detected in the retinal cells. Results of in situ hybridization for CMV, HSV, and HZV were negative as were tests for bacteria, fungi, and Toxoplasma; meanwhile, in situ hybridization revealed numerous atypical lymphocytes that were positive for EBV.

Chorioretinitis associated with EBV infection is a rare complication that has only recently been described.3,6 The pathogenesis of this complication, however, remains to be resolved. One mechanism that may explain this finding is bystander-killing activity that results from cytotoxic T cells.1,4,5 Fulminant hepatitis and necrotizing skin lesions, for example, occur in patients with XLPD although the parenchymal organs are not directly infected by the virus. Another possible mechanism that can explain the extensive retinal necrosis in the absence of EBV positivity in the retinal cells is lymphocytic vasculitis.7 The lymphocytic infiltrates, presence of thrombosed blood vessels, and extensive hemorrhagic necrosis of the retina seen in the retinal biopsy specimens in the current case suggest the possibility of an occlusive retinal vasculitis secondary to EBV.

Although the EBV DNA detected in the current case resided in B cells and not in retinal cells, we believe that the retinal necrosis was linked to EBV and may be explained by a secondary process such as ischemic injury from the vasculitis or a cytotoxic bystander-killing mechanism.

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Primary Orbital Extraskeletal Ewing Sarcoma

Extraskeletal Ewing sarcoma is a rare soft tissue sarcoma histologically indistinguishable from osseous Ewing sarcoma. Tefft et al1 first described the tumor in children with paravertebral soft tissue masses. Subsequent larger case series have shown that the tumor has a predilection for the paravertebral area and lower extremities.2 The tumor most often occurs in the extremities and paraspinal areas and has been reported to occur in the head and neck region in 5% to 11% of patients.3,5 While osseous Ewing sarcoma, both primary and metastatic, has been reported in the orbit,6 to our knowledge, ours is the first case of extraskeletal Ewing sarcoma to occur in the orbit. Furthermore, extraskeletal Ewing sarcoma manifesting as late as the sixth decade of life has not been reported, to our knowledge. We report a case of primary orbital extraskeletal Ewing sarcoma in a 56-year-old man, which was diagnosed using monoclonal antibody 013 to the p30/32 MIC2 gene product, CD99.

Report of a Case. A previously healthy 56-year-old white man had a 5-month history of progressive right upper eyelid swelling, diplopia, dizziness, and a right-sided headache. His medical history was significant for mild chronic obstructive pulmonary disease treated with albuterol inhalers as needed. On ophthalmic examination, the left eye was normal. His visual acuity was 20/100 OD and 20/30 OS, with a 1+ right afferent pupillary deficit. He had right upper eyelid swelling. Her tel measurements showed 8 mm of right exophthalmos. The right orbit exhibited resistance to retroptosis. Examination of ocular motility revealed limited movement of the right eye in all gaze positions. Funduscopic examination of the right eye revealed choroidal folds and mild optic nerve edema.
Axial and coronal magnetic resonance images of the orbits with and without gadolinium revealed a well-circumscribed enhancing nonhomogeneous intraconal mass in the right orbit, measuring 3.2 x 2.2 x 2.5 cm (Figure 1). No bony invasion was apparent. The nonhomogeneous areas within the tumor were interpreted as vascular flow voids. Based on the appearance of the tumor on magnetic resonance imaging, a diagnosis of cavernous hemangioma was suspected. The patient underwent a lateral orbitotomy via a swinging eyelid approach. The periorbita was found to be intact as it was dissected off the lateral orbital wall. The bone of the lateral orbital wall was removed to improve visualization and was found to be clinically normal.

On opening the periorbita, the large tumor was found to be a solid mass and a biopsy of the mass was performed. A frozen section pathologic examination showed sheets of cells with round to ovoid nuclei and scant cytoplasm (Figure 2). Further histopathologic studies on permanent sections showed no rosette formation.

Reactions were negative on immunohistochemical analyses using pancytokeratin, chromogranin, synaptophysin, CD34, S100 protein, and leukocyte common antigen. The tumor showed positive reaction with monoclonal antibody 013 to CD99 (Figure 3) and to neuron-specific enolase. Our evaluation, based on histopathologic appearance combined with immunohistochemical findings, established the diagnosis of extraskeletal Ewing sarcoma.

The patient underwent systemic evaluation, including a full-body bone scan and computed tomography of the chest. All test results were normal except for mild apical scarring in the lungs, consistent with his history of pulmonary disease. Computed tomography performed after the biopsy demonstrated an intact greater sphenoid wing of the lateral orbital wall, with an anterior surgical defect.

He underwent chemotherapy, consisting of intravenous ifosfamide (1800 mg/m²), intravenous mesna (360 mg/m²), and intravenous etoposide (100 mg/m²) for 5 days, followed 3 weeks later by a combination of vincristine (1.4 mg/m²), doxorubicin (50 mg/m²), and cytoxan (750 mg/m²). After 5 cycles of chemotherapy during 6 months, the results of clinical and radiologic examinations of the right orbit remained unchanged.

Subsequently, he received radiation therapy, with a total of 4500 rad (45 Gy) to the right orbit during 41 days. After radiation treatment, the patient’s right exophthalmos quickly improved. Positron emission tomography after radiation therapy showed at least 80% necrosis of the orbital mass, and magnetic resonance imaging showed a decrease in tumor size (Figure 4).

Thirty-three months after the initial examination, he remains clinically stable without evidence of metastatic disease. His visual acuity has improved to 20/25 OD, and the afferent pupillary defect has resolved. Hertel measurements reveal 1 mm of right exophthalmos. Ocular motility is now normal in both eyes.

Comment. The histologic appearance of extraskeletal Ewing sarcoma consists of uniform round cells with scant cytoplasm, making it indistinguishable from osseous Ewing sarcoma, and difficult to distin-
guish from other small cell tumors, such as neuroblastoma and rhabdomyosarcoma. Recent immunohistochemical studies have been devised to aid in distinguishing small round cell tumors. The crucial marker in distinguishing Ewing sarcoma, both osseous and extraskeletal, is antibody 013 to glycoprotein p30/32, or CD99.7 The tumor in our patient was strongly positive for this epitope. Although CD99 may be positive in other tumor types, such as lymphoblastic lymphoma or rhabdomyosarcoma, other immunohistochemical stains exclude these from the diagnosis.

Most cases of extraskeletal Ewing sarcoma occur during the second or third decade of life. Reports have indicated that the extremities are most often the initial site of involvement. The paravertebral area is also commonly involved. When extraskeletal Ewing sarcoma was first described, the prognosis for the disease was poor. Angervall and Enzinger2 reported a 63% mortality rate in 35 cases, with 12 of 20 deaths within 1 year of diagnosis. The mainstay of treatment in this study was surgical excision alone. Some patients were reported to receive postoperative radiation or chemotherapy, but in no standard doses. In contrast, the Intergroup Rhabdomyosarcoma Study reported a 64% disease-free survival rate, with a median follow-up of 2 years in 26 patients treated with radiation and chemotherapy.4 Subsequently, combined-modality treatment was established by Kinsella et al.,5 who reported 64% disease-free survival in 11 patients after radiation treatments (5000 rads [50 Gy] at 180-200 fractions during 5-6 weeks) and concomitant combination chemotherapy (vincristine, actinomycin, and cyclophosphamide) for 4 cycles.

Ahmad et al.6 studied 24 patients and found that tumor size did not have a significant effect on disease-free survival. Positive prognostic indicators included younger age at diagnosis and surgical resection with wide margins when combined with chemotherapy and irradiation. Chao et al.6 also advocates wide surgical excision, particularly when the spinal cord may be compromised.

In contrast, Kinsella et al’s study did not show radical surgical excision to be crucial in survival. The findings in our patient support those of Kinsella et al. Our patient underwent subtotal tumor excision. Nevertheless, he experienced improvement following chemotherapy and radiation therapy. Multiagent chemotherapy appeared to halt the growth of his tumor, but the tumor did not regress until radiation therapy was administered.

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7. Ambros IM, Ambros PF, Strehl S, Kovar H, Gudner H, Salzer-Kuntschik M. MIC2 is a specific marker of EWS and PNET: evidence for a common histogenesis of EWS and PNET from MIC2 expression and chromosome aberration. Can-
Long-term Administration of Topical Interferon Alfa-2β in the Treatment of Conjunctival Squamous Papilloma

Interferon alfa-2β is a well-known antiviral therapy with potent antiproliferative properties. Presumably, this has been the basis for its intralesional and short-term topical administration for squamous papillomas. Like other modalities used to treat these lesions, recurrence has been common with interferon therapy. However, recent evidence suggests that long-term administration of interferon alfa-2β is capable of inhibiting angiogenesis. Clinically, it has been used in this manner, for an 8-month duration, to successfully treat various vascular tumors such as hemangiomas, Kaposi sarcoma, and hemangiopericytomas as well as ocular surface neoplasia. We report the use of long-term topical therapy (8 months) with interferon alfa-2β in the successful treatment of recurrent squamous papilloma.

Report of a Case. A 27-year-old, healthy, white man complained of an enlarging itchy “lump” in the corner of his right eye. The patient had no significant medical history. His best-corrected visual acuity was 20/15 OU. Surrounding adnexa were unremarkable and there were no signs of adenopathy. A 3.7 × 2.8-mm sessile lesion consistent with a squamous papilloma (Figure) was identified in the medial canthal region. His anterior chamber and dilated fundus examination findings were also within normal limits.

After informed consent was obtained, the patient was treated with a total of 0.3 mL (6 mIU/mL) of interferon alfa-2β (Intron-A; Schering, Kenilworth, NJ) subconjunctivally and intralesionally. He was then placed on a regimen of topical interferon alfa-2β at a concentration of 1 mL/mL administered 4 times a day. Prompt regression of the lesion was noted at the patient’s 2-week follow-up appointment. Topical therapy was stopped. At the 6-week follow-up, a recurrence of the squamous papilloma was observed. Additional subconjunctival and intralesional injections were administered. Topical therapy was reinstalled 4 times a day for a total of 8 months. By the 6-week follow-up the tumor had regressed. At 8 months, treatment with the eyedrops was discontinued and the patient remained tumor free. There remains no sign of recurrence at the 18-month follow-up appointment. Complete examinations were performed at each visit and included visual acuity, slitlamp, intraocular pressure, and dilated fundus evaluations. The patient experienced no apparent local or systemic side effects related to this therapeutic regimen.

Comment. Conjunctival squamous papillomas are composed of a fibrovascular core surrounded by an acanthotic squamous epithelium. There remains a strong association with the human papilloma virus, specifically, types 6, 11, and 16.

Management of these lesions is often difficult and can be frustrating for both patients and physicians. Surgical excision, cryotherapy, CO2 laser ablation, mitomycin C, cisplatin, and acute interferon alfa-2β therapy have all been used. A recent article by Hawkins et al served as our source for the concentrations of the interferon alfa-2β. They describe the acute resolution of the tumor with this modality but the need for mitomycin C for permanent treatment. Unfortunately, despite the initial beneficial effects of most treatments, recurrence after cessation of therapy has been a noted outcome.

Interferon alfa-2β is traditionally known for its antiviral and antiproliferative properties. When given as long-term treatment, it has also been shown to possess antangiogenic effects. Dinney et al studied these effects on transitional cell carcinoma. Inhibition of angiogenesis was found to be highly associated with the decrease in basic fibroblast growth factor and, theoretically, was responsible for the inhibition of tumor growth. A similar process may account for the inhibition of recurrence of the squamous papilloma in our patient.

Topical interferon has been successful in treating conjunctival papillomas in 2 patients. These patients received topical interferon alfa-2β at a dose of 1 mL/mL 4 times a day until there was complete regression. Successful treatment of recurrent lacrimal papilloma with topical and intralesional injection has also been reported. In addition, there are 2 case series that document resolution of conjunctival and corneal intraepithelial neoplasia with