

nistic infections and potential concerns regarding medication compliance for HIV and mpox infections.

On hematoxylin-eosin staining, the inferior conjunctival sample showed acute conjunctivitis with subconjunctival edema and hemorrhage, mild acute neutrophilic infiltrates throughout the conjunctiva, and mild perivasculär lymphoplasmatic infiltrate. The superior conjunctival sample showed acute ulcerative conjunctivitis with necrosis and exudate, karyorrhectic neutrophilic debris, rare eosinophilic glassy nuclear pseudo-inclusions, and mixed acute and chronic infiltrate and subconjunctival edema (Figure 2). There were no cytoplasmic inclusions visible on hematoxylin-eosin stains. Results of immunohistochemical testing were positive for *Orthopoxvirus* antigen in the cytoplasm of cells in the ulcerated area, and electron microscopy demonstrated viral particles in the cytoplasm with none in the nucleus, typical of orthopox virus species (Figure 2). Differential diagnoses included ulcerating infections in the conjunctiva, including varicella-zoster virus, herpes simplex virus I and II, cytomegalovirus, and *Treponema pallidum*, for which results of all immunohistochemical stains were negative. The eye biopsy showed a necro-inflammatory ulcer with loss of conjunctival epithelium, while the skin biopsy showed acanthotic thickening with central necrosis. These pathologic differences manifested as an injected ulcerating conjunctival lesion and a pearly umbilicated centrally ulcerating skin papule, respectively.

The patient was treated systemically with intravenous tecovirimat, 200 mg, every 12 hours and oral valacyclovir, 1000 mg, every 8 hours. Left ocular treatment consisted of tobramycin-dexamethasone eye drops, a 10-day course of ganciclovir, 0.15%, ophthalmic gel, and 10-day course of ciprofloxacin, 0.3%, ophthalmic ointment. A few months posttreatment, the patient developed stromal scarring in the left eye and was treated with prednisolone acetate, 1%. Final visual acuity was 20/40 OS.

Conjunctivitis may present after treatment of mpox, as seen in this patient. Recurrence was noted by prior skin lesions, a new 2-cm forehead lesion, and left eye inflammation. While only a single case, full-thickness conjunctival biopsy of the eye lesion showed infection with positive results on immunohistochemical staining for orthopox. Though management can be challenging, an acceptable visual outcome can be achieved. Biopsy and laboratory examinations were instrumental in this case to determine *Monkeypox virus* in the conjunctiva and helped guide aggressive treatment to restore the patient's vision.

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Optical Coherence Tomography Feature of Retinoschisis in CRB1-Associated Maculopathy

CRB1-associated macular dystrophy (CAMD) presents initially with macular retinoschisis and in more advanced disease with degeneration of the macular outer retina.¹⁻⁵ CAMD differs clinically and genetically from otherwise retinawide *CRB1*-associated degeneration: it usually develops when 1 allele harbors the in-frame deletion c.498-506del that solely affects the CRB1-A isoform, thereby still allowing for full-length expression of the more abundant CRB1-B isoform.

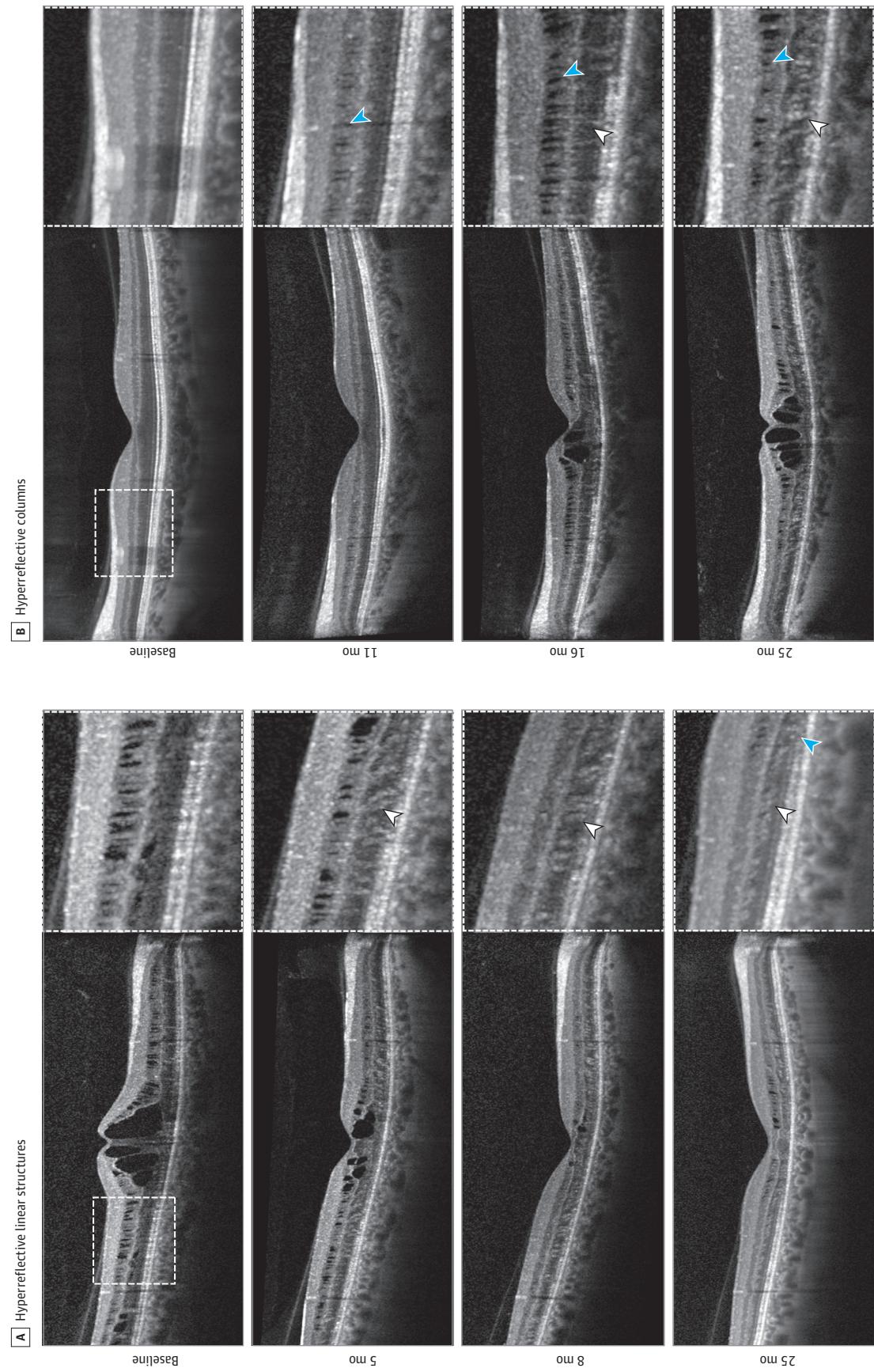
Here, we describe a phenotypic feature on optical coherence tomography (OCT) imaging that appears to be characteristic for CAMD-associated macular retinoschisis: hyperreflective columns in the outer nuclear layer. In 2 patients, OCT imaging showed macular retinoschisis with hyperreflective linear structures crossing the outer nuclear layer. The ellipsoid layer facing 1 end of these hyperreflective columns appeared interrupted.

Figure 1 presents longitudinal observations on OCT scans of a 39-year-old male patient who initially presented with unilateral macular changes, which allowed for monitoring of the evolution of the macular schisis and hyperreflective columns in the subsequently affected fellow eye. Schitic changes started in the paracentral inner nuclear layer and later involved the foveal outer nuclear layer. Visual acuity was 20/36 at baseline and 20/80 at 25 months' follow-up in the right eye and 20/20 at baseline and 20/60 at follow-up in the left eye. Genetic testing revealed the *CRB1* variant c.2490_2491del, p.(Tyr831fs) in trans with the in-frame deletion c.498-506del.

Figure 2 shows OCT scans of a 11-year-old female patient. The hyperreflective columns that were present at baseline examination remained partially visible after spontaneous resolution of the macular retinoschisis 10 months later. Visual acuity was 20/36 at baseline and 20/30 at 10 months' follow-up in the right eye and 20/40 at baseline and 20/25 at follow-up in the left eye. Genetic testing revealed the *CRB1* variant c.2234C>T, p.(Thr745Met), in trans with the in-frame deletion c.498-506del.

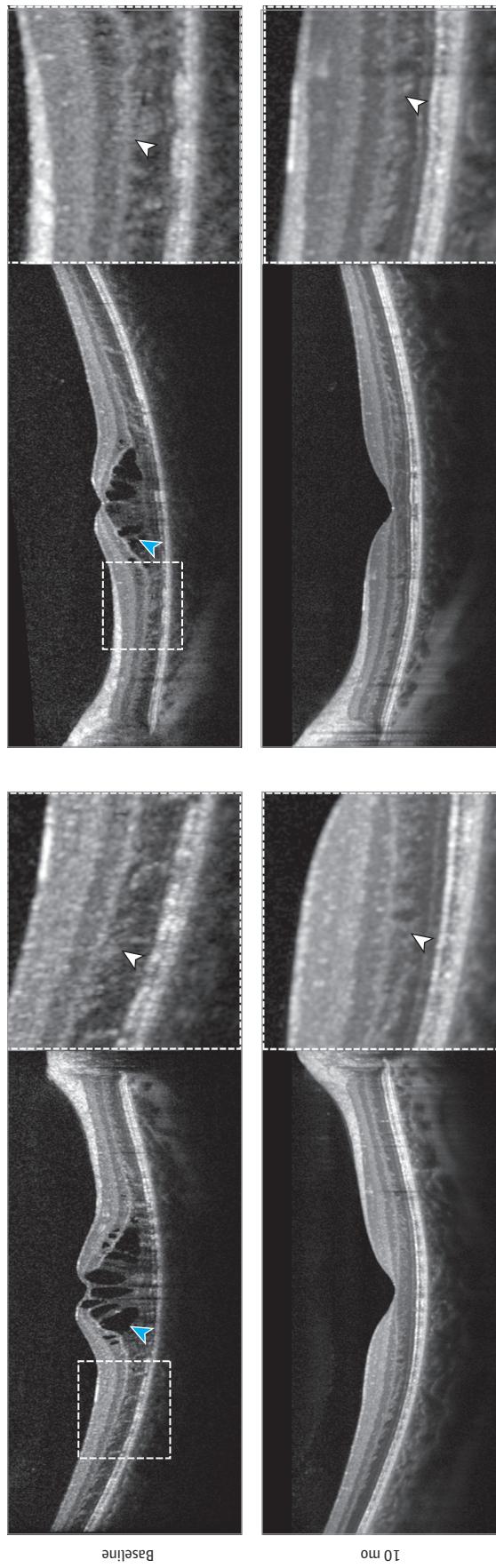
A literature review revealed hyperreflective columns in other early-stage CAMD cases with macular schisis^{2,5} but not in late-stages with macular degeneration.^{1,4} The hyperreflective

Figure 1. Longitudinal Optical Coherence Tomography Images of a 39-Year-Old Patient With Initially Unilateral CRB1-Associated Macular Dystrophy



A, Hyperreflective linear structures (white arrowheads) within the outer nuclear layer evolved over time and remained partially visible when the macular schisis developed degenerative changes of the outer retina (blue arrowheads). B, In the initially unaffected left eye, hyperreflective columns (white arrowheads) evolved after mild cystoid changes were observed in the inner nuclear layer (blue arrowheads).

Figure 2. Optical Coherence Tomography of an 11-Year-Old Patient With CRB1-Associated Macular Dystrophy



Hyperreflective linear structures (white arrowheads) that cross the outer nuclear layer were associated with the bilateral macular retinoschisis (blue arrowheads). Ten months later, these hyperreflective columns remained partially visible even though the macular anatomy had normalized spontaneously.

columns might be caused by a Müller cell pathology due to a selective effect of the in-frame deletion c.498-506del on this cell population. The recently described CRB1-B isoform has been shown to be the predominantly expressed isoform in the human retina, and mouse studies show its primary localization in photoreceptor cells, while the constitutive Crb1-A isoform is predominantly localized in the Müller cells.⁶ While this distribution has yet to be shown in humans, it could be hypothesized that a mutation selectively affecting the Crb1-A isoform, such as the in-frame deletion c.498-506del, could lead to a Müller cell pathology.

Diagnosing CAMD may be challenging due to its rarity, variable age at onset, possible initial unilaterality, or spontaneous fluctuation of scitic changes. Macular retinoschisis in patients with CAMD may differ with regards to disease course, prognosis, and inheritability from other genetic retinal diseases associated with macular retinoschisis. The herein presented OCT-based sign—hyperreflective columns in the outer nuclear layer—seems to be a characteristic phenotypic feature for CAMD-associated retinoschisis and may guide clinicians to consider genetic testing.

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COMMENT & RESPONSE

Silicone Oil From Syringes—A Potentially Overlooked Issue for Intravitreal Injections

To the Editor The study conducted by Bijon et al¹ addresses a potentially important and underestimated issue pertaining to intravitreal injections (IVIs). Given the substantial number of IVI procedures performed globally, even seemingly minor concerns might merit attention. For instance, the 2018 American Society of Retina Specialists Preferences and Trends survey revealed that 60% of US retina specialists had encountered at least 1 patient with silicone oil (SO) droplets following IVI of bevacizumab, 5% had resorted to vitrectomy to manage symptomatic floaters secondary to SO, and 2% had witnessed patients pursuing legal action due to SO-related floaters.² A recent publication has supported a much higher prevalence of SO in the vitreous than previously believed, affecting up to 80% of eyes undergoing routine IVI.³

Bijon et al¹ proposed that the forward and back movement of the plunger during IVI potentially could displace SO from the syringe, particularly when delivered with the final volume of the drug. While this hypothesis seems intuitive and plausible, a study⁴ conducted by our research group was unable to empirically confirm that these movements, referred to as “priming” in the article, could indeed trigger additional SO release. It has been reported that agitation plays a role in SO dispersion, ranging from typical flicking/tapping gestures that have been discouraged by some^{4,5} to more forceful shocks and unintentional falls during product handling, from manufacturing to distribution to the end users, especially when the syringe is pre-filled with the drug.^{5,6}

Another aspect that may warrant attention is the interaction between SO, agitation, protein aggregation, and potential inflammation. This combination may induce protein aggregation and conformational changes or increased formation of antidiug antibodies and cytokine release,⁵ which should be distinguished from the placement of SO, as a tamponade in the vitreous cavity is not known to cause inflammation. While this combination of factors has not yet been studied to our knowledge, in cases of severe vaso-occlusive retinal vasculitis associated with drugs like pegcetacoplan or brolocizumab, it is a consideration. One study⁷ reported that agitation of a siliconized syringe can induce subclinical anterior uveitis with afibercept whereas another suggested an agitated, siliconized syringe was associated with the development of clinically relevant anterior and posterior uveitis in a case-control study with the same drug.⁸ We are not aware of additional studies, especially prospective ones, addressing this issue. Therefore, it still is not possible to confirm a causal relationship between agitation of a siliconized syringe to remove air bubbles and the development of clinically meaningful inflammation, be it uveitis or vaso-occlusive retinal vasculitis, at this time point.