1. If these lesions were at the level of the RPE, one would expect them to be visualized on FAF imaging. However, they were completely silent on FAF imaging, suggesting that they may be located deeper than the RPE, at the level of the choriocapillaris. We distinguished 3 types of lesions based on their multimodal imaging characteristics in APMPPE. Type 1 lesions seem to be located at the level of the choriocapillaris and are transient. Type 2 and 3 lesions are at the level of the RPE and are permanent.

The pigmented lesions were distributed along the choroidal vasculature on AO imaging (Figure 2). They may correspond to pigment-laden macrophages or accumulation of pigment granules and may indicate a secondary reaction at the level of the RPE induced by an inflammatory process at the level of the choroidal vasculature. Their size and shape were not consistent with RPE cells.

Acute posterior multifocal placoid pigment epitheliopathy is characterized by prominent RPE changes, but the permanent RPE damage (type 2 and 3 lesions) may be secondary to an acute transient choroidal inflammatory process (type 1 lesions).

Sarah Mrejen, MD
Roberto Gallego-Pinazo, MD
Kenneth J. Wald, MD
K. Bailey Freund, MD

Author Affiliations: Vitreous Retina Macula Consultants of New York, New York (Mrejen, Gallego-Pinazo, Freund); LuEsther T. Mertz Retinal Research Center, Manhattan Eye and Ear-Throat Hospital, New York, New York (Mrejen, Gallego-Pinazo, Freund); Department of Ophthalmology, New York University School of Medicine, New York (Wald, Freund); Department of Ophthalmology, University of Polytechnic Hospital La Fe, Valencia, Spain (Gallego-Pinazo); Retina Associates of New York, New York (Wald).

Corresponding Author: K. Bailey Freund, MD, Vitreous Retina Macula Consultants of New York, 460 Park Ave, New York, NY 10022 (kbfrey@aol.com).
Author Contributions: Mrejen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mrejen, Gallego-Pinazo, Freund.
Acquisition of data: All authors.
Analysis and interpretation of data: Mrejen, Gallego-Pinazo, Freund.
Drafting of the manuscript: Mrejen, Freund.
Critical revision of the manuscript for important intellectual content: All authors.
Study supervision: Gallego-Pinazo, Wald.
Conflict of Interest Disclosures: None reported.
Funding/Support: This work was supported by The Macula Foundation, Inc.


Vismodegib as Eye-Sparing Adjuvant Treatment for Orbital Basal Cell Carcinoma
Orbital invasion of basal cell carcinoma (BCC) may lead to disfigurement, blindness, or even death.1 Orbital exenteration, although disfiguring and blinding, is often the only option for cure when incompletely excised medial canthal tumors extend into the orbit.2 The US Food and Drug Administration has recently approved a hedgehog pathway inhibitor3 with an adequate safety profile,4 vismodegib (Erivedge), for oral treatment of basal cell nevus syndrome5 and locally advanced or metastatic BCC.6 We describe a patient with BCC invading the
medial orbit who was treated with oral vismodegib, resulting in near-total tumor shrinkage that permitted complete excision with clear surgical margins. Histopathologically, the excised tissue contained scattered residual tumor cells exhibiting squamous differentiation and low proliferative capacity.

**Report of a Case** | A 79-year-old man developed left lower eyelid retraction 10 years after BCC excision. Examination demonstrated normal vision, limited left ductions, increased left tear lake, and left medial canthal fullness but no external skin lesion. Biopsy revealed aggressive-growth-pattern BCC (ie, morpheaform, with irregular strands of deeply invading cells) (Figure 1B and C). Following biopsy, magnetic resonance imaging showed a 2.7 × 1.6 × 1.9-cm medial orbital mass (Figure 1A). To avoid exenteration with loss of the eye, medical treatment with vismodegib, 150 mg/d by mouth, was begun 1 month later. During the next 5 months, the patient reported occasional nausea and diarrhea and progressively worsening muscle spasms—all known adverse effects of vismodegib therapy.4 Magnetic resonance imaging after 4 months of treatment showed reduction in tumor size to 0.7 × 0.7 × 0.5 cm (Figure 1D). Because of painful muscle spasms, the patient opted for surgical excision instead of continued vismodegib therapy. En bloc excision of the residual orbital mass was performed along with medial rectus muscle release using frozen-section control. Postfixation histopathologic evaluation revealed all margins to be clear of tumor. Vismodegib was discontinued at surgery. The patient has done well, with complete resolution of treatment adverse effects, including the muscle spasms, within 2 months of treatment cessation.

The excised tumor was submitted in toto and fully analyzed in sequential sections. The original, highly cellular, aggressive-growth-pattern BCC, with areas of squamous differentiation, stained positive for high-molecular-weight cytokeratin. The excised, treated mass revealed a reduction in tumor load (Figure 1B and C vs Figure 1E and F) with the vast majority of tissue composed of fibrotic and fibrovascular tissue with mild, scattered acute and chronic inflammation (Figure 2A and B). Single or small clusters of cytokeratin-positive cells with squamous differentiation, vesicular or smudged nuclei, and abundant eosinophilic cytoplasm were scattered multifocally in the fibrous matrix (Figure 2D). Foci of degenerating squamous cell clusters infiltrated by histiocytes (Figure 2E) and clusters of tumor ghost cells lacking nuclei (Figure 2C) were also present. Many infiltrating leukocytes were immunoreactive for the macrophage marker CD68 (Figure 2F). Importantly, the residual squamous cells not only exhibited degenerative cytologic features but also failed to exhibit nuclear immunoreactivity for the proliferation marker Ki-67 (Figure 2I), suggesting virtual loss of tumor cell proliferation (mitotic index <1%) following vismodegib treatment, in stark contrast to the original BCC (Figure 2G).

**Discussion** | Oral vismodegib is a novel therapy for the treatment of metastatic or locally advanced and organ-threatening BCC and may be considered for treatment of eligible patients with eye-threatening orbital BCC. Because the drug is newly approved and is associated with a range of adverse effects and health risks,4 additional experience and...
study will be required to better assess the risks of treatment and develop optimal treatment criteria. It is troubling to note that we still do not understand the cause of the debilitating muscle spasms that many patients experience, including our patient. To our knowledge, this is the first histopathologic description of the effects of vismodegib treatment of BCC. Tumor cell degeneration and elimination by leukocytes followed by fibrovascular proliferation and fibrosis appear to underlie tumor shrinkage. Although residual cells may have the capacity to reform the tumor if treatment is halted because of treatment adverse effects or if tumor cells develop resistance to vismodegib, it is likely that many of the residual cells are sufficiently damaged so as to have limited proliferative capacity. Nevertheless, en bloc excision with margin control may be prudent when the adverse effects become intolerable to the patient. While we urge caution, our recent experience suggests that vismodegib may be particularly useful as a neoadjuvant treatment, a possibility that warrants further study.

Alon Kahana, MD, PhD
Francis P. Worden, MD
Victor M. Elner, MD, PhD

Author Affiliations: Eye Plastic and Orbital Surgery Service, Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, Ann Arbor (Kahana, Elner); Hematology and Oncology Section, Department of Internal Medicine, University of Michigan, Ann Arbor (Worden).

Corresponding Author: Alon Kahana, MD, PhD. Department of Ophthalmology and Visual Sciences, 243 Kellogg Eye Center, 1000 Wall St, Ann Arbor, MI 48105 (akahana@med.umich.edu).

Published Online: August 1, 2013. doi:10.1001/jamaophthalmol.2013.4430.

Author Contributions: Study concept and design: All authors. Acquisition of data: Kahana, Elner. Analysis and interpretation of data: Kahana, Elner. Drafting of the manuscript: Kahana.

Critical revision of the manuscript for important intellectual content: All authors.

Obtained funding: Kahana. Administrative, technical, and material support: Kahana, Elner.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by a Career Development Award from Research to Prevent Blindness (Kahana), by grant K08 EY018689 from the National Eye Institute, and in part by the University of Michigan Cancer Center Support Grant P30 CA046592 from the National Institutes of Health, Vision Research Core Grant P30 EY007003 from the National Eye Institute, and an unrestricted departmental grant from Research to Prevent Blindness. Kahana is supported by the Helmut F. Stern Career Development Endowed Professorship in Ophthalmology and Visual Sciences. Elner is supported by the Ranitz Foundation Professorship in Ophthalmology and Visual Sciences.

Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.