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Case Report

The Relevance of Bacillary Layer Detachment and Choroidal flow Insufficiency in Unilateral Acute Idiopathic Maculopathy Associated with Hand, Foot, and Mouth Disease: A Case Report

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Abstract

In a case of unilateral acute idiopathic maculopathy (UAIM) following hand, foot, and mouth disease, we aim to discuss the decreased perfusion of choriocapillaris secondary to systemic inflammation as shown by optical coherence tomography angiography (OCTA) and to assess the prognostic significance of bacillary layer detachment (BALAD). A 33-year-old male presented with a decrease of vision in the right eye (OD) for 5 days preceding viral prodromal symptoms and vesicular lesions on bilateral palms and soles along with vesicles and ulcers on the oral mucosa. The best-corrected visual acuity was finger counting at 1 meter distance in OD and 20/20 in his left eye (OS). Dilated fundus examination revealed a circular white-grey dome-shaped elevated lesion at the macula indicative of serous retinal detachment in OD. Spectral-domain optical coherence tomography demonstrated BALAD associated with adjacent subretinal and intraretinal fluid along with pigment epithelium detachment and disruption of ellipsoid and interdigitation zones. OCTA showed decreased choriocapillaris perfusion. All the investigations were normal in OS. The resolution of BALAD occurred during the first 2 days, which was followed by gradual improvement of choriocapillaris flow that lasted 2 months. UAIM is associated with hand, foot, and mouth disease. OCTA demonstrates both qualitative and quantitative data by detecting alterations in the choriocapillaris flow, which could be monitored during the disease course.

Keywords: Bacillary layer detachment, coxsackievirus, foot-and-mouth disease, hand, unilateral acute idiopathic maculopathy

Introduction

Hand-foot-mouth disease (HFMD) is a common viral illness usually affecting infants and children but can affect adults. HFMD is characterized by a clinical presentation of low-grade fever accompanied by a maculopapular or papulovesicular rash on the hands and soles of the feet and painful oral ulcerations (1). HFMD is caused by human enteroviruses, most commonly serotypes coxsackievirus A16, A6, and enterovirus A71 (2).

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Unilateral acute idiopathic maculopathy (UAIM) is a rare disease of the retinal pigment epithelium (RPE) and outer retina that affects young adults (3). UAIM has been previous reported to be associated with coxsackievirus infection, (3,4) yellow fever disease (5) and H1N1 vaccine (6). Beck et al. were the first to describe the UAIM association with coxsackievirus, (4) followed by several publications which reported the association between HFMD and UAIM (7-11).

Bacillary layer detachment (BALAD) is described as the separation of the bacillary layer from the other retinal layers caused by an intra-photoreceptor split within the photoreceptor myoid zone. This term was introduced by Mehta et al.(12) which lately used to describe outer retinal layer findings in cases that include acute idiopathic maculopathy, Vogt-Koyanagi-Harada, acute posterior multifocal placoid pigment epitheliopathy (13,14). Another biomarker that is known to be affected is the choriocapillaris flow, where a resolving flow deficit is reported in previous cases (15,16).

Here, we report a case of UAIM associated with HFMD and describe transient presence and the course of bacillary layer detachment (BALAD) and choriocapillaris flow deficits.

Case Report

A 33-year-old young male presented with a history of decreased vision in his right eye (OD) for 5 days preceding viral prodromal symptoms and vesicular lesions on bilateral palms and soles along with vesicles and ulcers on the oral mucosa. The patient does not have any relevant past medical or ocular history. The best-corrected visual acuity (BCVA) was finger counting at 1-meter distance in OD and 20/20 in his left eye (OS) on Snellen chart. Biomicroscopic anterior segment examination and intraocular pressure were normal in his both eyes. Pupillary reactions were normal in both eyes. Dilated fundus examination revealed a circular white-gray dome-shaped elevated lesion at the macula indicative of serous retinal detachment in OD. Dilated fundus examination of OS was unremarkable.

The multimodal imaging features of the baseline visit are shown in Figure 1. Multicolor imaging revealed dehiscence of foveal reflex and discoloration at the macula suggestive of serous retinal detachment in OD (Fig. 1a) and was normal in OS (Fig. 1b). Fundus autofluorescence (FAF) of OD showed hypoautofluorescence corresponding to serous detachment in multicolor image (Fig. 1c). FAF was normal in OS (Fig. 1d). Spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering) demonstrated BALAD pattern, associated with adjacent subretinal and pigment epithelium detachment along with intraretinal cysts in OD (Fig. 1e), there was also disruption of ellipsoid and interdigitation zone. SD-OCT was unremarkable in OS (Fig. 1f). Optical coherence tomography angiography (OCTA) (Optovue, Inc.)

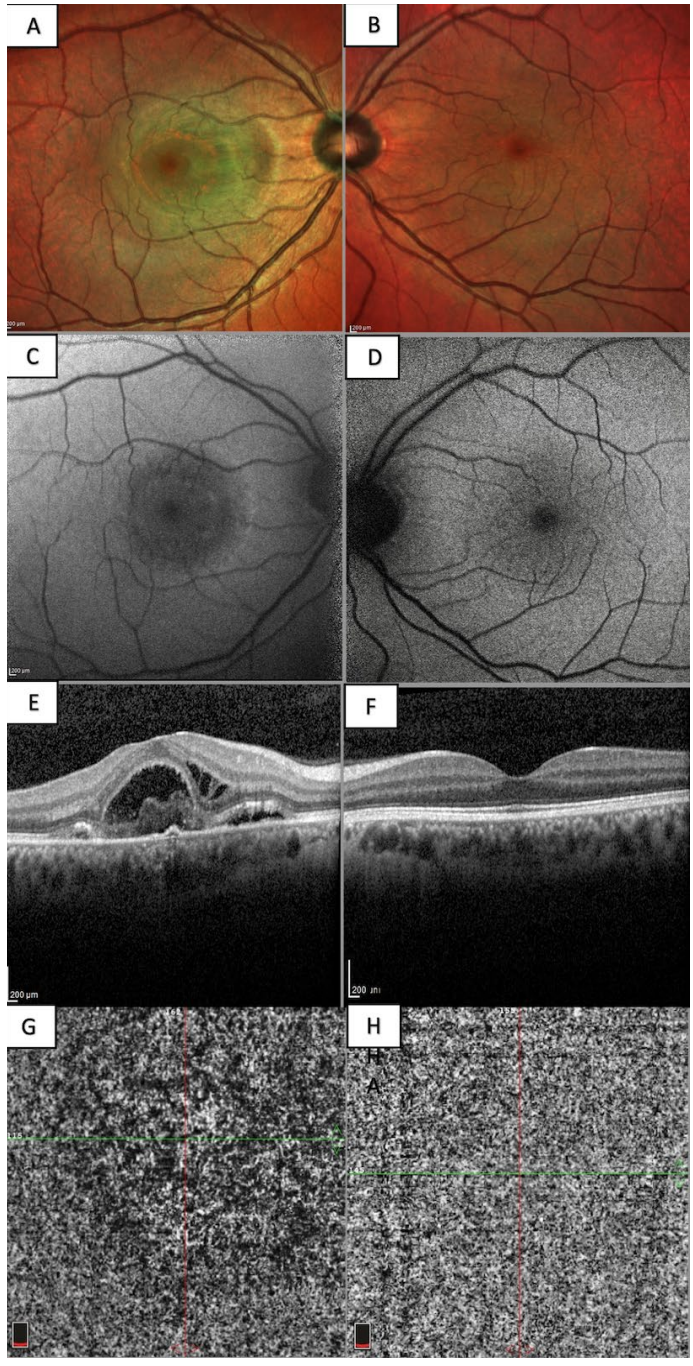

Figure 1. Multimodal imaging of a case of unilateral acute idiopathic maculopathy associated with hand, foot, and mouth disease. **(a)** Multicolor image of the right eye (OD) shows a circular area of grey-white dome-shaped dehiscent lesion at the center of macula. **(b)** Multicolor OCT image of the left eye (OS) is unremarkable. **(c)** FAF reveals hypoautofluorescence corresponding to dehiscence in OD. **(d)** FAF is normal in OS. **(e)** SD-OCT of OD shows bacillary detachment associated with and subretinal and pigment epithelium detachment along with intraretinal cysts and disruption of ellipsoid and interdigitation zone. **(f)** SD-OCT of OS is normal. **(g)** Optical coherence tomography angiography (OCTA) of OD demonstrates decrease choriocapillaris perfusion along with dilatation of vessels corresponding to the lesion and unremarkable in OS **(h)**.

showed decreased choriocapillaris perfusion along with dilatation of vessels corresponding to the lesion in OD, whereas superficial and deep plexus were normal (Fig. 1g). No significant finding was found on the OCTA of OS(Fig. 1h). Fundus fluorescein angiography (FA) demonstrated staining due to leakage in the early phase and pooling due to subretinal fluid in the late phase, and indocyanine green angiography (ICG) revealed hypocyanescent in early, mid, and late phases in OD. FA and ICG of OS were unremarkable (Fig. 2).

On the serological assessment, coxsackie IgM titer was 9.2 U/mL (Reference range negative if <10; Borderline if between 10 and 15; Positive if >15). Despite the seronegative result, initial clinical symptoms were indicative of HFMD. Therefore, the patient was diagnosed as UAIM secondary to HFMD. Supportive treatment was given. Paracetamol and ibuprofen were prescribed to control pain and fever. Adequate water intake, skin moisturizer, and oral care solution were recommended for his wounds. In terms of UAIM, he was followed up without any additional treatment. BALAD was resolved in the immediate 2-day follow-up time along with the resolution of subretinal and intraretinal fluids.

At the 2-month follow-up visit, BCVA gradually improved to 20/30 in OD. Multicolor image of OD demonstrated irregular hyperpigmented fovea surrounded by ring-like hypopigmentation in the parafoveal region (Fig. 3a). FAF revealed mixed hyper and hypoautofluorescent area, mostly the stippled hyperautofluorescent area at the rim of the lesion with irregular margin (Fig. 3b). SD-OCT showed hyperreflective subretinal material at the macula with some recovery of ellipsoid and interdigitation zone along with thinning of the outer retina (Fig. 3c). OCTA taken at the level of choriocapillaris segmentation line showed a dark pattern at

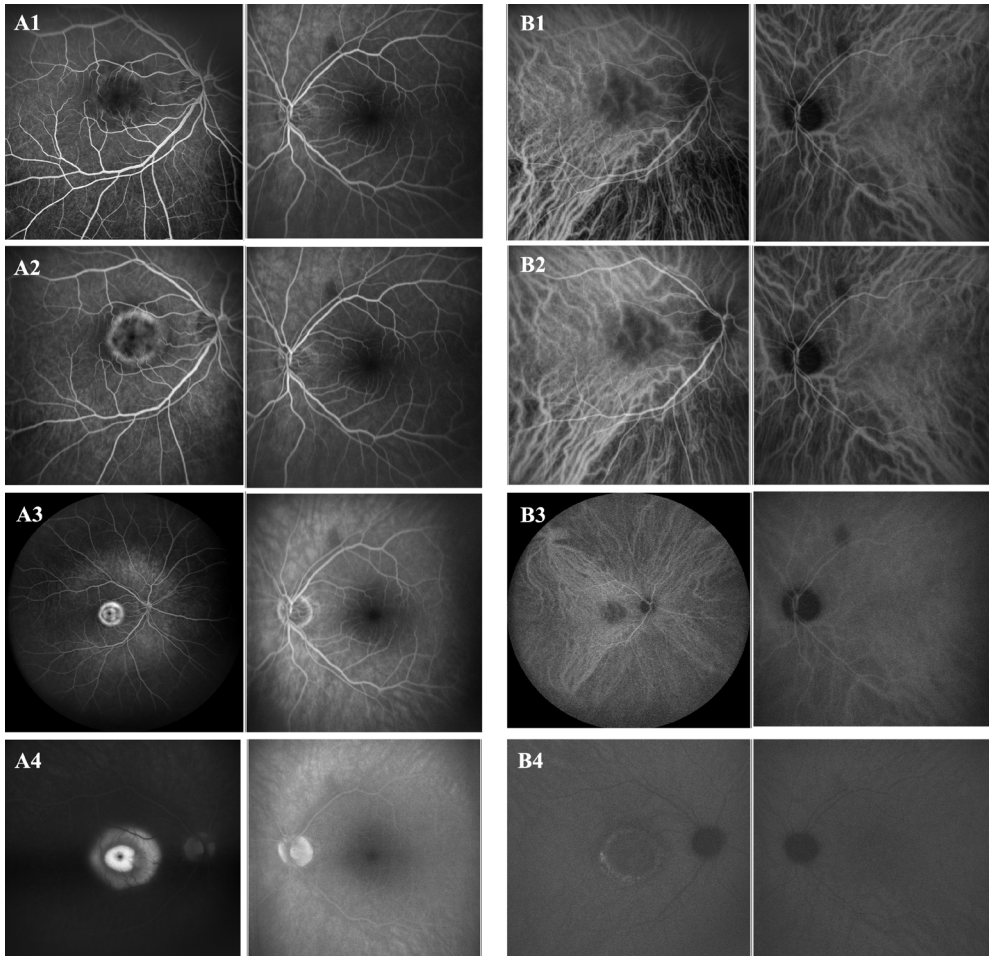

Figure 2. Fundus fluorescein angiography (FA) and ICG of a case of unilateral acute idiopathic maculopathy associated with hand, foot, and mouth disease at diagnosis. A1, A2, A3, and A4 show the early, mid, late, and 10th minute phases of FA, respectively. B1, B2, B3, and B4 indicate the early, early mid, late mid, and late stages of ICG, respectively. FA shows staining due to leakage in the early (A1) and mid-phase (A2) and pooling due to subretinal fluid in the late phase (A3 and A4), and ICG revealed hypocyanescence in early, mid and late phases (B1, B2, B3, and B4) in OD. FA and ICG of his left eye were unremarkable. Hypofluorescence in the upper vascular arcade was considered an artifact on his left eye.

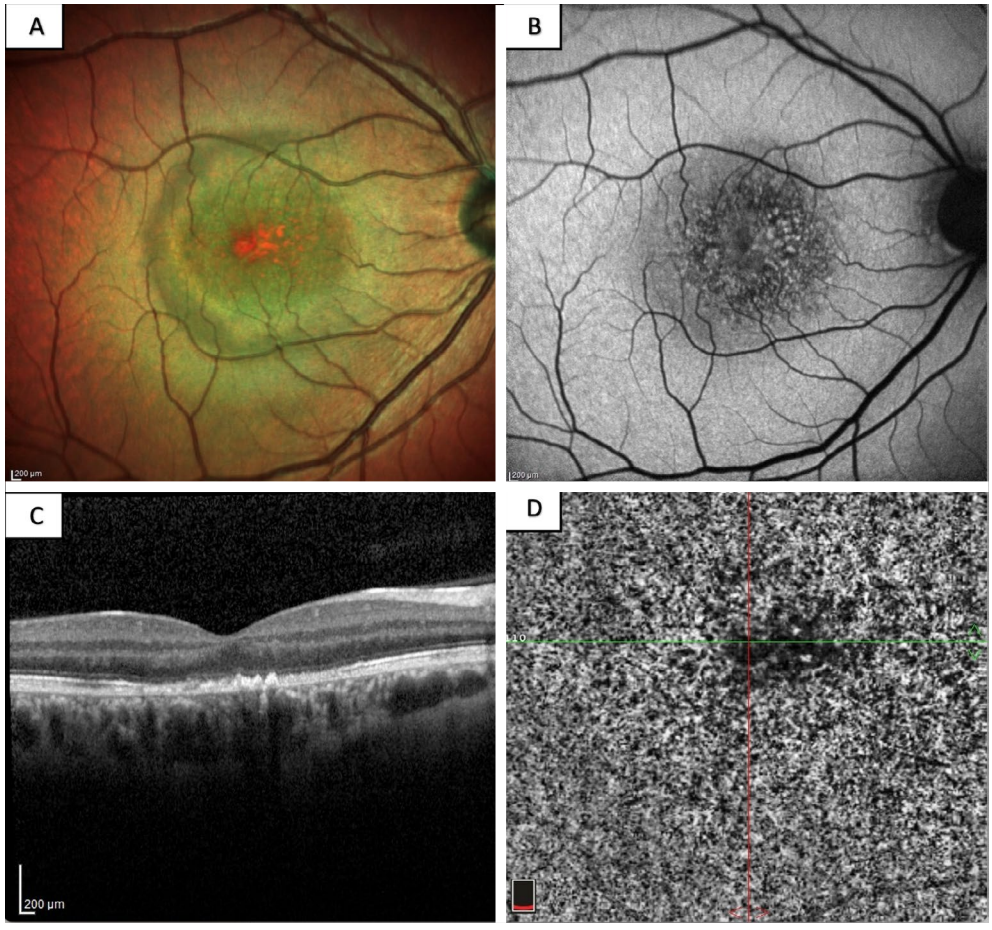

Figure 3. Follow-up investigations after 2 months. **(a)** SD-OCT Multicolor image demonstrates irregular hyperpigmented fovea surrounded by elevated ring-like hypopigmentation in the parafoveal region. **(b)** FAF illustrates mixed hyper and hypo fluorescent area, mostly the stippled hyperfluorescent area at the rim of the lesion with irregular margin. **(c)** SD-OCT reveals highly reflective subretinal material at the macula with some recovery of ellipsoid and interdigitation zone along with thinning of outer retina. **(d)** SD-OCTA taken at the level of choriocapillaris segmentation line shows dark pattern at the center, indicating flow deficits in that area.

the center indicating flow deficits (Fig. 3d), though there was a significant improvement in the blood flow to choriocapillaris as compared to baseline OCTA, but the resolution was not complete showing that the choroidal blood supply was not completely restored. Normal blood flow was observed in the superficial capillary plexus and deep capillary plexus on OCTA of the right eye at 2-month follow-up visit.

Choriocapillaris blood flow from the first to the last follow-up in the right eye was measured and compared to the choriocapillaris flow volume with a normal left eye. Flow measurement in the choriocapillaris (the circular area of 6.0 mm2 centered on the fovea is automatically delimitated by the OCTA software that calculates the flow in mm^2) is the total area of multiple bright areas corresponding to the choriocapillaris lobular meshwork. Since there was no abnormality in the OCTA of his left eye, we calculated the percentage of flow deficit using the left eye flow field as a normal reference. There is a 22% flow gap at presentation, which reduced to 16% flow gap at 5 days of presentation, and a 7% flow gap at 2 months (Fig. 4). Informed consent required for the case report was obtained from the patient.

Discussion

UAIM is a rare, self-limited, macular disease disproportionately affecting young men (1). We hereby reported a case of UAIM associated with HFMD. Even though we obtained a negative serology test, the patient presented with a classical history and physical finding similar to hand-food-mouth disease. Therefore, we reached the diagnosis of UAIM associated with coxsackievirus infection.

The natural course of UAIM is spontaneous recovery over a period of several weeks to months. It was first described in 1991 by Yannuzzi et al. (3) when they reported nine young patients who developed significant unilateral vi-

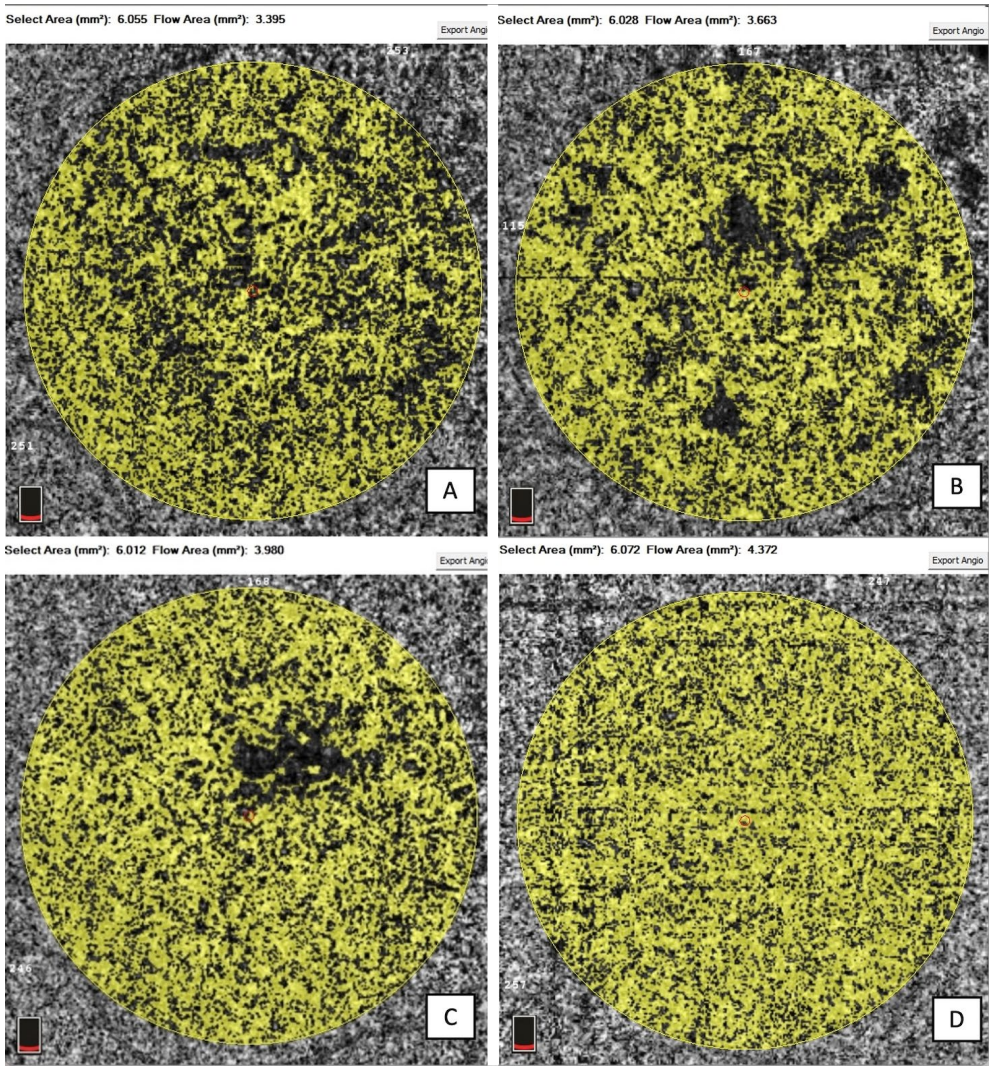

Figure 4. Measurement of measure of flow in choriocapillaris in right (OD) and left eye (OS). **(a)** Shows flow area of 3.39 mm^2 in the selected area of 6.05 mm^2 at the presentation in OD. **(b)** Shows flow area of 3.66 mm^2 in the selected area of 6.02 mm^2 in OD after 5 days. **(c)** Shows flow area of 3.98 mm^2 in the selected area of 6.01 mm^2 in OD after 2 months. **(d)** Shows flow area of 4.37 mm2 in the selected area of 6.0 mm^2 in OS at 2-month visit.

sion loss associated with exudative retinal detachment of the macula with grayish thickening of the underlying RPE. Patients experienced spontaneous recovery of vision over weeks to months, while a "bulls-eye" appearance in the macula persisted (3).

Some authors have even advised to name UIAM as "coxsackievirus maculopathy." The exact pathophysiology of UAIM is not yet very clear though Hashimoto et al. suggested choroidal involvement (17). Most patients experience spontaneous recovery over several weeks to months; however, the use of systemic steroids or topical NSAIDS has also been used in literature and it has shown to hasten the recovery time (7,18,19). Although there are several studies in literature stating the association of coxsackievirus with UAIM, the pathophysiological mechanism remains unknown. Huemer et al. have reported that coxsackievirus may infect the RPE (20). Fernández-Avellaneda et al. have otherwise concluded that the inner choroid was the primary site affected in UAIM associated with coxsackievirus infection (21). Anjou et al. have stated that the choriocapillaris could be initially involved, and thus RPE could be secondarily involved (22). In this study, we support inflammatory and reversible choroidal ischemia as an underlying cause of UAIM. Previous studies have indicated for choroidal flow insufficiency with the help of fluorescein angiography (FA), indocyanine green angiography (ICG), OCT, and OCTA (16,21,22). However, in the current case report, we present a quantitative choriocapillaris blood flow analysis of the affected eye compared to fellow

healthy eye. We found up to 22% flow deficit in the affected eye when compared with normal left eye. The gradient difference in choriocapillary flow gradually improved to 16% and 7% during the 2-month follow-up period. Choriocapillary blood flow improved in concordance with the partial restoration of outer retinal layers that were demonstrated in SD-OCT. Meanwhile, a residual choriocapillary flow deficit was present in the final visit that was corresponding to a subretinal hyperreflective material (SHRM) that was evident in SD-OCT. The present flow deficit might be due to an actual perfusion impairment or a masking effect of the overlying SHRM that results in a signal reduction in OCTA imaging.

The presence of BALAD seems a common finding when associated with UAIM (21). The mechanism of BALAD in UAIM could be due to the underlying outer retinal and/choroidal inflammation leading to the stress and splitting of the bacillary layer. The BALAD resolves once the inflammation subsides and the choroidal perfusion improves. BALAD in UAIM can serve as an imaging biomarker (23). Similarly, our case presents with BALAD in SD-OCT at the first presentation, which completely resolved within 2 days of presentation. However, following the resolution of BALAD, there was subretinal deposition of SHRM at 2 months with the final BCVA as 20/30 in the affected eye. We also note that disruption of ellipsoid and interdigitation zones might have contributed to the final visual acuity score in our patient. Since most of the literature related to UAIM has a very short follow-up of 4–6 months, a long-term effect of BALAD associated with UAIM on the vision of patient is unknown. Therefore, BALAD is currently known as a transient OCT finding that is possibly related to the inflammatory character of UAIM.

The most important limitation of our case report can be considered as the lack of photographs of the patient's skin lesions. He did not approve his photographs to be published. In addition, we could only perform Coxsackie IgM serology for diagnosis and it was negative. However, serology is not sensitive to making a diagnosis of HFMD. Coxsackievirus IG seropositivity is 60–70% and changes during the period from onset in HFMD (24,25). Moreover, other enterovirus serotypes, such as Enterovirus 71, may also cause HFMD. HFMD diagnosis is usually made clinically. Our patient had the typical clinic of HFMD.

Conclusion

We present a UAIM case associated with coxsackievirus, whose vision was partially restored. There was a slight disruption of ellipsoid and interdigitation zone on the macula on the last follow-up. We suggest that OCTA can be a beneficial non-invasive device for the quantitative measurement of choriocapillary blood flow in UAIM. In this case report, there was a reduced blood flow to choriocapillaris, indicating that definitive etiology may be choroidal origin. Moreover, the improvement of choriocapillary blood flow, along with the amount of SHRM, might also be indicative of inflammatory status and could be helpful on the assessment of visual function in UAIM cases. On the other hand, the prognostic relevance of the presence of BALAD as a baseline characteristic feature in UAIM requires further investigation in future studies.

Disclosures

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – M.H., Z.K., I.T.; Design – M.H.; Supervision – M.H.; Data Collection and/or Processing – R.T., C.K., U.Y.G.; Literature Search – R.T., C.K.; Writing – R.T., U.Y.G.; Critical Reviews – M.H., C.K.

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