tient-physician interactions and that general clinical questions do not cover the full spectrum of reasons for consulting a physician. For these reasons, authors caution against extrapolating their findings to real-world clinical settings. It appears these safety concerns are also a focus for ChatGPT's developers, with GPT-4 reportedly achieving a 29% improvement in responding to sensitive requests such as medical advice in accordance with policies.[6] The study by Mihalache et al[2] contributes to the ongoing debate surrounding the potential for large language models within medical education and beyond, but it is necessary to remain vigilant to ensure these tools are implemented in a way that is robust, reliable, safe, and fair.

Mark A. Chia, MBBS, MMed
Pearse A. Keane, MD

Author Affiliations: University College London, London, England (Chia, Keane); Moorfields Eye Hospital, London, England (Chia, Keane).

Corresponding Author: Pearse A. Keane, MD, University College London, 11-43 Bath Street, London EC1V 9EL, United Kingdom (p.keane@ucl.ac.uk).

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1. Hu K. ChatGPT sets record for fastest-growing user base-analyst note. Reuters. Published February 2, 2023, Accessed May 26, 2023. https://www.reuters.com/technology/chatgpt-sets-record-fastest-growing-user-base-analyst-note-2023-02-01/

2. Mihalache A, Huang RS, Popovic MM, Muni RH. Performance of an upgraded artificial intelligence chatbot for ophthalmic knowledge assessment. *JAMA Ophthalmol*. Published online July 13, 2023. doi:10.1001/jamaophthalmol.2023.2754

3. Mihalache A, Popovic MM, Muni RH. Performance of an artificial intelligence chatbot in ophthalmic knowledge assessment. *JAMA Ophthalmol*. Published online April 27, 2023. doi:10.1001/jamaophthalmol.2023.1144

4. Singhal K, Azizi S, Tu T, et al. Large language models encode clinical knowledge. Preprint posted December 26, 2022. doi:10.48550/arXiv.2212.13138

5. Kung TH, Cheatham M, Medenilla A, et al. Performance of ChatGPT on USMLE: potential for AI-assisted medical education using large language models. *PLOS Digit Health*. 2023;2(2):e0000198. doi:10.1371/journal.pdig.0000198

6. Open AI. GPT-4 technical report. Preprint revised March 27, 2023. doi:10.48550/arXiv.2303.08774

7. Susnjak T. ChatGPT: the end of online exam integrity? Preprint posted December 19, 2022. doi:10.48550/arXiv.2212.09292

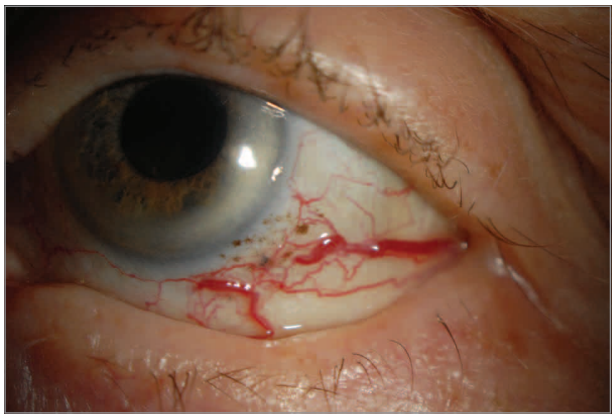
8. Ayers JW, Poliak A, Dredze M, et al. Comparing Physician and Artificial Intelligence Chatbot Responses to Patient Questions Posted to a Public Social Media Forum. *JAMA Intern Med*. Published online April 28, 2023. doi:10.1001/jamainternmed.2023.1838

OBSERVATION

Extrascleral Extension of Uveal Melanoma Along Intravitreal Needle Tracts Associated With Periodic Anti–Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration

This case illustrates an uncommon complication associated with periodic intravitreal injections of anti-vascular endothelial growth factor agents for age-related macular degeneration (AMD) in a patient with uveal melanoma.

Figure 1. Slitlamp Photograph



Multiple foci of stippled, well-defined episcleral pigment are present inferotemporally.

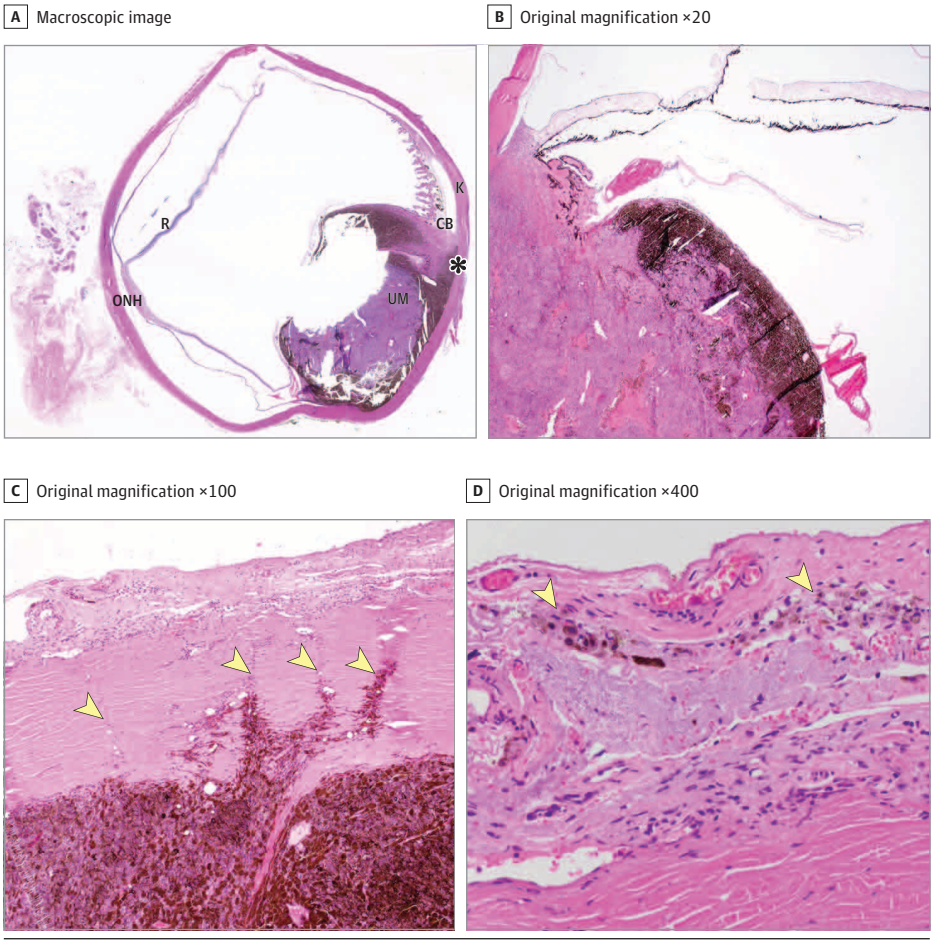
Report of a Case | A 94-year-old man was referred for evaluation of a left choroidal mass. He reported progressively worsening vision and photopsias in the left eye for several months. Outside records reported nonexudative AMD in the right eye and exudative AMD in the left. The left eye had been treated for at least 7 years with multiple intravitreal injections of aflibercept or ranibizumab, administered in the inferotemporal quadrant of the globe, most recently 1.5 years before presentation. A dilated examination 1 month before presentation did not describe a tumor, but the mass was seen on fundus photography and B-scan ultrasonography. It is unknown if prior photography had been ultrawide field. Medical history was notable for cutaneous melanoma behind the left ear 10 years earlier, with no known recurrence or metastases after wide local excision.

On examination, visual acuity was 20/40 in the right eye and counting fingers in the left eye. The inferotemporal quadrant of the left eye had stippled and mildly elevated episcleral pigmentation with associated prominently dilated vessels (**Figure 1**). The posterior segment could not be visualized.

Ultrasound biomicroscopy and B-scan ultrasonography demonstrated a large mushroom-shaped ciliochoroidal mass projecting into the anterior vitreous and filling nearly half of the globe. Liver function test results were normal; computed tomography of the chest and abdomen/pelvis revealed no metastases. Given the size of the mass and poor visual prognosis, enucleation was recommended. Fine-needle aspiration biopsy (FNAB) was performed on the enucleated eye after the surgical procedure; a scleral flap was created over the tumor, and the mass was sampled with a 25-gauge needle.

Histopathologic examination revealed a 1.3 × 1.2 × 1.1-cm uveal melanoma, with mixed epithelioid and spindle cell pattern, centered on the ciliary body with extension into the choroid (**Figure 2**A and B). Tumor cells coated the angle structures and the anterior and posterior surfaces of the iris. Within the inferotemporal sclera overlying the tumor, there were several vertical transscleral scars (Figure 2C). Intrascleral and extrascleral extension of tumor cells was present along these

Figure 2. Histopathologic Examination



A, Macroscopic image of the heavily but variably pigmented mass, predominantly in the anterior globe. The asterisk indicates the location of extrascleral extension (hematoxylin-eosin [H&E]). CB indicates ciliary body; K, peripheral cornea; ONH, peripheral aspect of the optic nerve head; R, retina; and UM, uveal melanoma. B, Low-power photomicroscopy shows a mushroom-shaped, variably pigmented mass centered in and replacing the CB (H&E). C, Four nonphysiologic vertical tracts through the sclera are seen, each containing intrascleral extension of the pigmented tumor cells (arrowheads) (H&E). D, Within the solar elastosis in the conjunctival substantia propria are hyperchromatic, epithelioid, pigmented melanocytes constituting extrascleral extension of tumor (arrowheads) (H&E).

tracts (Figure 2D). The tracts corresponded to sites of previous intravitreal injections, whereas extrascleral tumor cells in the conjunctival substantia propria corresponded to the episcleral stippled pigmentation seen clinically (Figure 1); the tracts were not in the location of the FNAB. Gene expression profiling (Castle Biosciences) revealed a class 2, preferentially expressed antigen in melanoma (PRAME)-positive tumor. With extrascleral extension, adjuvant orbital radiotherapy was considered but deferred given the patient's advanced age and uncertain benefit.

Discussion | Extrascleral extension of tumor cells along needle tracts is rare. Cases in the literature following FNAB usually occur several years after the procedure. Seeding of the needle tract has also been observed in enucleated globes immediately following FNAB.[1-4] Subsequent transscleral intravitreal injections can increase a patient's risk of extrascleral implantation of tumor cells.[5] Although the patient had a history of cutaneous melanoma, clinical and histopathologic features support this being a primary uveal melanoma.[6]

Uveal melanoma can be difficult to visualize when it involves the ciliary body. Detection relies on thorough ophthalmic examination and ancillary imaging. In this case, the patient had undergone frequent dilated examinations while being monitored and treated for AMD. Unfortunately, the anterior location of this tumor, poor baseline visual acuity in the left eye, along with relatively preserved acuity in the right eye may have been associated with delayed onset of symptoms and ultimately a delayed diagnosis of uveal melanoma. This case reinforces the importance of performing periodic ocular examinations, including retinal evaluations, in established patients receiving recurrent intravitreal injections.

Hursuong Vongsachang, MD, MPH
Anna M. Stagner, MD
Mary E. Aronow, MD
Natalie Wolkow, MD, PhD

Author Affiliations: Ophthalmic Plastic Surgery Service, Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston (Vongsachang, Wolkow); David G. Cogan Laboratory of Ophthalmic Pathology, Massachusetts Eye and Ear, Harvard Medical School, Boston (Stagner, Wolkow); Retina Service, Massachusetts Eye and Ear, Harvard Medical School, Boston (Aronow).

Corresponding Author: Natalie Wolkow, MD, PhD, Ophthalmic Plastic Surgery Service, Department of Ophthalmology, Massachusetts Eye and Ear, 243 Charles St, Boston, MA 02114 (natalie_wolkow@meei.harvard.edu).

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1. Karcioglu ZA, Gordon RA, Karcioglu GL. Tumor seeding in ocular fine needle aspiration biopsy. *Ophthalmology*. 1985;92(12):1763-1767. doi:10.1016/S0161-6420(85)34105-2

2. Ndulue JK, Mashayekhi A, Shields CL. Ciliary body seeding after pars plana transvitreal fine-needle aspiration biopsy of choroidal melanoma. *J Ophthalmic Vis Res*. 2020;15(2):252-255. doi:10.18502/jovr.v15i2.6744

3. Caminal JM, Sanz S, Carreras M, Català I, Arruga J, Roca G. Epibulbar seeding at the site of a transvitreal fine-needle aspiration biopsy. *Arch Ophthalmol*. 2006;124(4):587-589. doi:10.1001/archopht.124.4.587

4. Mashayekhi A, Lim RP, Shields CL, Eagle RC Jr, Shields JA. Extraocular extension of ciliochoroidal melanoma after transscleral fine-needle aspiration biopsy. *Retin Cases Brief Rep*. 2016;10(3):289-292. doi:10.1097/ICB.0000000000000253

5. Glasgow BJ, Brown HH, Zargoza AM, Foos RY. Quantitation of tumor seeding from fine needle aspiration of ocular melanomas. *Am J Ophthalmol*. 1988;105(5):538-546. doi:10.1016/0002-9394(88)90248-6

6. Rosenberg C, Finger PT. Cutaneous malignant melanoma metastatic to the eye, lids, and orbit. *Surv Ophthalmol*. 2008;53(3):187-202. doi:10.1016/j.survophthal.2008.02.003

COMMENT & RESPONSE

Photoreceptor Misalignment Contributes to Imaging Features During Acute Macular Neuroretinopathy

To the Editor We read with great interest the report by Kadomoto et al[1] about high-resolution imaging of a case of acute macular neuroretinopathy (AMNR). The images were impressive and in particular showed in great detail the changes in reflectivity of the outer nucleus layer and of the photoreceptor outer segments. The authors noted an attenuation of the interdigitation zone (IZ) (cone outer segment tip [COST]), which was more marked than that of the ellipsoid zone (EZ) (right eye and left eye); partial recovery was observed 2 months later. They speculated that this may be evidence of damage to outer segments by inflammation.

We believe that in their case another phenomenon may have contributed to the hyporeflectivity on infrared reflectance imaging and to the attenuation of the outer segment lines. Directional imaging, which is obtained by shifting the point of entry of light through the pupil, has been shown to be able to highlight additional contrasts of retinal structures on spectral-domain optical coherence tomography (OCT).[2] In the normal retina, directional variations of reflectance can be seen in the Henle fiber layer and the outer segments. In the outer segments, this phenomenon is called the optical Stiles-Crawford effect. Directional imaging typically shows a stronger modulation of the COST (IZ) than of the right eye and left eye (EZ),[3] possibly because there is a contribution of both rods and cones to the right eye and left eye, while the COST (IZ) is restricted to cone, which has a stronger Stiles-Crawford effect. We have previously reported that AMNR directional imaging may modify the reflectance of hyporeflectivefundus areas.[4] Such directional variability of the reflectance of affected areas was observed by scanning laser ophthalmoscopy, OCT, as well as flood-illuminated adaptive optics ophthalmoscopy. On OCT images, the variations of the COST (IZ) reflectance correlate strongly with the directional changes of fundus reflectance. We concluded that, during AMNR, photoreceptor outer segments misalignment may contribute to the hyporeflectivity on infrared reflectance imaging. The fact that the patients in the report of Kadomoto et al[1] showed a stronger attenuation of the COST (IZ) than of the right eye and left eye (EZ) supports the hypothesis of photoreceptor misalignment accounting, at least in part, for changes in reflectivity which were shown.

Michel Paques, MD, PhD
Sarah Mrejen, MD

Author Affiliations: Clinical Investigation Center 1423, Quinze-Vingts Hospital, Paris, France.

Corresponding Author: Michel Paques, MD, PhD, Department of Ophthalmology, Quinze-Vingts Hospital, Clinical Investigation Center 1423, 28 Rue de Charenton, Paris 75012, France (mpaques@15-20.fr).

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1. Kadomoto S, Muraoka Y, Ooto S, Tsujikawa A. Structural changes in acute macular neuroretinopathy revealed with adaptive optics optical coherence tomography. *JAMA Ophthalmol*. 2023;141(4):400-402. doi:10.1001/jamaophthalmol.2022.6394

2. Lujan BJ, Roorda A, Croskrey JA, et al. Directional optical coherence tomography provides accurate outer nuclear layer and henle fiber layer measurements. *Retina*. 2015;35(8):1511-1520. doi:10.1097/IAE.0000000000000527

3. Miloudi C, Rossant F, Bloch I, et al. The negative cone mosaic: a new manifestation of the optical stiles-crawford effect in normal eyes. *Invest Ophthalmol Vis Sci*. 2015;56(12):7043-7050. doi:10.1167/iovs.15-17022

4. Bottin C, Grieve K, Rossant F, Pedinielli A, Mrejen S, Paques M. Directional variability of fundus reflectance in acute macular neuroretinopathy: evidence for a contribution of the Stiles-Crawford effect. *Retin Cases Brief Rep*. 2018;12(suppl 1):S19-S24. doi:10.1097/ICB.0000000000000701

In Reply We thank Paques and Mrejen for their thoughtful letter regarding our findings on high-resolution adaptive optics (AO) imaging of patients with acute macular neuroretinopathy (AMN).[1] They suggested the potential contribution of photoreceptor misalignment seen in patients with AMN, which might correspond to the hyporeflective area on infrared reflectance (IR) images. We have acknowledged that directional imaging and the Stiles-Crawford effect modulate retinal structures on optical coherence tomography (OCT) images.[2,3]

In particular, their previous work on the directional variability of fundus reflectance in AMN is insightful.[4] Remarkably, wedge-shaped dark lesions in AMN on IR and flood-illumination AO images varied from hyporeflective to isoreflective when images were taken at different pupil entry points. Moreover, the directional imaging appears to affect the reflectivity of the interdigitation zone (IZ) band, which might show that different pupil entry points may attenuate the reflectivity even if the studied eyes were healthy.[3] The photoreceptor misalignment can be susceptible to directional imaging because photoreceptors display angular variability of absorbance and reflectance, known as the Stiles-Crawford effect.[5] Therefore, we agree that focal misalignment in photoreceptors can contribute to the hyporeflectivity observed on IR and AO-OCT imaging.

In our study,[1] we speculated that hyporeflectivity on the IR image could represent damage to the cone segment tip