Ki-1 Large Cell Lymphoma with Regressing Lesions in a Child

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Abstract: An 8-year-old boy was seen with a cutaneous Ki-1 anaplastic, large cell lymphoma with multiple lesions. Some of the lesions showed spontaneous regression. During more than seven years of disease no systemic involvement was observed, but recurrent, self-healing lesions did appear. Histopathologic examination of five lesions revealed a variety of findings, from an inflammatory infiltrate to a highly anaplastic pattern. The neoplastic cells expressed Ki-1 and leukocyte common antigens. Ultrastructurally, those cells showed ruffled indentations. The differential diagnosis includes microvillous malignant lymphoma. The patient has had a four-year follow-up without relapses.

In 1985 Stein et al (1) described an anaplastic large cell lymphoma (ALCL) that expressed a Hodgkin disease-associated antigen, Ki-1, an entity previously misdiagnosed as malignant histiocytosis or anaplastic carcinoma. The Ki-1 ALCL expresses T cell or, less frequently, B cell antigens, although occasionally neither antigen is expressed. Since that first description, approximately 170 cases have been published (2–21), half of which occurred in children (2,4,5,7,9,11,13,15,16,20).

Peripheral lymph nodes constitute the most frequent primary site of the tumor, but the skin, mediastinal lymph nodes, and stomach may also be involved in initial disease. The prognosis is more favorable when the skin is the primary site (3,11–14,18). The cutaneous lesions are represented by solitary or multiple nodules and, less frequently, infiltrated plaques or tumors. In 1986 Kadin et al (11)

described six children with Ki-1 ALCL with peripheral lymphadenopathy, three of whom had regressing skin nodules. Follow-up was limited, however, and biopsies were performed in just one lesion from each patient.

We cared for a child with cutaneous Ki-1 ALCL with regressing skin lesions for seven years. Histopathologic examination was performed on five lesions representing different stages of development.

CASE REPORT

A 6-year-old boy was admitted in July 1987 with a four-year history of spontaneously regressing cutaneous nodules on the abdomen. Two months before admission three new lesions had appeared in the same area, two of which had gradually increased in size and shown no evidence of involution. The child had no other complaints. The only remarkable

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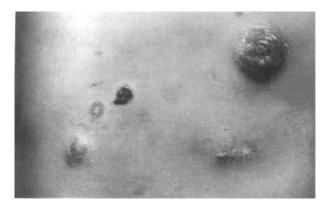


Figure 1. Two lesions, one surgical scar, and many small hyperchromic scars corresponding to involuted lesions.

physical findings were three abdominal nodules with a scaly, erythematous surface, measuring 3.3 \times 3.3 cm, 2.0 \times 2.0 cm, and 0.7 \times 0.7 cm, respectively (Fig. 1). Slightly depressed scars were seen on the surrounding skin. Physical examination revealed no other abnormalities.

The larger lesion was excised and a diagnosis of malignant fibrous histiocytoma was made. After this diagnosis the other two lesions were completely excised. Laboratory findings, bone marrow morphology, and a chest roentgenogram were unremarkable. No therapy was undertaken.

Ten months later the patient had a relapse on the surgical scar of the larger nodule that did not regress. At this time clinical and laboratory evaluation showed no other abnormalities. The lesion was excised and submitted for histopathologic study. Due to the diagnosis of Ki-1 ALCL, the patient underwent chemotherapy according to the LSA2-L2 protocol (22) as follows: induction phase—intravenous cyclophosphamide with radiation therapy, prednisone plus vincristine, intrathecal methotrexate, and intravenous daunomycin; consolidation phase—intravenous cytosine arabinoside and oral thioguanine, intravenous L-asparaginase, intrathecal methotrexate, and intravenous BCNU [1,3bis(2-chloroethyl)-1-nitrosourea]; and maintenance phase-five-day cycles of thioguanine, cyclophosphamide, hydroxyurea, daunomycin, methotrexate, BCNU, arabinosylcytosine, and vincristine followed by intrathecal methotrexate. This regimen continued for one year. Two weeks prior to conclusion of treatment the child developed five erythematous, papulonodular lesions on the chest, measuring from 1.0 to 0.2 cm, that disappeared completely in a few weeks. One of those lesions was excised and submitted for histopathologic examination. No other lesions developed. At the last evaluation in September 1991, no other abnormalities were observed.

LABORATORY STUDIES

Formalin-fixed tissue was processed routinely, embedded in paraffin, and stained with hematoxylin and eosin.

Histopathologic Studies

The histologic appearance of the three initial lesions was not uniform. The largest lesion exhibited an extensive pleomorphic infiltrate entirely replacing the dermis and subcutis. The infiltrate was predominantly composed of large, highly atypical, mononuclear and polynuclear cells with marked nuclear atypia and an abundant amphophilic cytoplasm (Fig. 2). Frequently the nuclei were indented and eccentrically placed in the cytoplasm, which had a prominent paranuclear halo. Multinucleated cells were present, some of which exhibited horseshoe and wreathlike disposition of nuclei. Chromatin tended to be granular and evenly distributed. A prominent nucleolus was generally observed. Mitotic figures, including atypical figures, were very common.

The medium-size lesion showed a diffuse infiltration replacing the dermis and part of the subcutis. The infiltrate was composed of small lymphocytes, histiocytes, polymorphonuclear leukocytes, and many mononuclear and polynuclear atypical cells with frequent mitosis. Cellular pleomorphism was less marked.

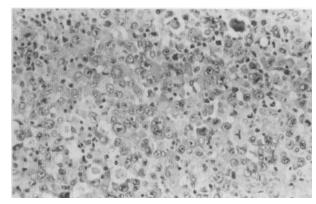


Figure 2. Large mononuclear cells with oval or reniform nuclei with prominent nucleoli and abundant cytoplasm. (Hematoxylin & eosin; magnification 400×.)

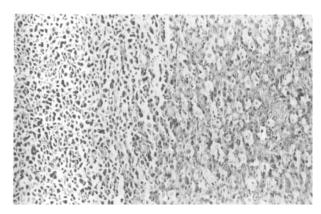


Figure 3. Section from the recurrent lesion. At left is a highly anaplastic infiltration with giant cells; at right are cohesive neoplastic cells with pale-staining macrophages among them. (Hematoxylin & eosin; magni-

The smaller lesion had a benign appearance, consisting of a diffuse infiltrate, with small lymphocytes and histiocytes replacing the dermis and the superficial part of the subcutis. Granulation-like tissue was observed on the superficial part of the lesion. Areas of hemorrhage and fibrosis were also seen.

The recurrent lesion was the most pleomorphic. It was almost entirely composed of pleomorphic cells with abundant eosinophilic cytoplasm. The neoplastic cells at the edge of the lesion in the subcutis appeared cohesive and had pale-staining macrophages among them, imparting a "starry-sky" pattern (Fig. 3). Giant tumor cells and mitosis were frequently seen. Infiltration by polymorphonuclear leukocytes was present only in small foci. Sparse binucleated cells resembling Reed-Sternberg cells were also observed. In all lesions the epidermis showed mild to moderate acanthosis, but no epidermotropism of neoplastic cells was observed. The last biopsied lesion showed an inflammatory infiltrate only.

Immunohistochemical Studies

Formalin-fixed and paraffin-embedded sections of the first large nodule were immunostained using commercially available antibodies (Table 1) and the avidin-biotin immunoperoxidase method (20). Biotinolated horse antimouse antibody and avidinbiotin peroxidase complex reagents were obtained from Vector Laboratories (Burlington, CA). Sections of the recurrent lesion were also tested with leukocyte common antigen (LCA) and HAM-56. Ber-H2 (CD30) and LCA (CD45) antibodies stained

TABLE 1. Panel of Antibodies

Antibodies	Source	Major Specificity
Leukocyte common antigen	D	Leukocytes
Ber-H2 (CD 30)	D	Ki-1 antigens, found on Reed-Sternberg cells, some large-cell lymphomas, activated lymphoid cells
Epithelial membrane antigen	D	Epithelial cells, plasma cells, some lymphomas
UCHL1 (CD45RO)	D	T cells
L-26	D	B cells
Leu-M1 (CD15)	BD	Myeloid, monocytic, Reed-Sternberg cells
HAM-56 (MA-935)	E	Monocytes, macrophages

D = Dako Corporation; BD = Beckton Dickson; E = Enzodiagnostiks.

all the neoplastic cells (Fig. 4). The other antibodies were negative.

Ultrastructural Studies

Small skin samples were immediately immersed in 2% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.3, at 4°C for one hour. Postfixation was in 1% osmium tetroxide in 0.15 M sodium cacodylate buffer, pH 7.3, at 4°C for one hour. Dehydration was performed in graded acetone. Tissue fragments were included in Epon 812 resin. Blocks were trimmed and semithin sections were stained with azur II-toluidine blue. Ultrathin sections were contrasted with uranyl acetate and lead citrate. Sections were evaluated using a transmission electron microscope (Zeiss model EM-109) at 50 kV.

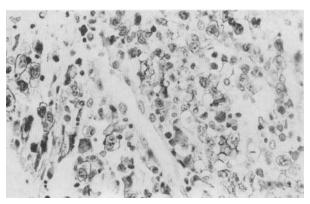


Figure 4. Ki-1-positive anaplastic cells (anti-Ki-1 paraffin section, immunoperoxidase procedure). (Magnification 400×.)

The neoplastic cells had abundant cytoplasm with many polyribosomes, few profiles of rough endoplasmic reticulum, variable numbers of mitochondria, and a small Golgi apparatus. Few neoplastic cells showed lysosomes. The cells frequently exhibited short cytoplasmic processes (Fig. 5) that occasionally interdigitated with other similar cells. The nuclei showed great variation in size and shape; sometimes nuclear indentations were present. The heterochromatin was usually present as a narrow rim adjacent to the inner nuclear membrane. One or two prominent nucleoli were present in the neoplastic cells. Frequently, atypical mitotic figures were seen. Phagocytosis of dead cells by macrophage-like cells was observed.

DISCUSSION

This patient had a primary cutaneous Ki-1 ALCL with an indolent clinical course characterized by regression of the lesions and a seven-year evolution without involvement of other organs.

A similar clinicopathologic picture was described in 1982 as regressing atypical histiocytosis (23). Up to now 11 cases of this entity have been described in the literature (24,25). Immunologic phenotyping and rearrangement of T cell receptor and chain genes suggested that regressing atypical histiocytosis represents an ALCL (26). In our patient the positivity of this tumor for LCA and Ki-1 antigens, and the lack of immunoreactivity for HAM-56, a histiocytic marker, permitted the differential diagnosis of regressing atypical histiocytosis and malignant histiocytosis.

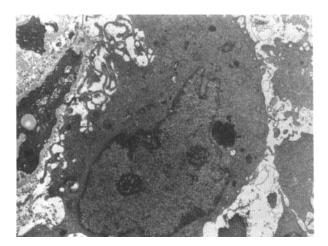


Figure 5. Electron microscopy demonstrates a cell with ruffled cytoplasmic membrane and indented nucleus. (Magnification 12,000×.)

Because of the presence of Reed-Sternberg-like cells in Ki-1 ALCL, the differential diagnosis with Hodgkin disease with skin involvement must be made with caution. Hodgkin disease limited only to the skin has been very rarely reported (27,28), however, and some authors doubt its existence (29,30). In debated cases, no immunohistochemical studies were performed, and probably they represented lymphomatoid papulosis (LP) or even ALCL (28– 30). In addition, the marked pleomorphism, the high mitotic rate, and the cohesive pattern of the neoplastic cells observed in our patient are not generally observed in Hodgkin disease (19), allowing a diagnosis of Ki-1 ALCL.

Lymphomatoid papulosis is also characterized by self-healing skin lesions, and consists of a mixed infiltration of inflammatory and anaplastic Ki-1positive cells similar to those of ALCL (31-33). However, in LP the lesions are smaller and more widespread, and show epidermotropism of the anaplastic cells. Those features have not been described in cutaneous Ki-1 ALCL. Considering the similarities between the disorders, and the fact that an association of inflammatory and neoplastic lesions (as described in LP) was also observed in our patient, we may speculate that regressing Ki-1. ALCL represents an intermediate entity between LP and cutaneous Ki-1 ALCL. Unfortunately, in the other four published cases of cutaneous regressing Ki-1 ALCL (11,26) the association of inflammatory and neoplastic features was not referred to, possibly because only one lesion of each patient was examined.

The diagnosis of this type of highly anaplastic cutaneous lymphoma must be made on the basis of Ki-1 reactivity to distinguish it from other highly malignant tumors, some of them metastatic to the skin. Negativity to epithelial and histiocytic markers and positivity for LCA and Ki-1 antigens make the diagnosis possible. One epithelial membrane antigen that is sometimes expressed by Ki-1 ALCL cells is EMA (10,20), but EMA was not observed in this patient. Also, no reactivity was observed with T and B cell markers. We cannot exclude the possibility that failure to demonstrate these antigens was the result of antigen loss due to tissue fixation and paraffin embedding.

The neoplastic cells observed in our patient had ultrastructurally ruffled cytoplasmic membranes and reniform nuclear indentations, aspects that suggest histiocytic differentiation, according to Burns et al (6). However, the organelles were not prominent, lysosomes were scarce, and phagocytosis by

tumor cells was not observed. Furthermore, immunolabeling with HAM-56, a monoclonal antibody considered to recognize histiocytes, was negative. Cytoplasmic projections have been observed in around 20% of cases of Ki-1 ALCL (34). Microvillous lymphomas have a similar ultrastructural appearance, but these tumors are Ki-1 negative (34).

Undoubtedly, cutaneous Ki-1 ALCL has a better prognosis than Ki-1 ALCL of extracutaneous localization and other large cell lymphomas. The experience with Ki-1 ALCL with self-healing tendency was limited to four cases, three of them associated with nodal involvement (11,24). All were treated with radiotherapy and/or chemotherapy. Those with nodal lesions had relapses but were alive 4 to 30 months after diagnosis. The patient without nodal involvement received radiotherapy only and was well two years after diagnosis, with no relapse (24). Our patient has had no relapse four years after treatment, indicating a good response to chemotherapy. However, as experience with cutaneous Ki-1 ALCL with regressing lesions is limited, it is difficult to delineate the best therapeutic approach.

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