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. 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. Successful treatment consisted of surgical debulking and intralesional 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 angiolympoid 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 the subconjunctival space, causing widespread chemosis and episcleral thickening (Figure 1C). Magnetic resonance imaging showed an enhancing right orbital lesion (arrow) (Figure 1D), and histopathologic analysis with hematoxylin-eosin staining showed lobular vascular proliferations and inflammation (original magnification ×40) (Figure 1E), which have been outlined (original magnification ×40) (Figure 1F), perivascular fibrosis (original magnification ×200) (Figure 1G), and plump endothelial cells (arrowheads) and inflammation with eosinophils (arrows) (original magnification ×400) (Figure 1H).
the orbit (Figure 1C). Magnetic resonance imaging demonstrated bilateral anterosuperior orbital lesions (Figure 1D). Biopsy of a firm, white lesion infiltrating the right preaponeurotic 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. Magnetic resonance imaging showed a right orbital lesion (Figure 2C), and histopathologic analysis with hematoxylin-eosin staining showed lobular vascular proliferations and inflammation (original magnification $\times 40$) (D), which have been outlined (original magnification $\times 40$) (E), and plump endothelial cells encroaching on the lumens as well as perivascular inflammation with eosinophils (original magnification $\times 400$) (F).

Figure 2. Case 2 had right eyelid fullness without inflammation (A) and left eyelid retraction and contour irregularity 2 years after biopsy and debulking (B). Magnetic resonance imaging showed a right orbital lesion (C), and histopathologic analysis with hematoxylin-eosin staining showed lobular vascular proliferations and inflammation (original magnification $\times 40$) (D), which have been outlined (original magnification $\times 40$) (E), and plump endothelial cells encroaching on the lumens as well as perivascular inflammation with eosinophils (original magnification $\times 400$) (F).

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 peri-vascular inflammatory infiltrates, but lymphoid follicles, granulomatous inflammation, and mitotic figures were absent. Many vascular lob-ules were surrounded by myxofibrous tissue. Mature areas had re-duced vascularity and inflammation with increased perilobular and in-terlobular fibrosis.

Comment. Periocular EH is a rare, localized entity that has a predilec-tion for young women, is occasion-ally bilateral, and often involves the superior orbit.1,4 Symptoms in-clude eyelid swelling, proptosis, and pruri-tus.4

The histopathologic diagnosis of EH depends on recognizing its dis-tinctive architecture. The character-istic 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 hyperpla-sia with eosinophilia5 but are un-derappreciated 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 patho-genesis of EH lesions, while variabil-ity 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 re-naming angiolymphoid hyperplasia with eosinophilia as EH. The peri-lobular myxofibrotic changes and interlobular fibrosis in mature areas, seen in all 3 cases, correlate with EH’s mild clinical course and ten-dency toward involution.3

Currently, EH is recognized as dist-inct 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. Histo-pathologic misdiagnosis of EH as id-iopathic orbital inflammation re-mains common, often leading to clinical confusion in managing pa-tients 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 re-sults in very low recurrence rates.5 In our 3 cases, infiltrative perioc-uclar EH lesions required biopsy for di-aagnosis and debulking without dam-aged vital structures, resulting in clinical improvement. Thus, incompletely excised periocular EH lesions may become less sympto-matic 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 per-sistent, corticosteroid-resistant EH responded dramatically and repeated-ly to bevacizumab injections, without complications. Because per-iorcular and intraocular injections are safe off-label uses of bevacizumab, such injections may be useful in recurrent, symptomatic periocular EH. The rapid response and sus-tained remission induced by beva-cizumab support vascular prolifer-a-tion as the primary process in EH.

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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 whippelii, and the presence of organisms was confirmed by polyclonal anti-T. whippelii 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).