Epithelioid hemangioma (EH), also known as angiolymphoid hyperplasia with eosinophilia, may affect the eyelids and orbit, mimic idiopathic orbital inflammation, and respond poorly to corticosteroids.1,2 We describe a patient with chronic, bilateral orbital EH unresponsive to corticosteroids. Histopathologic analysis showed lobular vascular proliferations containing plump endothelial cells with surrounding mixed leukocytic infiltrates diagnostic of EH.3 Successful treatment consisted of surgical debulking and intraliesional bevacizumab. Periocular EH lesions of 2 additional patients treated by debulking also showed prominent lobular vascular proliferations, highlighting them as the basis of this benign tumor. We conclude that EH is primarily a vascular tumor that can respond to bevacizumab.

Report of Cases. A retrospective review of patients with periocular EH treated at the University of Michigan was performed with institutional review board approval. A PubMed search using the terms angiolymphoid hyperplasia, epithelioid hemangioma, bevacizumab, Avastin, ranibizumab, Lucentis, orbit, and eyelid returned no matches.

Case 1. An otherwise healthy 22-year-old woman was referred for recurrent bilateral upper eyelid swelling since infancy. Although thought to be allergic conjunctivitis and dermatitis, allergy testing results were negative and topical olopatadine hydrochloride was ineffective. Ophthalmic examination showed predominantly preseptal bilateral upper eyelid edema and erythema, worse on the right (Figure 1A). Upper eyelid eversion revealed vascularized episcleral lesions extending into

Figure 1. Case 1 had a thickened, erythematous eyelid (A) that improved after debulking and bevacizumab (B). Upper eyelid eversion revealed episcleral thickening and redness (arrows) (C), magnetic resonance imaging showed an enhancing right orbital lesion (arrow) (D), and histopathologic analysis with hematoxylin-eosin staining showed lobular vascular proliferations and inflammation (original magnification ×40) (E), which have been outlined (original magnification ×40) (F), perivascular fibrosis (original magnification ×200) (G), and plump endothelial cells (arrowheads) and inflammation with eosinophils (arrows) (original magnification ×400) (H).
the orbit (Figure 1C). Magnetic resonance imaging demonstrated bilateral anterosuperior orbital lesions (Figure 1D). Biopsy of a firm, white lesion infiltrating the right periorbital fat revealed diagnostic findings for EH, with prominent lobular vascular proliferations surrounded by dense inflammatory infiltrates containing eosinophils but no lymphoid follicles (Figure 1E-H).

Bilateral surgical debulking and blepharoptosis repair were successful (Figure 1B), but recurrent redness, swelling, and irritation persisted despite topical and oral corticosteroids. Because vascular proliferations were prominent histopathologically, bilateral local bevacizumab injections were administered (3.75 mg; 2.5 mg/mL) followed by 3 additional monthly right orbital injections (7.5 mg each). Prophylactic antibiotics, sterile site preparation, and postinjection therapy were not used. Prior to injections, proparacaine hydrochloride eyedrops were administered and a proparacaine-moistened cotton swab was held over the injection sites for 1 minute. To distribute the drug, 2 or 3 separate injections with some movement within the lesion were performed. The injections were well tolerated, without any significant discomfort or pain. Owing to the small dosage of bevacizumab used, it was deemed unlikely to cause hypertension and blood pressure was not measured. Flare-ups ceased while the lesions’ sizes remained stable. Nineteen months later, a right-sided flare-up was treated by bevacizumab injection (7.5 mg) that was repeated twice at 1-month intervals. Symptoms improved after the first injection and quiescence was obtained after the second injection; the lesion’s size remained stable. The last injection was given prophylactically in the absence of disease activity before the patient’s wedding and she has remained without active disease since.

Case 2. A 19-year-old woman developed left upper eyelid swelling 2 years prior to consultation. Magnetic resonance imaging revealed a left superior orbital mass, and biopsy findings were interpreted as idiopathic orbital inflammation. The mass regressed clinically and radiographically. Right upper eyelid swelling and soreness developed 18 months later (Figure 2A). Magnetic resonance imaging showed left-sided improvement with a new right superior orbital lesion (Figure 2C). Repeated biopsy findings were interpreted as idiopathic orbital inflammation. The patient was referred for consultation after poor responses to courses of oral prednisone. Ophthalmic examination showed mild left upper eyelid retraction and right upper eyelid fullness, without signs of inflammation (Figure 2A and B). Histopathologic review of the biopsies led to a diagnosis of EH (Figure 2D-F). Owing to a lack of clinical activity and modest corticosteroid responses, observation was recommended.

Case 3. A 22-year-old woman had recurrent right upper eyelid swelling, soreness, and purple discoloration for 2 years. Ophthalmic examination revealed diffuse, soft, lobular swelling with nodular purple areas that blanched with pressure, causing secondary ptosis (Figure 3A). Orbital computed tomography demonstrated diffuse, enhancing infiltration of the right anterosuperior orbit (Figure 3C). Histopathologic analysis of the subtotal resection specimen revealed EH (Figure 3D-F). Gradual improvement of eyelid swelling, discomfort, and ptosis occurred within 9 months (Figure 3B).

Histopathologic Findings. All cases demonstrated similar findings diagnostic for EH. In each case, orbital fat was largely effaced by prominent, lobular vascular proliferations, each with a surrounding variably dense, mixed leukocytic infiltrate containing eosinophils (Figure 1E-H, Figure 2D-F, and Figure 3D-F). Many of the vascular lobules, prominent at low and me-
dium magnification (Figure 1E-G, Figure 2D and E, and Figure 3D and E), contained enlarged endothelial cells crowding the lumens, best seen at high magnification (Figure 1H, Figure 2F, and Figure 3F). Eosinophils were prominent in the perivascular inflammatory infiltrates, but lymphoid follicles, granulomatous inflammation, and mitotic figures were absent. Many vascular lobules were surrounded by myxofibrous tissue. Mature areas had reduced vascularity and inflammation with increased perilobular and interlobular fibrosis.

Comment. Periocular EH is a rare, localized entity that has a predilection for young women, is occasionally bilateral, and often involves the superior orbit.1,4 Symptoms include eyelid swelling, proptosis, and pruritus.4

The histopathologic diagnosis of EH depends on recognizing its distinctive architecture. The characteristic lobular vascular proliferations of medium-sized and small vessels of EH (Figure 2), present in all 3 cases, are briefly mentioned in a few reports of angiolymphoid hyperplasia with eosinophilia5 but are underappreciated because they are often camouflaged by a superimposed, intense mixed leukocytic infiltrate. The presence of plump endothelial cells lining many vessels under-

scores the vasoproliferative pathogenesis of EH lesions, while variability of the perilobular leukocytic infiltrates suggests that inflammation is not the primary pathologic finding of EH. The nonophthalmic literature recognizes the primary role of vasoproliferation, leading to renaming angiolymphoid hyperplasia with eosinophilia as EH. The perilobular myxofibrotic changes and interlobular fibrosis in mature areas, seen in all 3 cases, correlate with EH’s mild clinical course and tendency toward involution.3

Currently, EH is recognized as distinct from Kimura disease, which shows prominent lymphoid proliferation with follicles and secondary vascular proliferations with flat or spindle-shaped endothelial cells. However, reports of 2 patients with Kimura disease and EH suggest that the 2 diseases may be related. Histopathologic misdiagnosis of EH as idiopathic orbital inflammation remains common, often leading to clinical confusion in managing patients unresponsive to corticosteroids.

Surgical debulking, performed in all of our cases, may be important in treating periocular EH. In other sites, complete excision of EH results in very low recurrence rates.5 In our 3 cases, infiltrative periocular EH lesions required biopsy for diagnosis and debulking without damaging vital structures, resulting in clinical improvement. Thus, incompletely excised periocular EH lesions may become less symptomatic by accelerating the tendency of EH lesions to fibrose and involute.

Persistent EH may require medical management, but corticosteroid-responsive periocular EH is reported in only 2 patients.2 Our case of persistent, corticosteroid-resistant EH responded dramatically and repeatedly to bevacizumab injections, without complications. Because periocular and intraocular injections are safe off-label uses of bevacizumab, such injections may be useful in recurrent, symptomatic periocular EH. The rapid response and sustained remission induced by bevacizumab support vascular proliferation as the primary process in EH.

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**Ophthalmic Images**

Whipple Disease With Crystalline Keratopathy and Chronic Uveitis

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A 50-year-old man with endocarditis, chronic uveitis, and crystalline keratopathy (A and B). Numerous foamy macrophages were visible on hematoxylin-eosin aortic valve tissue sections (C; original magnification ×20) that stained robustly with periodic acid–Schiff diastase (D; original magnification ×20). The result from polymerase chain reaction was positive for *Tropheryma whipplei*, and the presence of organisms was confirmed by polyclonal anti-*T. whipplei* antibody (red stain, inset; original magnification ×20). Inset reprinted courtesy of the Infectious Disease Pathology Branch at the Centers for Disease Control and Prevention, Atlanta, Georgia (http://www.cdc.gov/ncezid/dhcpp/infectious_disease/index.html).