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Coxsackie Retinopathy

Clinical Case:

A 42 year-old man presented with a peripheral scotoma in the left eye for two weeks. His best corrected visual acuity was 20/15 in the right eye, and 20/20 in the left eye. His pupils, extraocular motility, and intraocular pressures were within normal limits. His external and anterior segment exam were within normal limits. On fundus exam, the right eye was normal, and the left eye revealed a yellowish subretinal lesion approximately one disc diameter in size. There was no associated subretinal fluid or vitritis. He had no past medical history other than a recent fever and sore throat.

Diagnostic imaging with fundus Optos fundus photography (Figure 1A) showed an unremarkable right eye, and a yellow-white subretinal lesion superior to the optic nerve in the left eye. The lesion had blurred margins and was associated with mild retinal thickening but no obvious fluid or vitritis. Fundus autofluorescence (Figure 1B) revealed hyperautofluorescence associated with the lesion. Optical coherence tomography (OCT) through the macula was normal in both eyes, however OCT through the lesion in the left eye revealed mild retinal thickening and notably, outer retinal disruption at the level of the ellipsoid zone and the retinal pigment epithelium (RPE) (Figure 1C). Fluorescein angiography (FA) of the right eye was within normal limits, whereas the left eye showed early staining and late mild leakage associated with the lesion (Figure 1D).

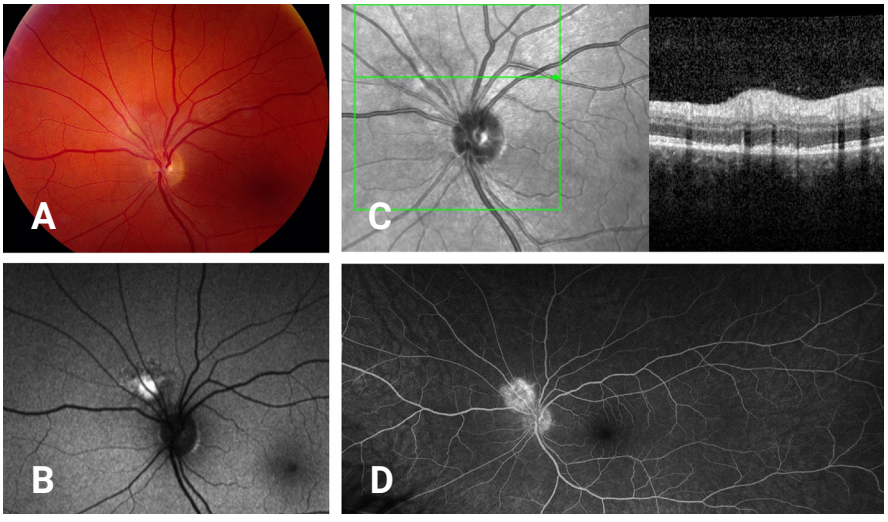

Figure 1: A) Color fundus photo of the left eye demonstrating a yellow-white lesion superonasal to the optic nerve. **B)** Fundus autofluorescence imaging of the left eye demonstrating hyperautofluorescence associated with the lesion. **C)** Optical coherence tomography of the left eye showing mild retinal thickening and loss of ellipsoid zone with retinal pigment epithelium mottling. **D)** Fluorescein angiogram of the left eye showing staining and mild late leakage at 5 minutes at 55 seconds.

Indocyanine green angiography (ICGA) was grossly normal in both eyes. The left eye ICGA had possible mild blocking in the area of the lesion on that left side, but no obvious choroidal neovascularization or other choroidal vascular abnormalities were seen.

Differential diagnosis:

In a 42 year-old man with a subretinal yellow-white lesion associated with a peripheral scotoma, the differential is broad. Inflammatory, infectious, vascular, and neoplastic etiologies should be considered. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) can present like this but typically with more lesions and often bilateral. Sarcoidosis and Vogt–Koyanagi–Harada can also present with focal lesions but typically demonstrate more inflammation as well as more systemic associations of which the patient had none. Infectious causes to be considered are Lyme disease, Syphilis, Tuberculosis, Zika, Bartonella, Chikungunya, and Coxsackie disease, as well as other nonspecific viral illness. Risk factors for these diseases may be elicited through history as well as laboratory work up. Viral retinitis from herpetic viruses should also be on the differential but usually will present with more inflammation and more fulminant involvement, even in an immunosuppressed patient with cytomegalovirus retinitis. Vascular etiologies on the differential include choroidal neovascular membrane, in this case peripapillary, as well as a central serous retinopathy variant, with focal choroidopathy and pigment epitheliopathy. Neoplastic causes should always be considered as well. An atypical choroidal nevus could be considered, whereas focal hamartomas and gliotic lesions are more typically intraretinal or preretinal. As a diagnosis of exclusion, acute idiopathic maculopathy (AIM) can be considered, with or without a viral prodrome.

In this case, the patient's recent viral prodrome was relevant. Upon further questioning, it was revealed that his two children had Coxsackie disease, also known as hand-foot-mouth disease, a common self-limited viral illness. The patient himself had a fever and painful sore throat, without upper or lower extremity rash.

Laboratory workup was negative for Lyme, Bartonella, Zika, Chikungunya, ACE, ANCA, QuantiFERON Gold, RPR, and FTA-Abs. However, his Coxsackie titers were positive, with Coxsackie A4 antibody >1:64, and Coxsackie B4 antibody 1:80. Although reference values are laboratory-specific, in this case, an A4 level ≥ 1:32 indicated recent infection, where as a B4 level ≥ 1:32 indicated past or current infection.

Discussion:

Coxsackie retinopathy is a rare clinical entity seen in the setting of hand, foot and mouth disease. Coxsackie is an enterovirus that is associated with a viral prodrome and a papular-vesicular rash of the palms, soles, lips, and pharynx. Although it commonly affects children, adults without prior exposure can be affected when exposed to children with Coxsackie virus. Adult presentations are often associated with more severe symptoms.

Classically, Coxsackie retinopathy is associated with an exudative macular detachment with outer retinal disruption. It's usually seen unilaterally and centrally. However, there can be bilateral as well as extra macular involvement and lack of subretinal fluid. Rarely, Coxsackie retinopathy presents with papillitis, vitritis and/or vasculitis. It's a self-limited disease and the visual prognosis is usually good with full recovery unless there is macular scarring or secondary choroidal neovascular membrane formation centrally.

Coxsackie retinopathy and acute idiopathic maculopathy (AIM) may be clinically related, although, by definition, it's no longer idiopathic when Coxsackie is identified as a contributing factor. Some authors have proposed that Coxsackie is actually the primary and most common cause of AIM, whereas others suggest that it is one of many possible causes of AIM. In the original descriptions of unilateral AIM by Yannuzzi et al., there were nine patients all of whom had macular subretinal fluid. All had a viral prodrome, but there were no serologies or other diagnostic imaging obtained. Later studies did closely associate acute positive titers of coxsackie antibodies with AIM which is what led to the proposition that

Coxsackie may be the cause of acute idiopathic maculopathy. Recent studies have also demonstrated an expanded clinical spectrum of Coxsackie retinopathy with less common presentations including extrafoveal involvement such as in the case presented here with a peripheral lesion.

As Coxsackie disease and Coxsackie retinopathy is considered to be self-limited, the patient was observed. In his case, 20/20 vision was maintained, and the solitaryperipheral lesion demonstrated spontaneous regression (Figure 2). In summary, Coxsackie retinopathy is associated with acute idiopathic maculopathy. It can present either unilaterally or bilaterally, with macular or extramacular involvement, and with either exudative detachment or focal ellipsoid zone disruption. Most cases have good visual prognosis, depending on extent and location of fluid. It is important to always obtain a full medical history, as Coxsackie retinopathy may be more common than previously realized.

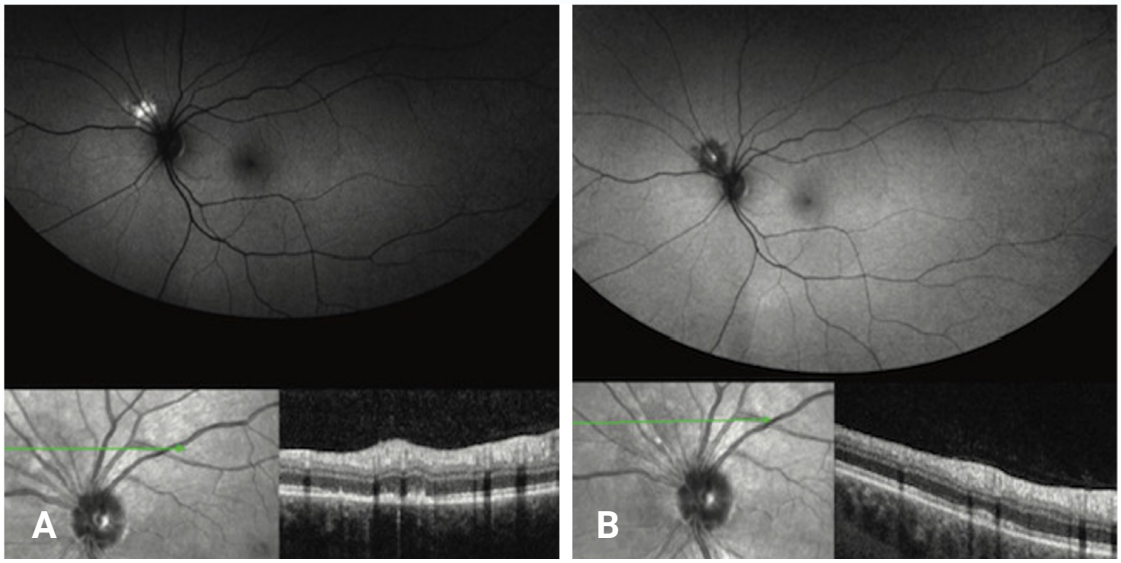

Figure 2: A) Fundus autofluorescence *(top)* and optical coherence tomography *(bottom)* of the left eye at initial presentation. **B)** Fundus autofluorescence *(top)* and optical coherence tomography *(bottom)* of the left eye at 6 months follow up.

References:

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- Freund KB, Yannuzzi LA, Barile GR, Spaide RF, Milewski SA, GuyerDR. The expanding clinical spectrum of unilateral acute idiopathic maculopathy. Arch Ophthalmol. 1996;114(5):555-559.
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NJRetina continuously conducts clinical trials at key locations. Our clinical research coordinators will be happy to discuss the inclusion/ exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

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Enrolling Studies:

Wet AMD
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Opthea Coast: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Aflibercept, Compared with Aflibercept Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

Toms River
Opthea ShORe: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

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Elevatum: A Phase IIIB/IV, Multicenter, Open-Label, Single-Arm Study to investigate Faricimab treatment in response to treatment-naïve, underrepresented patients with Diabetic Macular Edema

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Luna: A Multi-Center, Randomized, Double-Masked Phase 2 Study to Assess Safety and Efficacy of ADVM-022 (AAV.7m8-aflibercept) in Anti-VEGF Treatment Experienced Patients with Neovascular (Wet) Age[1]related Macular Degeneration

Diabetic Retinopathy
Teaneck
Ocuterra: A Phase 2 Randomized, Double-Masked, Vehicle[1] Controlled, Multicenter Study to Evaluate the Safety and Efficacy of OTT166 Ophthalmic Solution in the Treatment of Diabetic Retinopathy (DR)

Toms River
PAVIA: A Phase 2, Multicenter, Prospective, Double-masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), compared to Sham for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy (NPDR)

GA / Dry AMD
Teaneck
Alexion: A Phase 2, Double-Masked, Placebo-Controlled, Dose Range Finding Study of Danicopan (ALXN2040) in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Upcoming Studies:

RVO
Teaneck, Toms River, Edison
Bayer Study: A Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg With Macula Edema due to Retinal Vein Occlusion

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