Systemic Anaplastic Large Cell Lymphoma Presenting With Conjunctival Involvement

Ocular and ocular adnexal lymphomas are uncommon and may have protean clinical presentations. They may be either primary neoplasms or secondary manifestations of systemic disease. The recognition of both nodal and extranodal lymphomas and the use of molecular biological techniques to delineate these entities have lead to diagnostically accurate and prognostically significant classification schemas. Anaplastic large cell lymphoma is a distinct entity recognized in the World Health Organization (WHO) classification of lymphomas. It is characterized by large cells with reniform nuclei and constant CD30 antibody expression. It may arise de novo or follow anaplastic transformation of another lymphoma. We report the fifth case of anaplastic large cell lymphoma involving the ocular adnexae.

Report of a Case. Clinical Evaluation. A 16-year-old girl sought treatment at an ophthalmology clinic for a painless growth in the upper eyelid. She had a raised 5 × 6-mm salmon-pink patch involving the conjunctiva of the superior fornix of the right eye. Snellen visual acuity was 20/30 OU. There were no cells in the vitreous, and the anterior chamber was devoid of cells and flares. The patient was systemically unwell and had generalized lymphadenopathy, pallor, and fever. No skin lesions were present. She was admitted to the hospital and transferred to the hematology department following a conjunctival biopsy; the biopsy specimen showed anaplastic large cell lymphoma of the T-cell type. She developed septic shock caused by septicemia and required intensive care unit admission and ventilatory support. The patient had generalized seizures, most likely due to electrolyte disturbance, because a computed tomographic scan showed no cerebral involvement by lymphoma. A chest radiograph showed hilar lymphadenopathy and bronchopneumonic change in the left upper lobe. Bone marrow aspirate was 2% large atypical cells but was not diagnostic of lymphoma. The result of a test for human immunodeficiency virus was negative. Treatment included cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone, and allopurinol. Despite her initial response to therapy, the patient died of respiratory failure.

Microscopic Evaluation. Histological sections of the biopsy specimen showed a diffuse sheetlike infiltrate of malignant cells beneath attenuated conjunctival epithelium. The tumor cells were pleomorphic, with cosinophilic cytoplasm and large vesicular to hyperchromatic lobulated nuclei. There were scattered cells with reniform or “horseshoe” nuclei. Some cells had single, distinct nucleoli. Mitoses were brisk, with atypical forms noted (Figure 1). The differential diagnoses considered included lymphoma, melanoma, and carcinoma. A panel of tests for immunohistochemical markers was performed, including the hematolymphoid marker leukocyte common antigen, the T-cell markers CD3, UCHL-1, and MT-1; the B-cell markers CD20 and CD79a; and anaplastic lymphoma kinase (ALK-1); CD30; the epithelial markers AE1/AE3 and epithelial membrane antigen; the melanoma markers S100 protein and HMB45; the proliferation marker MIB-1; and the tumor suppressor gene p53. Tumor cells were positive for leukocyte common antigen and ALK-1 and showed membrane staining (Figure 2) and paranuclear dotlike accentuation with CD30. In addition, there was diffuse staining with epithelial membrane antigen. Tumor cells were positive for the T-cell marker UCHL-1 (Figure 3), although cells were negative for other T-cell markers. The MIB-1 proliferation index was 70%, and scattered nuclei were positive for p53. Tumor cells were negative for all other markers. A di-

Figure 1. Diffuse infiltrate of large cells with vesicular to hyperchromatic lobulated nuclei. Isolated cells have reniform nuclei.
agnosis of anaplastic large cell lymphoma of the T-cell type was made.

**Comment.** Lymphomas involving the ocular adnexa (conjunctiva, eyelid, lacrimal gland, lacrimal sac, and orbit) may be either primary or secondary manifestations of systemic disease. The primary category represents 8% of extranodal lymphomas. Classification of these neoplasms, which form a spectrum ranging from reactive lymphoid hyperplasia to lymphoma, has proven difficult. Inaccuracy of isolated histological assessment has led to some lesions being classified as having indeterminate significance. Immunohistochemical and molecular techniques have eroded this indeterminate subset and, along with the Revised European and American Lymphoma (REAL) and WHO classifications and their recognition of both nodal and extranodal lymphomas, are proving indispensable adjuncts in the accurate classification and prognostication of these neoplasms.

Analysis of 2 large studies (112 and 53 cases) of lymphoproliferative lesions of the ocular adnexa employing the REAL classification showed extranodal marginal-zone lymphoma to be the most common lymphoma, followed by diffuse large cell lymphoma, follicle center-cell lymphoma, and lymphoplasmacytic lymphoma. Immunohistological analysis and polymerase chain reaction facilitated accurate classification, and only 1 case was relegated to the clinically unhelpful indeterminate subset. In the second study, it was also noted that one third of the extranodal marginal-zone lymphomas had previously been diagnosed as reactive lymphoid hyperplasia. The usual discrepancy observed between the diagnosis of reactive lymphoid hyperplasia and clinical follow-up was not observed in this study, indicating the accuracy of the above-mentioned immunohistochemical and molecular techniques.

Anaplastic large cell lymphoma involving the ocular adnexae, either primary or secondary, is not common; only 4 cases have been reported (Table). Anaplastic large cell lymphoma was recognized in 1985 and has been incorporated into both the REAL and WHO classifications. It is a distinct lymphoma composed of large lymphoid cells with constant CD30 expression.

There is a primary form and a secondary form, in which anaplastic transformation occurs in another lymphoma, usually mycosis fungoides, peripheral T-cell lymphoma, Hodgkin disease, or lymphomatoid papulosis. Systemic and primary cutaneous forms exist.

Three immunophenotypes are discernible on staining for T- and B-cell markers. The T-cell type is the most frequent. Although the null-cell type is the second most common, it seems that most anaplastic large cell lymphomas are T-cell type if sufficient antigens and T-cell receptor genes are investigated. The B-cell type has been included in the Kiel classification as a B large cell anaplastic high-grade Ki-1+ lymphoma. The REAL and WHO classifications regard this as a variant of diffuse large B-cell lymphoma. The molecular pathogenesis of this lymphoma involves a 2:5 chromosomal translocation, juxtaposing the NMP gene and the receptor tyrosine kinase anaplastic lymphoma kinase gene. Anaplastic lymphoma kinase immunostaining is confined to the T-cell subset anaplastic large cell lymphomas and confers a better prognosis.

Of the reported ocular adnexal cases in which CD30 positivity was confirmed, 3 were of the T-cell type. The case reported by Hu et al had a T-cell phenotype. However, no men-
tion is made of CD30 staining. The microscopy illustrated in the text is consistent with anaplastic large cell lymphoma. The case we report is also of the T-cell type. Of the 2 cases reported by Coupland et al, only 1 was ALK positive.

Initial symptoms of conjunctival lymphoma may include a mass, irritation, ptosis, epiphora, blurred vision, proptosis, or diplopia; thus, the diagnosis requires a high index of clinical suspicion. It is important to consider lymphoma in patients with unresponsive chronic conjunctivitis. Of the ocular adnexal lymphomas, conjunctival involvement is purported to have the best prognosis, with stage and category being determinants of outcome. In the series of 117 cases reported by Shields et al, the midbulbar and fornix conjunctiva were noted to be the most common sites. Factors predictive of the presence or development of systemic lymphoma are location of the tumor at an extralimbal site (fornix midbulbar conjunctiva) and multiplicity of tumors. Immunohistochemical detection of p53 and high Ki-67 (MIB1) expression also correlate with disease stage at the initial visit and aggressive disease course and mortality. In our case, the MIB1 proliferation index was high, 70%, and scattered nuclei were positive for p53.

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Optic Neuropathy and Macular Chorioretinal Folds Caused by Orbital Cherubism

Cherubism is a rare fibro-osseous disease of the maxilla and mandible usually seen in childhood. Orbital manifestations are proptosis, lower eyelid retraction, and upward displacement of the globes. Previous cases of orbital cherubism with unspecified visual change have been documented. We present a case of orbital cherubism with visual loss directly attributable to optic neuropathy and macular striae scarring that resulted from the effect of the mass or tumor pushing on the eye of the orbital lesion.

Clinicopathologic Report. A 31-year-old Hispanic woman with a known history of cherubism was referred by...