Aspergillus Infection of the Orbital Apex Masquerading as Tolosa-Hunt Syndrome

Painful ophthalmoplegia can be caused by numerous pathologic conditions such as aneurysm; neoplasms such as chondrosarcoma, lymphoma, and nasopharyngeal carcinoma; diabetes mellitus; infection; and inflammatory disorders such as sarcoidosis and Tolosa-Hunt syndrome (THS). Described by Tolosa in 1954 and Hunt et al in 1961, THS is an idiopathic, self-limited inflammatory disorder characterized by painful ophthalmoplegia that has a rapid response to systemic corticosteroid therapy. We describe a patient who initially appeared to have THS but at autopsy was found to have an Aspergillus infection that involved the carotid artery and caused her death.

Report of a Case. A 70-year-old previously healthy woman with no history of diabetes or immunosuppression developed pain around the right eye and then impaired vision for approximately 2 months. She denied symptoms of diplopia, scalp tenderness, weight loss, or jaw claudication. Two 2-week courses of oral corticosteroid therapy (prednisone, starting at 60 mg/d for 2 days and then tapered during 2 weeks) had produced transient relief of the pain, but the symptoms had recurred when the use of prednisone was discontinued.

Examination on November 14, 2003, showed a visual acuity of 2/200 OD and 20/20 OS. The eyes appeared normal externally (Figure 1), and the exophthalmometry values were 17 mm OD and 15 mm OS. The ocular motility showed mild impairment of abduction in the right eye. The pupils were equal and showed a moderate relative afferent pupillary defect in the right eye. Humphrey visual field (Swedish Interactive Threshold Algorithm [SITA] Standard 24-2) testing showed a central scotoma in the right eye, which extended inferiorly (Figure 2), and a normal visual field in the left eye. The anterior segment, intraocular pressure, and fundi were normal in both eyes.

Laboratory testing revealed a hematocrit value of 40%, a white blood cell count of 5200/µL with a normal differential, and an erythrocyte sedimentation rate of 45 mm/h. Review of a previous magnetic resonance image (MRI) of the brain and orbits performed on October 30, 2003, with gadolinium showed a diffuse, enhancing lesion that involved the right orbital apex and cavernous sinus. The ill-defined process was consistent with inflammation, lymphoma, or metastasis.
The patient was treated with oral prednisone and was much improved 11 days later, when the visual acuity was 20/30 OD. On December 9, 2003, she was continuing to improve, and a subsequent MRI showed no definite radiographic change (Figure 3). The corticosteroids were tapered. On January 20, 2004, while the patient was taking 2.5 mg of prednisone on alternate days, the pain and vision impairment recurred with counting fingers OD. Another course of prednisone was initiated. In the week before her death, the patient was seen at an outside urgent care facility because of malaise, vomiting, and...
diarrhea, which were suggestive of influenza. Although she improved for a couple of days, she went to bed with a headache on the night before she was found dead, on the morning of February 22, 2004.

Autopsy revealed that an acute subarachnoid hemorrhage centered posterior to the right orbit was the cause of death. Histopathologic analysis demonstrated many Aspergillus organisms in the dura mater and leptomeninges that surrounded the internal carotid artery and invaded the wall of the artery (Figure 4).

Serial histologic sections of the patient’s optic chiasm and optic nerves demonstrated inflammation and necrosis with Aspergillus organisms that involved the dura mater and extended into the right optic nerve at the level of the orbital apex (Figure 5 and Figure 6). The lumen of the right ophthalmic artery was markedly narrowed relative to the lumen of the left ophthalmic artery (Figure 7). The right optic nerve exhibited pallor of staining, indicating a reduction in myelinated fibers, inflammation, and gliosis (Figure 8).

**Comment.** The underlying cause of THS is idiopathic granulomatous inflammation in the region of the cavernous sinus and posterior orbit. The condition affects structures traversing the cavernous sinus and may affect the optic nerve.4

Established by Hunt and others in 1961, the diagnostic criteria for THS consist of (1) steady, gnawing pain behind the eye with ophthalmoplegia; (2) involvement of nerves running through the cavernous sinus; (3) duration of symptoms of days to weeks; (4) spontaneous remission with residual deficit; (5) recurrent attacks at intervals of months or years; and (6) exclusion of all other disease processes.3 The MRIs in patients with THS typically show an enhancing, cavernous sinus soft tissue mass that tends to resolve after corticosteroid treatment.5 Although Hunt and colleagues noted responsiveness to corticosteroid treatment as a diagnostic tool, recent reports have cautioned against using this clinical pattern as a diagnostic criterion. Life-threatening diseases, such as lymphoma, aneurysms, and cavernous sinus metastasis, may be missed if corticosteroid responsiveness is considered pathognomonic for this syndrome.5

In our case, arterial aspergillosis masqueraded as a corticosteroid-responsive, idiopathic painful process that affected primarily the orbital apex. With increasing use of chemotherapy, corticosteroids, and antibiotics and an increasing prevalence of diabetes mellitus, more cases of orbital and central nervous system aspergillosis have been reported,7,8 some with intracranial hemorrhage.8,9 Although aspergillosis is commonly suspected in immunocompromised patients, some immunocompetent patients have also been noted to have orbital or central nervous system aspergillosis.7 In a case similar to ours, Suzuki et al9 described a healthy 83-year-old woman who had visual impairment and frontal headache in the distribu-
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.\(^7\)\(^8\) 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 infection and facilitating 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.\(^7\)\(^8\)

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 markedly increased 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 a subarachnoid hemorrhage due to an aneurysm of the middle cerebral artery causing a fatal subarachnoid hemorrhage. The 2 others, ages 8 and 10 years, a maternal grandmother had breast cancer at ages 20 and 31 years, and a maternal great-grandmother also had breast cancer at age 31 years, 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 1A 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 intracanal, inhomogeneous mass, 2.8 cm in maximum dimension, in the superomedial aspect of the left orbit (Figure 2A). Magnetic resonance imaging (Figure 2B) 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 3A). The cells contained pale, indistinct cytoplasm and oval or elongated hyperchromatic nuclei with homogenous chromatin and inconspicuous nucleoli. Scattered throughout were spindled, polygonal, or rounded rhabdomyoblasts with distinct, brightly eosinophilic cytoplasm (Figure 3B). 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 4A 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 4C). 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 1C) with a more than 20% increase in tumor size based on magnetic resonance imaging (Figure 2C). 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