tion of the ophthalmic branch of the trigeminal nerve. The patient subsequently died of a subarachnoid hemorrhage due to an aneurysm caused by Aspergillus infection. Although Aspergillus commonly originates in the lungs, more cases of paranasal sinus aspergillosis are being reported.7,9 It is possible that our patient had a paranasal sinus Aspergillus infection that extended into the orbital apex and carotid artery, although imaging studies did not indicate such an infection. The corticosteroid therapy, despite alleviating the symptoms, may have exacerbated the resulting intracranial hemorrhage. Although some patients survive with aggressive early treatment, approximately 60% of patients with central nervous system aspergillosis are either unsuccessfully treated or die.7,9

Painful ophthalmoplegia with visual loss merits careful evaluation. Although the underlying cause may not be apparent, the diagnosis of THS requires careful monitoring to ensure that other diseases have been excluded. The physician should have a low threshold to seek histopathologic clarification of the diagnosis.

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Orbital Rhabdomyosarcoma in Li-Fraumeni Syndrome

Rhabdomyosarcoma is the most common malignant orbital neoplasm in children. Li-Fraumeni syndrome (LFS) is an autosomal dominant disorder often resulting from germline mutations impairing the antitumor functions of p53.1,2 Li-Fraumeni syndrome is characterized by a marked increase in familial disposition to cancers, including rhabdomyosarcoma. We report, to our knowledge, the first clinicopathologic description of orbital rhabdomyosarcoma in LFS in the ophthalmic literature.

Report of a Case. A 23-month-old boy developed progressive left proptosis over 4 days. His medical history was unremarkable, but his family history was positive for cancer in multiple generations. His mother developed Paget disease of the breast at age 31 years, a maternal uncle died of an unknown cancer at age 12 years, a maternal grandmother had bilateral breast cancer at ages 20 and 31 years, and a maternal great-grandmother also had breast cancer. One of 3 maternal half-siblings developed alveolar rhabdomyosarcoma of the tongue at age 4 years. The 2 others, ages 8 and 10 years, were in good health.

Examination revealed proptosis (Figure 1 A and B), increased resistance to retropulsion, inferolateral dystopia, and limited vertical ductions of the left eye. The remainder of the ophthalmic examination results were unremarkable. Computerized tomography demonstrated a predominantly intracranal, inhomogeneous mass, 2.8 cm in maximum dimension, in the superomedial aspect of the left orbit (Figure 2 A). Magnetic resonance imaging (Figure 2 B) confirmed the computerized tomographic findings, including heterogenous contrast enhancement. A transcaruncular orbital biopsy was performed.

Histopathologic Findings. The biopsy specimen showed a moderately cellular spindle cell neoplasm composed of well-formed interlacing fascicles of tumor cells cut in longitudinal and cross sections (Figure 3 A). The cells contained pale, indistinct cytoplasm and oval or elongated hyperchromatic nuclei with homogenous chromatin and inconspicuous nucleoli. Scattered throughout were spindle, polygonal, or rounded rhabdomyoblasts with distinct, brightly eosinophilic cytoplasm (Figure 3 B). There was moderate nuclear pleomorphism. Mitoses were rare. No necrosis was identified. Distinct immunostaining of the tumor cells, particularly the rhabdomyoblasts, with antibodies against desmin and myogenin was observed (Figure 4 A and B). Muscle-specific actin immunoreactivity was also present (not shown). The proliferation marker MIB-1 was positive in most tumor cells (not shown). Immunoreactivity for the tumor suppressor p53 was highly positive in the majority of tumor cells (Figure 4 C). A diagnosis of embryonal rhabdomyosarcoma with prominent spindle cell differentiation was made.

Clinical Course. Low-risk protocol treatment was begun for stage I, clinical group III embryonal rhabdomyosarcoma limited to the orbit. The patient received several cycles of vincristine sulfate, actinomycin, and cyclophosphamide followed by radiotherapy. After 12 weeks of treatment, however, he showed evidence of regrowth on clinical examination (Figure 1 C) with a more than 20% increase in tumor size based on magnetic resonance imaging (Figure 2 C). Therefore, a relapse protocol with ifosfamide, etoposide phosphate, doxorubicin hydrochloride, and cyclophosphamide was initiated with apparent response.

A diagnosis of LFS was made based on his strong family history of cancer. After informed consent was obtained, a peripheral blood sample...
was sent to University of Minnesota Physicians Outreach Laboratory, and DNA sequencing of selected exons confirmed the diagnosis by detecting a germline mutation 13203 G>A within exon 5 of the p53 gene, which results in change of amino acid 175 from arginine to histidine (R175H).

Comment. Orbital rhabdomyosarcomas are typically sporadic but can occur in the setting of syndromes such as LFS. Li-Fraumeni syndrome is a cancer predisposition syndrome in which soft tissue sarcomas, osteosarcomas, premenopausal breast cancers, adrenocortical carcinomas, brain tumors, and leukemias occur in affected family members. Rhabdomyosarcoma is the most common sarcoma in LFS. Criteria for the diagnosis include a proband with sarcoma occurring before age 45 years, a first-degree relative with any cancer diagnosed before age 45 years, and another first- or second-degree relative with any cancer diagnosed before age 45 years or sarcoma diagnosed at any age. Studies estimate a cancer risk of 42% by age 16 years and 85% by age 85 years in mutation carriers in LFS.

Germline p53 mutations are found in approximately 85% of individuals with family histories meeting criteria for LFS and up to 23% of patients with rhabdomyosarcoma diagnosed at younger than 3 years. A nuclear phosphoprotein, p53 halts progression of the cell cycle in the G1 phase when DNA damage, gamma irradiation, or hypoxia is present; p53 also plays a role in tumor apoptosis. Although mutations have been documented at several loci in the p53 tumor suppressor gene on chromosome 17, codon 175 represents a germline mutational hot spot. The p53 R175H mutant has also been shown to impair cellular apoptosis and promote proliferation in mouse models and tissue culture.

Antibodies that bind the R175H mutant p53 protein restore induction of apoptosis and abrogate mutant p53-mediated cellular proliferation. Inasmuch as the efficacy of chemotherapeutic drugs and radiotherapy relies on their ability to trigger tumor cell apoptosis, mutation-induced loss of p53 function may reduce tumor sensitivity to apoptosis and, thus, the efficacy of anticancer drugs and radiotherapy.

Based on data from the Intergroup Rhabdomyosarcoma Study, patients treated for embryonal tu-

Figure 1. Patient with proptotic left eye. A and B, Initial examination. C, Twelve-week follow-up with worsening proptosis.

Figure 2. Radiographic imaging. A, Computed tomographic scan at initial examination demonstrating predominantly intracanal, inhomogeneous mass in the left orbit. B, T1-weighted magnetic resonance image at initial examination demonstrating mass in superomedial aspect of the left orbit. C, T1-weighted magnetic resonance image at 12-week follow-up showing increased tumor size.
mors have 5-year survival rates of 87%, and those with primary orbital rhabdomyosarcomas approach 100% survival.9 Our patient’s tumor was classified as an embryonal rhabdomyosarcoma with prominent spindle cell differentiation. Among the unusual features of this embryonal tumor, however, were its prominent fascicles imparting a striking resemblance to leiomyosarcoma, reduced cellularity and pleomorphism when compared with typical embryonal rhabdomyosarcomas, and low mitotic rate. These histopathologic characteristics may underlie the poor response to chemotherapy and radiotherapy in this case, similar to the poorer prognosis of adults with a spindle cell subtype.10

Given the high incidence of germline p53 mutations in children with rhabdomyosarcoma who are younger than 3 years,5 it is likely that LFS is present, but not recognized, in some cases of orbital rhabdomyosarcoma. Obtaining a family history of cancer is the best method of detecting LFS, which may then be further supported by genetic analysis of the patient. Immunohistochemical staining is inadequate because mutant p53 may be robustly expressed in orbital rhabdomyosarcomas in LFS but lack tumor suppressor function. The diagnosis of LFS may be

Figure 3. Orbital rhabdomyosarcoma. A, Neoplastic cells with spindled, hyperchromatic nuclei arranged in vaguely delineated bundles. Necrosis is absent (hematoxylin-eosin, original magnification × 200). B, Rhabdomyoblasts containing moderate amounts of eosinophilic cytoplasm (arrows). Mitotic figures and marked nuclear pleomorphism are absent (hematoxylin-eosin, original magnification × 360).

Figure 4. Orbital rhabdomyosarcoma. Rhabdomyosarcoma cells are decorated with antibodies to desmin (A), myogenin (B), and p53 (C) (original magnification × 360).
life saving in affected patients and their families.

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Improvement of Noninfectious Uveitis
With Fumaric Acid Esters: Results of a Pilot Study

Noninfectious endogenous uveitis often improves under corticosteroid therapy, second-line immunosuppressive drugs, or “biologics.” Although they are very helpful, their use might be limited by their adverse effects.

The aim of this pilot study was to investigate the effect of fumaric acid esters (FAEs), which are used for the treatment of psoriasis on endogenous noninfectious intermediate or posterior uveitis. Besides the clinical response, treatment-related modulation of the peripheral blood mononuclear cells was investigated.

Methods. Inclusion criteria were noninfectious endogenous uveitis and vision-threatening complications without inflammatory quiescence under current systemic steroid medication or a maintenance dosage that would otherwise be an indication for a second-line immunosuppressive medication. Visual acuity was above 20/200 in the better eye. The study design complied with the Declaration of Helsinki ethical standards. The local ethics committee approved the study. Informed consent was obtained from the patients. Overall, 4 patients with bilateral uveitis were treated with FAEs and were followed up prospectively (Table 1).

After we established the diagnosis, all patients were first treated with systemic steroids with an initial dosage of approximately 1 mg per kilogram of body weight. After achieving quiescence of inflammation, the steroid dosage was tapered off. When inflammation recurred (a cell increase of ≥2 steps in the aqueous humor or the vitreous) or deterioration of visual acuity (≥2 Snellen lines) or cystoid macular edema occurred, treatment with FAEs was started. The increase of FAE dosage was performed every week in accordance with recommended guidelines.¹

All patients were seen at baseline; after 2, 6, and 12 weeks; and then at 3-month intervals. At each follow-up visit, we performed a routine clinical examination, including optical coherence tomography and fluorescein angiography. Blood tests, including assessments of leukocytes, lymphocytes, and subpopulations, were performed according to generally accepted protocols.

Results. The epidemiological data and the previous and current anti-inflammatory therapy of the patients are summarized in Table 1. In 3 patients, the FAE dose could be increased to the maximal effective dose. One patient developed gastrointestinal adverse effects, so the maintenance dose was reduced. Two patients were able to stop additional steroid medication under a maintenance dose of FAEs. In the patient treated with a lower FAE dose, the systemic steroids could be reduced from 20 mg (0.3 mg/kg) to 5 mg (0.08 mg/kg). In another patient with intermediate uveitis, prednisone was tapered down from 20 mg (0.28 mg/kg) daily to 6 mg (0.09 mg/kg). Tapering off the oral steroids was, in general, possible after the 12-week visit. At this point, a clinical improvement was also evident in all 4 patients.

The clinical course of uveitis noted under treatment is summarized in Table 2. Vision improved over time in all patients who had reduced visual acuity at the baseline visit. Cystoid macular edema was present at the last visit only in 1 eye by angiographic means, but this was not detectable by optical coherence tomography. In the other patients, cystoid macular edema was no longer detected (Figure 1). No significant numbers of anterior chamber cells were seen in any patient during the whole follow-up period. Uveitis did not recur in any of the patients under therapy. Fumaric acid ester therapy was continued in all patients, and no additional complications from uveitis developed during the follow-up period.

Compared with the baseline before FAE institution, average ± SD leukocyte counts dropped from 100% before FAE treatment to 79.9±13.6 (P=.03) and the lymphocyte count to 77.2±25.6 (P=.08) after 3 months of treatment. Figure 2A shows the pattern of peripheral blood leukocytes, lymphocytes, and their subpopulations of all patients. Additionally, Figure 2B describes a shift in T lymphocytes with an increased CD4+/CD8− ratio.

No significant change in the liver enzyme, creatinine, or urea levels occurred during the whole treatment