Ki-1–Positive Anaplastic Large-Cell Lymphoma of the Eyelid

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Ki-1–positive anaplastic large-cell lymphoma is an uncommon form of non-Hodgkin lymphoma. It lies within a spectrum of recently identified lymphoproliferative disorders. The entities within this spectrum share similar clinical and histopathologic characteristics that can make the diagnosis challenging. We report a case of Ki-1–positive anaplastic large-cell lymphoma involving the right upper eyelid of a 45-year-old woman and describe the light microscopic, immunohistochemical, and ultrastructural features. A pertinent review of the English-language literature is presented.

REPORT OF A CASE

A 45-year-old woman came to us with a 4-week history of a rapidly enlarging tender mass involving the right upper eyelid. She described antecedent local trauma during which she was gored in that region by the horns of a goat. She denied having a recent illness or weight loss. Medical history included non–insulin-dependent diabetes mellitus, controlled with an oral hypoglycemic agent, and mild asthma. Family and social histories were unremarkable. Ophthalmologic examination revealed a large (17 × 14 × 12-mm), friable, pedunculated lesion with focal areas of crusting and hemorrhage located on the right upper eyelid nasally (Figure 1). There was surrounding edema and erythema as well as edema tracking to the left upper eyelid. No proptosis was present and extraocular movements were full. The ocular examination was otherwise unremarkable. Systemic evaluation disclosed tender preauricular and submandibular adenopathologic findings on the right side. No hepatosplenomegaly was noted. Chest x-ray films and laboratory profile on admission were normal.

A shave biopsy of the right upper eyelid lesion was performed. Histopathologic examination of the skin revealed pseudoepitheliomatous hyperplasia of the epidermis that was focally covered by a parakeratotic and necrotic crust (Figure 2). The dermis was diffusely infiltrated by numerous atypical cells with large, pleomorphic, vesicular nuclei and prominent nucleoli admixed with small, well-differentiated lymphocytes. There was no evidence of epidermotropism of the atypical cells. Mitotic figures were numerous (Figure 3). The results of immunohistochemical testing disclosed diffuse immunopositivity for T cells.
Figure 1. Clinical appearance of the large right upper lid mass. Note the surface crusting and ulceration and the surrounding eyelid erythema and edema. Milder edema of the left upper eyelid is also present.

Figure 2. Light microscopy of the mass revealing pseudoepitheliomatous hyperplasia of the epidermis that is covered by a parakeratotic and necrotic crust (asterisk). An area of surface ulceration is seen (arrow) (hematoxylin-eosin, original magnification x 10).

Figure 3. The neoplastic lymphocytes disclose large, vesicular nuclei and prominent nucleoli. Many of these cells demonstrate nuclear membrane indentation. Five mitotic figures are present in this field (arrowheads) (hematoxylin-eosin, original magnification x 160).

(CD3) (Figure 4, left), and trace immunostaining for B cells (L26) (Figure 4, right). The large atypical cells were strongly immunopositive for BerH2/Ki-1 (Figure 5) and were immunonegative for cytokeratin (AE1,3) and epithelial membrane antigen. The smaller, well-differentiated lymphocytes were BerH2 immunonegative. These features supported a diagnosis of a Ki-1–positive ALCL, T-cell phenotype.

Transmission electron microscopy was performed on thin sections of deparaffinized tissue stained with uranyl acetate–lead citrate. The neoplastic lymphocytes disclosed large, pleomorphic nuclei containing condensed chromatin and prominent nucleoli. The nuclear membranes were irregular and often convoluted. Short segments of rough endoplasmic reticulum were present within the cytoplasm. Scattered neighboring inflammatory cells were observed (Figure 6).

The patient was seen only once after the shave biopsy (1 day postoperatively), at which time there was total resolution of the eyelid edema and no evidence of residual tumor. The nature of her lymphadenopathy remains unclear, as she was subsequently lost to follow-up.

**COMMENT**

Ki-1–positive ALCL is a recently recognized entity. First described in 1982, the Ki-1 antibody was believed to be specific for Reed-Sternberg cells of Hodgkin lymphoma; however, it has subsequently been shown to identify a variety of benign and malignant conditions including LyP and Ki-1–positive ALCL. Ki-1–positive ALCL is considered to be high grade in the updated Kiel classification for lymphoma. It can be of B-, T-, or null-cell lineage, with the T-cell phenotype being the most common.

Disease is usually localized to lymph nodes; sites of extranodal disease include the skin, lung, gastrointestinal tract, soft tissue, cerebrospinal fluid, and bone. In the skin, the disease may arise either de novo (primary cutaneous Ki-1–positive ALCL) or from a preexisting lymphoma or benign condition of the skin, such as dermatitis (secondary cutaneous Ki-1–positive ALCL). The Ki-1–positive neoplastic cells are pleomorphic, contain abundant cytoplasm, and show large, indented nuclei with prominent nucleoli. Mitotic figures can be numerous.

Within the spectrum of Ki-1–positive cutaneous lymphoproliferative disorders, it is often difficult to differentiate the more benign process of LyP from ALCL because they share many of the clinical, morphologic, and immunohistochemical features. Differences do exist; however, they may be subtle. The extent and size of the lesions may vary.
Lymphomatoid papulosis typically presents as a generalized or regional papulonodular eruption that spontaneously heals in 4 to 6 weeks, leaving a dermal scar or area of altered pigmentation. Cutaneous Ki-1–positive ALCL is more likely to present as an aggressive solitary skin nodule or tumor, which regresses only occasionally. Histopathologic features suggestive of lymphoma include a high ratio of atypical cells to inflammatory cells, large cohesive sheets of Ki-1–positive cells, and a high percentage of Ki-1 positivity (>75%) among the atypical cells. Infiltration of the subcutis by neoplastic lymphocytes remains a highly reliable criterion for Ki-1–positive ALCL because this has not been documented to occur with LyP. Cutaneous Ki-1–positive ALCL is readily differentiated from other cutaneous T-cell lymphomas histologically because mycosis fungoides and Sézary syndrome are characterized by an epidermotropic infiltrate, whereas Ki-1–positive ALCL rarely demonstrates epidermotropism. Recent studies have delineated major differences in the clinical behavior of primary cutaneous and noncutaneous (nodal) Ki-1–positive ALCL. Nodal ALCL has a much less favorable prognosis than does cutaneous ALCL. Nodal ALCL demonstrates a bimodal age distribution, with 1 peak occurring between ages 10 and 30 years and another beyond age 60 years. Cutaneous ALCL occurs in all age groups but preponderantly after the third decade of life without a bimodal distribution. Whereas there are occasional case reports of spontaneous regression of cutaneous Ki-1–positive ALCL, spontaneous regression has not been described in nodal ALCL. Although cutaneous and nodal ALCL have identical histopathologic features, immunohistochemical differences in cell surface marker expression have been described. Expression of epithelial membrane antigen stains greater than 80% of nodal Ki-1–positive ALCL tumor cells, whereas none of the cutaneous Ki-1–positive ALCL tumor cells show immunopositivity for epithelial membrane antigen. Loss of T-cell antigens, in particular CD2 and CD3, is more pronounced in nodal ALCL. These major differences in clinical behavior and immunohistocharacteristics of nodal and cutaneous Ki-1–positive ALCL suggest a fundamental difference in the biological makeup of these neoplasms.

Treatment of the Ki-1–positive lymphoproliferative disorders has not been standardized owing to the limited clinical experience with this entity. Within the range of Ki-1–positive lymphoproliferative disorders, the term "Ki-1–positive" may be applied to a variety of malignant lymphomas. ALCL is a lymphoma that shows an aggressive clinical course, with a high frequency of extracutaneous dissemination and a poor overall survival even in the absence of extracutaneous disease. The use of multiagent chemotherapy has improved the survival of patients with nodal ALCL, but the outcomes of patients with cutaneous ALCL remain poor. In addition, the role of radiation therapy in the treatment of ALCL remains controversial.

**Figure 4.** Immunohistochemistry. Left, The dermal infiltrate is strongly immunopositive for T-cell markers (CD3). Right, Few scattered cells are immunopositive for B-cell markers (L26) (avidin-biotin complex method with hematoxylin counterstain, original magnification ×32).

**Figure 5.** The atypical cells show strong cytoplasmic immunoreactivity for BerH2/Ki-1 (avidin-biotin complex method with hematoxylin counterstain, original magnification ×100).

**Figure 6.** Transmission electron micrograph of the neoplastic lymphocytes demonstrates large, pleomorphic nuclei that contain multiple large nucleoli. Nuclear membrane convolutions (asterisk) and short segments of rough endoplasmic reticulum within the cytoplasm are noted. A neighboring inflammatory cell is seen (arrow).
disorders, it is important to recognize the entities characterized by a benign clinical course to avoid unnecessary therapy. However, close observation of LyP is warranted as these patients are at an increased risk of developing either a cutaneous or a systemic malignant lymphoma. While the treatment of primary cutaneous Ki-1–positive ALCL has ranged from simple excision to systemic chemotherapy, local radiotherapy or complete excision is preferred for patients with solitary lesions. All patients with cutaneous Ki-1–positive ALCL require continued clinical follow-up for local recurrence or development of systemic lymphoma.

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