Case Report

Multimodal Imaging of Unilateral Acute Maculopathy Associated with Hand, Foot, and Mouth Disease: A Case Series

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Keywords
Acute maculopathy · Coxsackie virus · Hand, foot, and mouth disease · Multimodal imaging/methods · Optical coherence tomography · Fluorescein angiography

Abstract
We described clinical and multimodal imaging findings in 4 patients with unilateral acute idiopathic maculopathy (UAIM) associated with hand, foot, and mouth disease. Four eyes of 4 patients (3 women and 1 man) with a mean age of 35 years (range: 24–40 years) were included. A bacillary detachment was observed in 3 out of the 4 eyes and was strongly suspected in the remaining eye. This particular detachment was resolved within 5–10 days in our series. A cho- riocapillaris involvement was supported by the multimodal imaging findings. On indocyanine green angiography, a hypofluorescence was observed throughout the sequence, and OCT angiography showed a defect of the choriocapillaris perfusion. In this case series, a complete multimodal retinal assessment allowed identifying the choriocapillaris as the primary tissue involved in UAIM associated with coxsackie virus infection. In 3 out of our 4 cases, a bacillary detachment with a transient evolution was identified.
**Introduction**

Unilateral acute idiopathic maculopathy (UAIM) is a rare inflammatory maculopathy involving the outer retina and retinal pigment epithelium (RPE) described for the first time by Yanuzzi et al. [1] in a case series published in 1991. The acute manifestations are characterized by a sudden, severe, unilateral central visual loss associated with a transient serous macular detachment with persistent outer retinal changes after resolution. The evolution is marked by a spontaneous recovery within several weeks. In the literature, a flu-like syndrome has been reported to precede the visual symptoms in several cases. Beck et al. [2] in 2004 were the first to describe this condition associated with hand, foot, and mouth disease (HFMD). This acute viral infection caused by the coxsackie virus is characterized by multiple maculopapular or vesicular lesions on the hands and feet, and oral ulcerative lesions. It mainly affects children, but adults can also be infected. Several scientific publications have reported the association between HFMD and UAIM in young adults [2–8]. However, despite the increasing use of multimodal imaging in the management of retinal diseases, imaging findings remain limited in the scientific literature. To our knowledge, this case series is the first to report the clinical manifestations of 4 patients with UAIM associated with HFMD with complete imaging findings using fluorescein angiography (FA) (Sanotek, Heidelberg Engineering, Spectralis), indocyanine green angiography (ICGA) (Sanotek, Heidelberg Engineering, Spectralis), fundus autofluorescence (FAF) (Sanotek, Heidelberg Engineering, Spectralis), spectral-domain optical coherence tomography (SD-OCT) (Sanotek, Heidelberg Engineering, Spectralis), with analysis of the choroidal thickness, and optical coherence tomography angiography (OCTA) (Zeiss Cirrus 5000 AngioPlex®).

**Case Report/Case Presentation**

**Case 1**

A 40-year-old woman presented with a painless sudden visual loss and a central scotoma in the left eye (ocular sinister [OS]) for 3 days. She had a history of pulmonary embolism 13 years ago. A week earlier, she experienced fever, sore throat, mouth ulcers, and an acute maculopapular palmoplantar eruption. The diagnosis of HFMD was made.

At presentation, her best-corrected visual acuity (BCVA) was 20/20 in the right eye (OD) and 20/200 OS. The intraocular pressure and slit-lamp examination were normal in both eyes without any cell in the anterior chamber and vitreous. The fundus examination revealed the loss of the foveal reflex with a foveal elevation surrounded by a hypopigmented parafoveal hemi-ring located on the nasal border of the fovea OS (Fig. 1a). FAF revealed a hyper-autofluorescence at this hemi-ring (Fig. 1b). OD was normal. SD-OCT showed a central dome-shaped cystic retinal space with a bacillary detachment pattern associated with a small area of subretinal fluid (Fig. 1c).

OCTA allowed detecting the choriocapillaris and revealed a reduced flow at initial presentation (Fig. 1d). FA showed focal macular hypofluorescent dots in the early phase (Fig. 1e), and a progressive pooling of the intraretinal cyst in the late phase (Fig. 1f). ICGA showed a central hypofluorescence in the early and late phases (Fig. 1g–i).

Evolution: After 2 days (Fig. 2a), a significant decrease in intraretinal space volume was observed (Fig. 2b). After 1 week, SD-OCT (Fig. 2c) confirmed the complete resolution of the intraretinal cyst and showed a focal attenuation and irregularity of the ellipsoid zone, and a disruption of the interdigitation zone in the central and parafoveal areas. The fundus and FAF (Fig. 2d) appeared unremarkable. The choroidal thickness was 600 microns. OCTA showed an improvement in the choriocapillaris flow (Fig. 2e). After 3 weeks, the BCVA spontaneously improved to 20/25 OS. The examination OD was unremarkable.
Fig. 1. Multimodal imaging of patient 1 at initial presentation. Color fundus photography showed a serous macular detachment (a). FAF (b) revealed a hyper-autofluorescence at this hemi-ring. SD-OCT (c) showed a central dome-shaped cystic retinal space with a bacillary detachment pattern associated with a small area of subretinal fluid. OCTA (d) revealed a reduced flow. FA showed focal macular hypofluorescent dots in the early phase (e), and a progressive pooling of the intraretinal cyst in the late phase (f). ICGA showed a central hypofluorescence in the early and late phases (g–i).

Fig. 2. Evolution of case 1: the fundus appeared unremarkable (a). SD-OCT confirmed a partial resolution after 2 days (b) and a complete resolution after 1 week (c) of the intraretinal cyst and showed a focal attenuation and irregularity of the ellipsoid zone, and a disruption of the interdigitation zone in the central and parafoveal areas. The choroidal thickness was 600 microns. FAF was unremarkable (d). OCTA (e) showed an improvement in the choriocapillaris flow.

Case 2
A 36-year-old healthy woman presented with an acute painless vision loss OD for 3 days associated with a relative central scotoma. The visual symptoms appeared 3 days after a sore throat associated with a rash on the hands and feet.

At presentation, the BCVA was 20/100 OD and 20/20 OS. The slit-lamp examination was unremarkable, and the intraocular pressure was normal in both eyes. The fundus examination OS found a normal foveal reflex. The examination OD showed a central retinal elevation surrounded by a circular area of discoloration, and small retinal hemorrhages were visible in the perimacular area. SD-OCT (Fig. 3) showed a dome-shaped retinal elevation with an outer retinal cystic space with a bacillary detachment pattern associated with a subretinal detachment. OCTA revealed a reduction in choriocapillaris flow signal. A hypofluorescence was observed in the early phase of FA, and a dye pooling in the central
Evolution: A week later, the BCVA remained unchanged. On funduscopy, the macular lesion was still present but the macular hemorrhages had resolved (Fig. 4). FAF revealed a mix of hypo- and hyper-autofluorescence in the central part of the lesion with a hyper-autofluorescent rim. SD-OCT revealed a resolution of the cystic space and an almost complete resolution of the subretinal fluid with a focal disruption of the external limiting membrane and multiple interruptions of the ellipsoid and interdigitation zones with a thick and irregular RPE. On OCTA, the choriocapillaris flow defect was still present. FA showed a hypofluorescence in the early phase, and a progressive dye leakage in the late phase. On ICGA, a hypofluorescence was observed throughout the entire sequence and extended beyond the fluorescein angiographic borders.

part of the lesion surrounded by a dye leakage corresponding to the subretinal detachment was seen in the late phase.

Evolution: A week later, the BCVA remained unchanged. On funduscopy, the macular lesion was still present but the macular hemorrhages had resolved (Fig. 4). FAF revealed a mix of hypo- and hyper-autofluorescence in the central part of the lesion with a hyper-autofluorescent rim. SD-OCT revealed a resolution of the cystic space and an almost complete resolution of the subretinal fluid with a focal disruption of the external limiting membrane and multiple interruptions of the ellipsoid and interdigitation zones with a thick and irregular RPE. On OCTA, the choriocapillaris flow defect was still present. The choroidal thickness was 368 microns. FA showed a hypofluorescence in the early phase and a progressive leakage. On ICGA, a hypofluorescence was observed throughout the entire sequence and extended beyond the fluorescein angiographic borders.
Case 3

A 40-year-old man without past medical history reported a sudden vision loss with central scotoma and metamorphopsia OD for 1 week. The symptoms appeared after a viral infection characterized by the presence of spots on the hands, feet, and mouth. The initial examination revealed a BCVA at 20/32 OD and 20/20 OS. The slit-lamp examination and intraocular pressure were normal in both eyes. Dilated fundus examination revealed a serous macular detachment OD without associated abnormality.

The patient was referred to our clinic 1 week after the onset of symptoms. On fundus examination, the central retinal elevation was resolved (Fig. 5). A heterogeneous but mostly hypo-autofluorescent circular lesion temporal to the macula was observed on FAF. On SD-OCT, no intraretinal cyst or subretinal fluid were visible. The B-scan encompassing the lesion showed multiple alterations of the ellipsoid zone and an irregular and thick RPE. On follow-up OCTA, the reduced choriocapillaris perfusion was still present at month 3.

Evolution: The symptoms completely resolved after 2 weeks. At the last examination at 5 months, the BCVA was at 20/20.

Case 4

A 24-year-old woman without past medical history reported a visual decrease in OD for less than 2 days. She experienced a maculopapular eruption with sore throat with a positive coxsackie virus serology for 1 week. The initial examination revealed a VA at 10/200 OD and 20/20 OS. The anterior segment and vitreous were unremarkable. Color fundus photography (Fig. 6) revealed a yellowish central macular lesion with an aspect suggesting a subretinal detachment. On OCT, a large intraretinal cyst with a bacillary detachment pattern associated with an adjacent subretinal detachment was observed. On FA, there was a progressive dye leakage in the area of the subretinal fluid with a progressive highly hyperfluorescent pooling in the central part of the lesion, corresponding to the intraretinal cyst. The intraretinal cyst was hypofluorescent on ICGA throughout the anterior sequence, whereas a progressive hyperfluorescence appeared in the subretinal detachment area.
Fig. 6. Multimodal imaging of case 4. Color fundus photography (a) revealed a yellowish central macular lesion with an aspect suggesting a subretinal detachment. On infrared imaging (b), a dome-shaped elevation was observed. On OCT (c), a large intraretinal cyst with a bacillary detachment pattern associated with an adjacent subretinal detachment was observed, and B-scan OCT after resolution (j). On FA (d–f), a progressive dye leakage was observed in the subretinal fluid area with a progressive highly hyperfluorescent pooling in the central part of the lesion, corresponding to the intraretinal cyst. The intraretinal cyst was hypofluorescent on ICGA (g–i) throughout the anterior sequence, whereas a progressive hyperfluorescence appeared in the subretinal detachment. Three days later, the OCT B-scan showed a complete resolution of the subretinal fluid and intraretinal cyst with a residual thickening of the RPE and adjacent outer retina.

Evolution: 3 days later, the subretinal fluid and intraretinal cyst were completely resolved with a residual thickening of the RPE and adjacent outer retina. The VA remained unchanged. At 2 months, the VA was at 20/20, and on SD-OCT, a heterogeneous RPE thickening was observed.

Discussion/Conclusion

In this case series, a complete multimodal retinal evaluation identified the choriocapillaris as the primary tissue involved in UAIM associated with coxsackie virus infection. In 3 out of our 4 cases, a bacillary detachment with a transient evolution was identified.

Various retinopathies associated with HFMD have been reported such as UAIM [2–9], unilateral multifocal retinitis [10], bilateral obstructive retinal vasculitis [11], and unilateral chorioretinitis [12]. UAIM associated with HFMD is most commonly described with more than a dozen cases. The pathophysiological mechanisms remain unknown. Direct viral infection of the outer retina and an autoimmune response are the two main hypotheses. Huemer et al. [13] have reported that coxsackie virus may infect the RPE. At the opposite, based on an OCT and OCTA evaluation, Fernández-Avellaneda et al. [14] have concluded that the inner choroid was the primary site affected in UAIM associated with coxsackie virus infection. In their paper, neither FA
nor ICGA findings were described. In our series, ICGA and FA strongly supported an initial involvement of the inner choroid. Indeed, in this condition, a hypofluorescence could be observed in the early phase of FA (case 1) and throughout the ICGA sequence. These data highlight the role of inner choroid, and subretinal fluid is indeed a confounder when analyzing the choriocapillaris via OCTA. In case 1, no significant alteration of the RPE was observed after the resolution of the bacillary detachment. No atrophy or hyperplasia of the RPE was observed on color fundus photography or on FAF. Furthermore, the irregularities and thickening of the RPE line observed on OCT in cases 2, 3, and 4 were absent in case 1. In this case, OCT showed an interruption of the interdigitation zone with a normal appearance of the RPE after resolution of the bacillary detachment (Fig. 2).

Based on these cases, we assumed that the choriocapillaris could be initially involved, and that the RPE could be secondarily involved. We assumed that the choriocapillaris involvement was less aggressive/intense in case 1 and, therefore, had no impact on the RPE and could spare the RPE cells.

In the acute stage of the disease, a bacillary layer detachment was observed on SD-OCT along with a thickened inner choroid in 3 out of the 4 cases. The remaining patient was referred to our center 1 week after the onset of symptoms, for metamorphopsia associated with an aspect of serous retinal detachment on initial SD-OCT. On OCT performed in our center at day 7, no exudation was present and we assumed that the serous retinal detachment pattern for which the patient was referred was in fact a bacillary layer detachment also in this case. This specific detachment was associated with specific findings on FA, including a highly hyperfluorescent central pooling pattern surrounded by a progressive dye leakage.

The presence of a bacillary detachment could be considered a very common finding associated with this condition. However, this finding may be unnoticed if patients are examined several days after the first symptoms. Indeed, this finding disappeared partially (Fig. 2b) or totally (Fig. 5) as early as at day 5 in our series (cases 1 and 4) and always in less than 10 days.

A bacillary detachment has already been described in UAIM secondary to coxsackie virus infection and can occur in other maculopathies such as Vogt-Koyanagi-Harada syndrome, toxoplasmosis, tuberculosis, acute posterior multifocal placoid pigment epitheliopathy, posterior scleritis, and trauma [14–21]. Although the mechanism for bacillary detachment remains unknown, several hypotheses have been suggested in the literature to explain the location of the split associated with the bacillary detachment. This separation of the photoreceptor layer at the inner segment myoid could be explained by the following hypotheses:

- Kohli et al. [17] have suggested that the underlying choroidal ischemia could participate in the photoreceptor (bacillary layer) stress and splitting. The compromised perfusion could lead to a splitting of the bacillary layer, and the bacillary detachment could resolve once inflammation has resolved and the blood flow has improved [17].

- Other authors have proposed that hydrostatic forces resulting from choroidal inflammation could contribute to the occurrence of a bacillary detachment [15]. In inflammatory diseases, subretinal fibrin increases the adherence between the RPE and the interdigitation zone and creates a separation within the photoreceptors at the most fragile structure, i.e., the inner segment myoid [18].

Finally, one limitation of our case series is the absence of serology or/and anterior chamber or vitreous fluid aspiration to detect the coxsackie virus via PCR or cell cultured in patients. However, in these 4 cases, the diagnosis was established based on the typical clinical symptomatology. In conclusion, in this case series, we described new imaging findings based on FA and ICGA suggesting an initial choriocapillaris involvement in the pathophysiology of UAIM secondary to coxsackie virus infection and we described the very transient aspect of the bacillary layer detachment that could disappear as early as 5 days after the onset of the disease.
Statement of Ethics

Written informed consent was obtained from all the 4 patients for publication of the details of their medical case and any accompanying images. Reporting these cases was accepted by the France Macula Federation Committee, approval number 00008856.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mickaël Anjou collected and interpreted data, drafted the work, and gave final approval and agreement for all aspects of the work. Franck Fajnkuchen and Audrey Giocanti-Aurégan interpreted data, helped to draft the work, corrected the draft, prepared the final version of the work, and gave final approval and agreement for all aspects of the work. Nicolas Nabholz, Sylvia Nghiem-Buffet, and Sarah Mrejen contributed to the design of the work, helped to draft the work, and gave final approval and agreement for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Yannuzzi LA, Jampol LM, Rabb MF, Sorenson JA, Beyrer C, Wilcox LM Jr. Unilateral acute idiopathic maculopathy. Arch Ophthalmol. 1991;109(10):1411–6.
2 Beck AP, Jampol LM, Glasser DA, Glasser DA, Pollack JS. Is Coxsackievirus the cause of unilateral acute idiopathic maculopathy? Arch Ophthalmol. 2004;122(1):121–3.
3 Agrawal R, Bhan K, Balaggan K, Lee RWJ, Pavesio CE, Addison PKF. Unilateral acute maculopathy associated with adult onset hand, foot and mouth disease: case report and review of literature. J Ophthalmic Inflamm Infect. 2015;5:2.
4 Demirel S, Batıoğlu F, Özşert E, Batıoğlu F. Unilateral acute maculopathy related to hand, foot, and mouth disease: OCT and fluorescein angiography findings of a very rare disease. Eur J Ophthalmol. 2014;24(1):131–3.
5 Duman R, Duman N, Kutluksaman B, Çetinkaya E, Inan S, Inan UU. A review of unilateral acute idiopathic maculopathy related to hand-foot-mouth disease with a representative case. Int Ophthalmol. 2016;36(3):445–52.
6 Maxfield SD, Barkmeier AJ. Exudative macular detachment after viral illness with rash. JAMA Ophthalmol. 2016;134(3):335–6.
7 Reich M, Calır B, Cvetkoski S, Lang SJ, Stahl A, Ness T, et al. Acute unilateral maculopathy associated with adult onset of hand, foot and mouth disease: a case report. BMC Ophthalmol. 2019;19(1):104.
8 Vaz-Pereira S, Macedo M, De Salvo G, Pal B. Multimodal imaging of exudative maculopathy associated with hand-foot-mouth disease. Ophthalmic Surg Lasers Imaging Retina. 2014;45 Online:14–7.
9 Jung CS, Payne JF, Bergstrom CS, Cribbs BE, Yan J, Hubbard GB, et al. Multimodality diagnostic imaging in unilateral acute idiopathic maculopathy. Arch Ophthalmol. 2012;130(1):50–6.
10 Balaratnasingam C, Lally DR, Tawse KL, Freund KB, Maisel I, Waheed NK, et al. A unique posterior segment phenotypic manifestation of Coxsackie virus infection. Retin Cases Brief Rep. 2016;10(3):278–82.
11 Mine I, Taguchi M, Sakurai Y, Takeuchi M. Bilateral idiopathic retinal vasculitis following Coxsackievirus A4 infection: a case report. BMC Ophthalmol. 2017;17(1):128.
12 Kadrmas EF, Buzney SM. Coxsackievirus B4 as a cause of adult chorioretinitis. Am J Ophthalmol. 1999;127(3):347–9.
13 Huemer HP, Larcher C, Kirchebner W, Klingenschmid J, Göttiniger W, Irschick EU. Susceptibility of human retinal pigment epithelial cells to different viruses. Graefes Arch Clin Exp Ophthalmol. 1996;234(3):177–85.
14 Fernández-Avellaneda P, Breazzano MP, Fragiotta S, Xu X, Zhang Q, Wang RK, et al. Bacillary layer detachment overlying reduced choriocapillaris flow in acute idiopathic maculopathy. Retin Cases Brief Rep. 2022;16(1):59–66.
15 Agarwal AK, Freund KB, Kumar A, Aggarwal K, Sharma D, Katoch D, et al. Bacillary layer detachment in acute Vogt-Koyanagi-Harada disease: a novel swept-source optical coherence tomography analysis. Retina. 2021;41(4):774–83.
16 Markan A, Aggarwal K, Gupta V, Agarwal A. Bacillary layer detachment in tubercular choroidal granuloma: a new optical coherence tomography finding. Indian J Ophthalmol. 2020;68(9):1944–6.
17 Kohli GM, Bhatia P, Shenoy P, Sen A, Gupta A. Bacillary layer detachment in hyper-acute stage of acute posterior multifocal placoid pigment epitheliopathy: a case series. Ocul Immunol Inflamm. 2020 Sep. Epub ahead of print.
18 Mehta N, Chong J, Tsui E, Duncan JL, Curcio CA, Freund KB, et al. Presumed foveal bacillary layer detachment in a patient with toxoplasmosis chorioretinitis and pachychoroid disease. Retin Cases Brief Rep. 2021;15(4):391–8.
19 Tekin K, Teke MY. Bacillary layer detachment: a novel optical coherence tomography finding as part of blunt eye trauma. Clin Exp Optom. 2019;102(3):343–4.
20 Ramtohul P, Denis D, Gascon P. Bacillary layer detachment in acute posterior multifocal placoid pigment epitheliopathy: a multimodal imaging analysis. Retina. 2021;41(2):e12–14.
21 Cicinelli MV, Giuffré C, Marchese A, Jampol LM, Introini U, Miserocchi E, et al. The bacillary detachment in posterior segment ocular diseases. Ophthalmol Retina. 2020;4(4):454–6.