1958, HFMD occurred as an outbreak of vesicular and ulcerative sto-



**Figure 3.** Color fundus photograph, fundus autofluorescence, and spectral-domain optical coherence tomography findings in patient 1 at 1 week (A, B, and E) and 2 months (C, D, and F) after symptom onset. There is a loss of the gray-white discoloration and an increase in retinal pigment hyperplasia later in the disease course. The fundus autofluorescence shows less stippled autofluorescent areas (B) that evolve to a more stellate-shaped autofluorescence pattern with loss of background autofluorescence (D). Spectral-domain optical coherence tomography shows hyporeflexivity of the outer photoreceptor layer (E, arrows) that are partially restored (F, arrowheads) at the 2-month follow-up visit. Note that the external limiting membrane remains intact in both E and F, yet the apical debris on the retinal pigment epithelium has diminished.



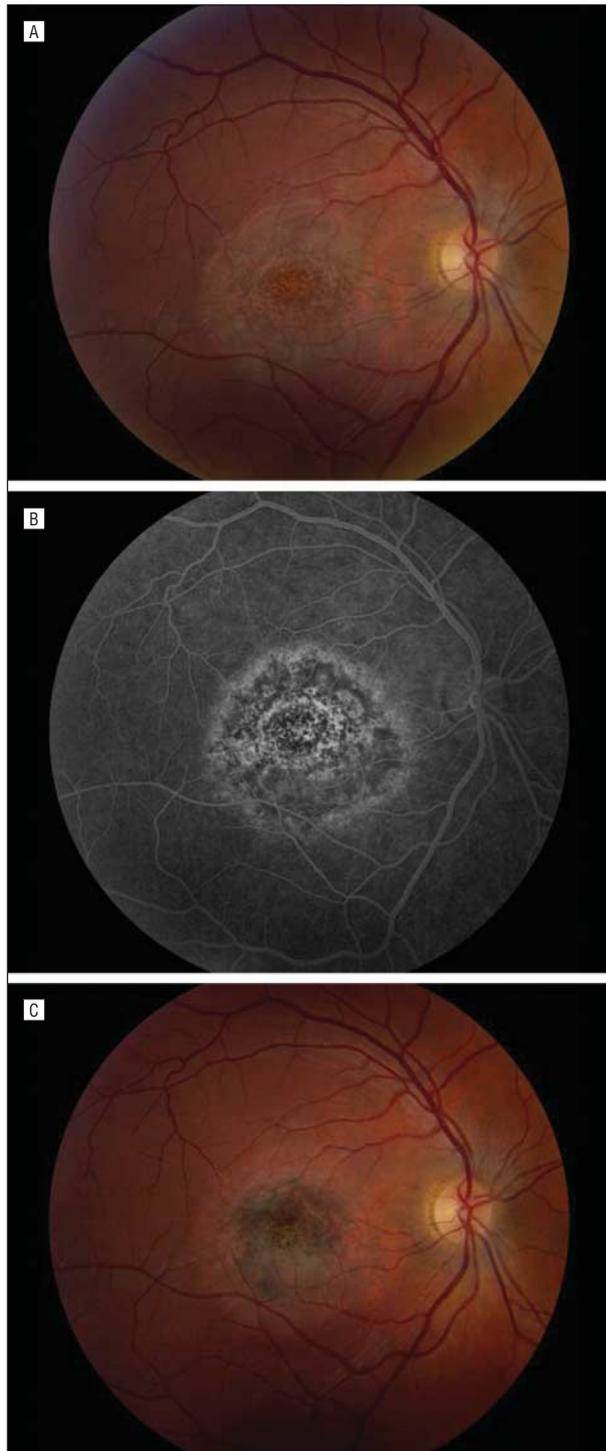
**Figure 4.** Six weeks after symptom onset in patient 2, there is increased retinal pigment hyperplasia (A) and late subretinal staining on fluorescein angiography (B and C). Fundus autofluorescence (D) shows a stippled pattern of autofluorescence and loss of background autofluorescence. The spectral-domain optical coherence tomography (E) reveals disruption and irregularity of the outer photoreceptors and debris on the apical side of the retinal pigment epithelium.

matitis associated with a maculopapular rash and vesicles on the hands and feet.<sup>16</sup> Hand-foot-mouth disease is usually a self-limited, benign condition in children younger

than 10 years, but adults may also be affected.<sup>16</sup> Hand-foot-mouth disease is most frequently associated with coxsackievirus serotype A16 or enterovirus 71, but multiple serotypes, including A2, A5, A7, A9, A10, B1, B2, B3, B4, and B6, have been reported in association with HFMD.<sup>5,17-19</sup> In this study, 1 patient had clinical signs of HFMD, developed vision loss in temporal proximity with the evolution of the rash, and had an elevated coxsackie A9 viral titer. Although 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.<sup>18</sup> In addition to HFMD, the coxsackievirus has been associated with orchitis, epididymitis, and other ophthalmic pathologies.<sup>5,17,19-26</sup>

Uveitis associated with coxsackievirus has been reported in several cases.<sup>19-23</sup> One patient with a serotype B4 infection developed iridocyclitis and an occlusive retinal vasculitis.<sup>22</sup> In addition, coxsackievirus B3 and B4 serotypes have been implicated in posterior segment inflammatory conditions with lesions similar to those seen in UAIM.<sup>20-23</sup> Coxsackievirus A16 and B6 antibodies were also found to be elevated in a case report of a 30-year old woman with UAIM.<sup>5</sup> 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 2 patients with UAIM. A comprehensive medical history and review of systems was especially helpful in raising our clinical suspicion of UAIM. Specifically, 2 patients reported viral prodromes and 2 had positive coxsackievirus antibodies. One patient was given a diagnosis of HFMD and 2 developed orchitis or epididymitis before the visual loss. Interestingly, 3 of our 4 patients (75%) developed symptoms during the late summer to early fall. Given



**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 fluorescein angiography (B). Seven weeks after symptom onset, there is increased retinal pigment hyperplasia (C).

that coxsackievirus transmission is highest during these months, it is feasible that patients with UAIM may seek care more frequently during this season.

The strong association of UAIM with coxsackievirus, viral prodromal illness, and systemic comorbidities, including orchitis and epididymitis, suggests that 2 broad categories of disease mechanism may be involved. First,

UAIM may result from direct viral infection. Second, UAIM also may 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.<sup>27</sup> Another category of disease mechanism relates to immune-mediated damage, as typified by coxsackievirus-associated myocarditis.<sup>28</sup> Specifically, molecular mimicry from coxsackievirus proteins may lead to activation of the host immune response and the failure of autoreactive T cells to distinguish between non-self (ie, coxsackievirus) and self-antigen (eg, 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, most patients with UAIM experience improvement in vision and spontaneous resolution of serous retinal detachments. The use of corticosteroids in this condition could potentially expedite visual recovery by limiting tissue damage. However, because of 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, high-lighting disease evolution and associated ultrastructural characteristics. Abnormalities on fluorescein angiography, ICG angiography, and FAF suggest the critical role of inflammation at the level of the inner choroid, RPE, and outer retinal layers. Spectral-domain OCT was especially valuable in highlighting the partially reversible disruption of the outer photoreceptor layer. Specifically, the disruption of the IS/OS junction during acute illness was correlated with visual loss, whereas its partial restoration during the convalescent phase of illness corresponded to visual recovery. Although most 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.

**Submitted for Publication:** April 17, 2011; accepted June 17, 2011.

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**Author Contributions:** Dr Yeh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported in part by a National Eye Institute Core Grant for Vision Research (P30 EY 006360) and an unrestricted departmental grant from Research to Prevent Blindness, Inc.

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