ules were present over the entire fovea, as in cases 2 and 3 in our series. In addition, on SD-OCT images from case 1, the lesions highly scatter and block OCT signal from penetrating to deeper retinal layers. In cases 2 and 3, conversely, the lesions are finer, are located along a thin portion of the inner fovea, and span the entire foveola.

In cases 2 and 3, there is some evidence of partial PVD with vitreofoveal attachment on OCT. Although this OCT appearance occurs as a normal stage of PVD progression, it is possible that the white granules may form secondary to mild, persistent vitreofoveal traction. This is speculation, however, and it remains unclear why the granular opacities form.

In summary, we describe SD-OCT findings in 3 patients with white dot fovea. In this condition, hyperreflective granular material is visualized in the inner retinal layers of the fovea both clinically as well as on OCT. Darkly pigmented fundi seem to enhance visualization of the white foveal granules. It is unknown what the granules are composed of or what structure of the retina they represent, and further studies are needed to elucidate the pathogenesis, prevalence, and potential risk associations of white dot fovea.

**Figure 4.** Spectral-domain optical coherence tomography images of the right (OD) (A) and left (OS) (B) macula of case 3 reveal fine, highly reflective granular material within the innermost layer of the fovea. Original magnification ×2 images of the fovea are shown, and an arrow points to the white, hyperreflective material. Again, although the granules seem to be concentrated in the perifoveal region clinically, the hyperreflective material seems to be more uniformly distributed across the entire inner fovea on spectral-domain optical coherence tomography. A partial vitreous detachment with vitreofoveal attachment is evident in both eyes.

**Thrombophilia in Patients With Retinoblastoma Receiving Ophthalmic Artery Chemosurgery**

We have previously reported on our experience of ophthalmic artery chemosurgery (OAC) for the treatment of retinoblastoma, during which heparinization is intended to reduce the risk of thromboemboli forming at the catheter contact site. After femoral artery puncture but prior to catheterization, intravenous heparin is given to reach a target activated coagulation time (ACT) of 200 to 300 seconds (or 2-3 times the baseline), usually achieved with a single bolus of 70 IU/kg. Furthermore, the femoral arterial sheath is slowly flushed with a heparinized saline solution (500 IU of heparin in 500 mL of saline). Since the procedure usually lasts less than 1 hour, no further heparin is given. Herein, we report on 3 patients with heritable thrombophilic conditions: 1 that was known and prophylactically managed prior to catheterization and 2 that were identified following adverse events related to chemosurgery.

**Report of Cases.** Case 1. An 11-month-old girl with unilateral retinoblastoma, Reese-Ellsworth group 5B, International Classification D, received 5 cycles of OAC. Given a history of Factor V Leiden in the maternal grandmother, the patient underwent a coagulation workup and was found to have a heterozygous prothrombin mutation. At the beginning of the procedure, it was discovered the usual dose of heparin was insufficient, and 125 IU/kg of heparin were required to reach the target ACT. Chemosurgery was performed via the orbital branch of the middle meningeal artery in 2 cycles and was balloon assisted for 3 cycles. All OAC sessions showed good ophthalmic artery filling and choroidal blush, and her treatment course was uneventful. Following adjuvant laser, cryotherapy, and plaque brachytherapy, tumor control was achieved.

**Case 2.** As previously reported, a 27-month-old boy with unilateral retinoblastoma, Reese-Ellsworth...
group 5A, International Classification D, received an initial OAC treatment using melphalan and topotecan hydrochloride with good intraoperative choroidal blush. Follow-up at 1 month revealed vitreous hemorrhage and tumor response. During the second OAC treatment, the ophthalmic artery filled, but the choroidal blush had vanished. Follow-up ultrasonography displayed massive choroidal material that was inhomogeneous and of low to medium reflectivity. Because of concerns of choroidal invasion, the eye was enucleated. Histopathological examination indicated subretinal hemorrhage and a completely calcified tumor. Hemoglobin electrophoresis was performed and revealed a diagnosis of sickle cell trait.

Case 3. An 8-month-old girl with bilateral retinoblastoma, Reese-Ellsworth group VB, International Classification C in the right eye and Reese-Ellsworth group VA, International Classification D in the left eye, presented with total retinal detachment in the left eye. Electroretinogram responses were normal in the right eye and extinguished in the left eye. Initial OAC treatment demonstrated good arterial filling and choroidal blush. A second OAC treatment to the right eye was uneventful, but vasospasm of the left ophthalmic artery was initially noted and resolved with time. Recatheterization in the left eye was successful with good arterial filling and choroidal blush before and after catheterization. Following the second OAC treatment, the family noticed decreased vision and the patient was noted to have no light perception or pupillary responses in either eye. Her right fundus revealed a pale, edematous perifoveal and juxtapapillary retina with “boxcarring” and attenuation of the vessels (Figure 1A). Scattered retinal and subconjunctival hemorrhages were evident in the left eye (Figure 1B), along with purpura on both lower extremities (Figure 2). Neurological evaluation, computed tomography, and magnetic resonance imaging findings were all normal. The family reported a viral prodrome prior to the second OAC treatment. The patient was given sildenafil citrate, steroids, and antihypertensive drops, and over the next week, the retinal vascular tree returned to normal in the right eye (Figure 3A) and the hemorrhages resolved in the left eye (Figure 3B). Retinal and choroidal flow were confirmed with fluorescein angiography. Four months later, the child gained fixation and following vision in the left eye, and with resolution of the retinal detach-
ment, the electroretinogram improved to recordable “fair” levels. In the right eye, electroretinogram responses decreased from “very good” to “good.” With local therapy, disease was controlled in both eyes at 6 months’ follow-up. Given concerns for an occlusive event, a coagulation workup was performed and, in addition to elevated acute phase reactants, a plasminogen activator inhibitor-1 4G/5G polymorphism was found with elevated plasminogen activator levels.

Comment. It is estimated that 15% of the population carries a heritable thrombophilic condition or antiphospholipid syndrome (Table). Thrombosis formation is more common in patients with malignancy, and thromboemboli are the second most common cause of death in adult cancer patients. When combined with endovascular intervention consisting of small vessel catheterization, certain chemotherapy, or even heritable thrombophilia, this risk may increase further.

In light of this, we routinely screen for patient or family history of thrombotic disorders and maintain a target ACT with adjusted heparin dosing. With this method, we diagnosed a patient with a heterozygous prothrombin mutation prior to catheterization and successfully prophylactically treated her with a higher heparin dose. However, in 2 other patients, a diagnosis of sickle cell trait and a plasminogen activator inhibitor-1 4G/5G polymorphism were not established until after an adverse event with OAC. It is unclear whether the blood condition was the sole cause or a contributor to the adverse event. These patients gave no pertinent family history and had no prior symptoms. All 3 heritable conditions have been associated with varying degrees of vascular obstruction; they not only share systemic manifestations such as stroke and pulmonary embolism but also ocular pathology including occlusion of the retinal vasculature.

Activated coagulation time is a functional measure of both the intrinsic and final common pathway of the coagulation cascade and is used to guide heparin dosing during endovascular procedures. One study established ACT as an adequate preprocedure screening test for bleeding complications in patients with no known bleeding disorder, but thrombophilia was not addressed. Some groups have debated on the utility of universal screening for heritable thrombophilia, particularly in at-risk populations. However, data are insufficient to determine whether this is justified and many argue for selective screening instead. Knöfler et al7 show that 14% of children with malignancy developed thrombosis after a central venous catheter insertion, and 64% of these had inherited prothrombotic risk factors. We suggest a patient or family history be established and if pertinent, then a selective screening performed before deciding on OAC as a treatment option, for instance, testing for sickle cell trait in African American patients (8%-10% are at risk). In the

<table>
<thead>
<tr>
<th>Condition or Protein</th>
<th>Defect</th>
<th>Prevalence, %</th>
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<tr>
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<tr>
<td>Protein C</td>
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<td>HbAS</td>
<td>1c</td>
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<td>Antiphospholipid syndrome</td>
<td>Lupus anticoagulant, anticoardioplin</td>
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*a Elevated levels of factor VIII, IX, and XI, hyperhomocysteinemia, and elevated levels of lipoprotein (a), plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor confer thrombotic risk with a prevalence varying between 5% and 25% for each, depending on normal laboratory reference values.

*b Data from Unal et al,2 Fegan et al,3 and the Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology.4

*c Eight percent of African American population = 1% of US population.
context of a known heritable condition, the heparin dose can be adjusted, as was done in our patient. In highly suspicious cases (or those with a previous adverse event), treatment modalities other than OAC may need to be considered. As OAC is adopted more widely, it is important for clinicians to be aware of these prothrombotic states, the adverse events associated with them, and how to prophylactically manage them.

Jasmine H. Francis, MD
Y. Pierre Gobin, MD
Aaron Nagiel, MD, PhD
Ira J. Dunkel, MD
Nicole Kucine, MD
Brian P. Marr, MD
Scott E. Brodie, MD, PhD
David H. Abramson, MD

Author Affiliations: Ophthalmic Oncology Service (Drs Francis, Nagiel, Marr, and Abramson) and Department of Pediatrics (Dr Dunkel), Memorial Sloan-Kettering Cancer Center, Service of Interventional Neuroradiology, Departments of Neurosurgery, Neurology, and Radiology (Dr Gobin) and Pediatric Hematology/Oncology (Dr Kucine), Weill Cornell Medical College of New York-Presbyterian Hospital, and Department of Ophthalmology, Mount Sinai School of Medicine (Dr Brodie), New York.

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REFERENCES


Epidermal Growth Factor Receptor Inhibitors for Treatment of Orbital Squamous Cell Carcinoma

Orbital and periorbital squamous cell carcinomas (SCCs) are treated with surgical resection as the primary modality and radiation therapy as adjuvant treatment in patients with perineural invasion or concerns for microscopically positive margins. For advanced cases, extensive surgery such as orbital exenteration may be needed to fully extirpate the tumor. Orbital exenteration leads to loss of the eye and significant facial disfigurement but has the potential to produce long-term cure. The extensive surgical treatments required for advanced cases of orbital and periorbital SCC entail long periods of general anesthesia and inpatient hospitalization; thus, in patients with poor performance status, advanced age, or multiple medical comorbidities, surgery may not be the best option.

Several epidermal growth factor receptor (EGFR) inhibitors have recently been developed and have shown efficacy in treatment of non-small cell lung cancer, pancreatic cancer, colon cancer, and mucosal head and neck squamous cell carcinomas.1-3 We herein report 2 elderly patients with recurrent advanced orbital SCC who were treated with EGFR inhibitors—erlotinib, an oral tyrosine kinase inhibitor, and cetuximab, a monoclonal antibody—and had striking initial responses to this treatment.

Report of Cases. Case 1. A 90-year-old woman with a history of SCC of the left lateral canthus that had been excised at another institution 2 years prior presented with a firm orbital mass causing proptosis, displacement of the globe, and severe orbital congestion and pain (Figure 1A). On examination, she had decreased vision, limited ocular motility, and choroidal striae. There was also a palpable mass in the parotid gland on the left side.

Computed tomography confirmed the presence of a mass with an orbital component measuring 3.2 × 3.1 × 4 cm and a zygomatic component in the masticator space measuring 4.2 × 2.3 × 2.5 cm (Figure 2A). The mass eroded through the orbital floor and inferolateral wall of the orbit and extended into the inferior orbital fissure posteriorly. Also, the patient had a mass in the parotid gland measuring 1.5 × 1.2 cm, consistent with a probable metastasis.

Biopsies of the orbital mass and the parotid mass were consistent with invasive SCC. We discussed with the patient the standard treatment: a wide surgical resection, including an orbital exenteration with removal of the extension of the tumor in the temporalis fossa and masticator space; a parotidectomy; an ipsilateral neck dissection; a free-flap reconstruction of the orbital socket; and postoperative high-dose radiation therapy. The patient declined surgery because of her advanced age and her multiple medical comorbidities.

She was referred to the Department of Medical Oncology for consideration of palliative chemotherapy and biologic therapies. She was prescribed 150 mg of oral erlotinib (Tarceva) daily. The patient reported that within 4 weeks of initiation of therapy, her orbital pain resolved and she experienced marked improvement in orbital congestion and ocular motility. She returned for her first follow-up visit 12 weeks after initiation of erlotinib therapy and was noted to have a remarkable improvement in her clinical findings (Figure 1B) and improved visual acuity from counting fingers before treatment to 20/80. She also had significant reduction in tumor size as measured with repeated computed tomography.