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Primary and Secondary Cutaneous Ki-1$^+$ (CD30$^+$) Anaplastic Large Cell Lymphomas

Morphologic, Immunohistologic, and Clinical Characteristics

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Skin biopsies were collected from 15 patients with cutaneous tumors morphologically similar to Ki-1$^+$ anaplastic large cell (ALC) lymphoma of the lymph nodes, including Ki-1$^+$ ALC lymphoma of childhood. The histology and immunophenotype of these cutaneous tumors are reported and follow-up data on the patients are given. The tumorous infiltrates were composed of large, sometimes very bizarre cells with one nucleolus or multiple nucleoli. All tumor cells expressed the lymphoid cell activation antigen Ki-1 (CD30) in conjunction with CD25 and the β-chain of the T cell receptor. In 11 patients, Ki-1$^+$ cutaneous tumors developed primarily in the skin. In nine patients, these were restricted to the skin in follow-up periods ranging from 3 months to 6 years. Two patients developed lymph node involvement after 2 months and 2 years, indicating the spreading potential of these cutaneous tumors. Morphologic and immunophenotypical identity of the atypical cells found in primary cutaneous ALC lymphoma, in regressing atypical histiocytosis (RAH), and in lymphomatoid papulosis (LyP) of type A, together with the protracted clinical course in all three conditions, suggests that primary cutaneous ALC lymphoma, RAH, and LyP of type A represent clinical variants of the same lymphoma entity. Secondary development of Ki-1$^+$ ALC skin tumors was observed in two patients with cutaneous T cell lymphomas of mycosis fungoides type. These secondary Ki-1$^+$ ALC lymphomas of the skin showed rapid systemic progression similar to the primary lymphonodal Ki-1$^+$ ALC lymphomas. Concomitant or subsequent occurrence of Ki-1$^+$ ALC tumors in cutaneous T cell lymphomas thus may be a bad prognostic sign. (Am J Pathol 1989, 135:359–367)

Skin is a preferential external site for the manifestation of peripheral T cell lymphomas. In most cases, these cutaneous T cell lymphomas are composed of small lymphoid cells and are of low grade malignancy. The classical representatives are mycosis fungoides (MF) and Sezary's syndrome (SS). Pleomorphic and immunoblastic T cell lymphoma is composed of larger sized cells and usually exhibit a more rapid clinical course. In these cases, however, infiltration of the skin rarely precedes the involvement of the lymph nodes.[1,2]

Recently, anaplastic large cell (ALC) lymphomas arising primarily in lymph nodes were identified in a series of patients.[3] Based on morphology, most of these cases were erroneously identified as true histiocytic lymphomas or as anaplastic carcinomas. The detection of T or B cell antigens in conjunction with the lymphoid cell activation antigen Ki-1,[3–5] however, clearly established the lymphoid nature of the tumor cells. Lymphomas with the same morphology, designated Ki-1 lymphomas, were reported to occur in children as well.[6,7] These tumors, now being morphologically and immunophenotypically precisely defined, represent a distinct morphologic entity[8,9] and were thus incorporated into the updated Kiel Classification.[10]

In the present article, we describe cutaneous ALC lymphomas without detectable lymph node involvement at diagnosis (Figure 1), but with morphologic and immunophenotypic features identical to the Ki-1$^+$ ALC lymphomas arising primarily in lymph nodes. In the past, these primary large cell skin lymphomas were described as re-

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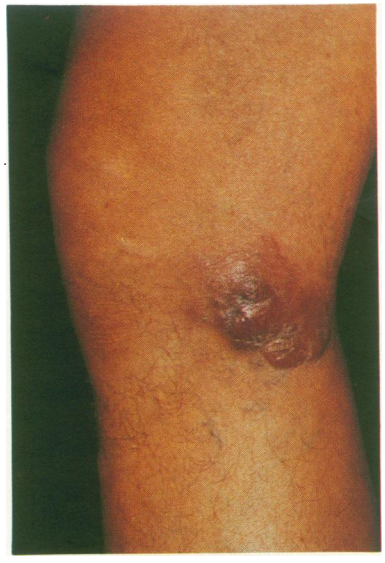

Figure 1. *Clinical presentation of Ki-1$^+$ primary ALC lymphoma (patient 4).*

gressing atypical histiocytosis[11] or malignant histiocytosis,[12] and, in some instances, as lymphomatoid papulosis (LyP) of type A.[13]

Patients and Methods

Relevant clinical data of patients included in the present study are given in Table 1. In patients 1 through 11, cutaneous infiltrates of large atypical cells developed in previously normal skin. Skin tumors of identical cellular composition occurred concomitantly with LyP in patients 12 and 13, and MF in patients 14 and 15. Surgically removed biopsies of the skin tumor were cut in half, and one half was immediately snap frozen in liquid nitrogen while the other was processed for routine histology. Cryostat sections were labeled with a panel of monoclonal antibodies (mAbs) and a polyclonal antilysozyme antibody, detailed in Table 2. The mAb Ber-H2 (Table 2) was used on paraffin sections. Cryostat and paraffin sections were labeled according to the method described by Cordell et al,[14] using the APAAP complex from DAKOPATTS, Copenhagen, Denmark, in conjunction with the new fuchsin development.

Results

Histologic Findings

The 15 cases in this study had certain morphologic features in common. The dermis was permeated by a diffuse cellular infiltrate of varying density that penetrates the subcutaneous tissue in some areas. As shown in Figure 2, the infiltrate was almost exclusively composed of large and often bizarre cells with rounded, oval, or irregularly shaped nuclei, abundant chromatin, and one nucleolus or multiple nucleoli. Multinucleated cells ranged from few to many. Many mitotic figures were found. Tumor cells formed cohesive sheets in most of the cutaneous infiltrates. A moderately dense reactive infiltrate of small, regularly shaped lymphocytes, some histiocytes, and eosinophils occasionally forming clusters was present. The reactive cell compartment was concentrated at the close vicinity of the large atypical cell infiltrate and occasionally was found around blood vessels in the large cell areas. Epidermotropism of the large tumor cells was not observed in any of the cases.

The anaplastic large tumor cells in biopsies from patients with concomitant MF (cases 14 and 15) tended to show the highest degree of anaplasia and the most bizarre morphology in our series of cutaneous Ki-1$^+$ ALC lymphomas. Some atypical cells in patients 14 and 15 were considerably smaller than the bizarre large anaplastic tumor cells. They had hyperconvoluted nuclei and condensation of chromatin. Such cells were concentrated in areas located at the margins of the large cell component of the infiltrate. The presence of the large cell component was understandable because patients 14 and 15 suffered from MF for approximately 6 years and still displayed some MF skin lesions of plaque-forming type at the time an ALC lymphoma was detected. The MF was diagnosed on morphologic and clinical grounds. Reviewing of the original histologic slides confirmed the diagnosis of MF.

Immunologic Findings

Immunolabeling results from the biopsies of all patients included in this study are given in Table 3. All tumor cells were labeled by the antibodies Ki-1 and Ber-H2, recognizing different epitopes on the Ki-1 antigen (Figure 3). Staining of paraffin sections with Ber-H2 showed that the expression of the CD30 antigen was consistently restricted to the tumor cells. On cryostat sections, most CD30$^+$ cells reacted with CD2 and CD3 antibodies in patients 1 through 13. Staining intensity was considerably weaker on the tumor cells than on the small lymphocytes of the reactive infiltrate. CD4 and CD5 antigens were inconsistently expressed on CD30$^+$ atypical cells, and staining intensity was weaker than on normal reactive lymphocytes. In patients 14 and 15 with secondary ALC lymphomas of the skin, the T cell antigens CD2, CD3, and CD5 were not detectable on the malignant cells, whereas weak staining was observed with anti-CD4 antibodies. In paraffin sections, staining with the CD45R mAb DF-T1 was positive on most of the tumor cells, with some strongly stained Hodgkin and Reed-Sternberg cells (Figure 4). The β-chain of the T cell receptor (β-TCR) was detected by the antibody β-F1 on atypical cells in cryostat sections of all cases studied, although the staining was less intense

Table 1. *Clinical Features of Ki-1$^+$ (CD30$^+$) Cutaneous ALC Lymphomas*

Case number	Age/sex	Date of first manifestation	Date of histologic diagnosis	Presenting skin lesion	Size of lesion (cm)	Extracutaneous manifestation at presentation	Initial histopathologic diagnosis	Preceding or accompanying lymphoma	Therapy	Present status
1	87/M	7/85	7/86	Multiple tumors	4 × 3	Not detectable	Histiocytic lymphoma	None	Excision irradiation	No recurrence
2	79/M	5/82; 9/86	5/82; 10/86	Solitary tumor	2.2 × 1 2 × 1.4	Not detectable	Immunoblastic lymphoma	None	Excision irradiation	Recurrence of skin tumor
3	76/M	6/86	5/87	Localized plaques and tumors	1.5 (tumor) 10 × 15 (plaque)	Not detectable	Malignant lymphoma	None	Excision	No recurrence
4	46/M	11/83	2/84	Solitary tumor (Figure 1)	8 × 4	Not detectable	Malignant histiocytic lymphoma	None	Excision	No recurrence
5	50/F	1/88	2/88	Solitary nodule	3 × 2	Not detectable	Malignant lymphoma	None	Excision	No recurrence
6	60/M	12/85	3/86	Solitary tumor	2.5 × 1.8	Not detectable	Anaplastic malignant tumor	None	Excision irradiation	Recurrence of skin tumor
7	53/M	6/88	7/88	Solitary tumor	4 × 3	Not detectable	Squamous cell carcinoma	None	Excision irradiation of tumor	Local recurrence
8	45/M	12/85	2/86	Multiple plaques and tumors	2 × 3 (tumor) 1.5 × 1 (pap)	Not detectable	Reticulum cell sarcoma	None	Irradiation CHOP	Specific lymph-adenopathy; died 12/87
9	71/F	8/85	3/86	Subcutaneous tumor	4 × 5	Not detectable	Panniculitis	None	Excision irradiation	Recurrence of skin tumors
10	87/F	2/88	5/88	Solitary tumor	3 × 4	Not detectable	Large-cell lymphoma	None	Excision	No recurrence
11	53/M	3/88	4/88	Localized tumors	3 × 4	Not detectable	B cell lymphoma	None	Excision	Local recurrence
12	48/F	4/87	4/87	Solitary tumor	2 × 1	Not detectable	Anaplastic malignant tumor	LyP	Excision	No recurrence
13	24/M	7/88	9/88	Solitary tumor	2 × 3	Lymph-adenopathy	Large cell lymphoma	LyP	Excision COPBLAM	Specific lymph-adenopathy
14	55/F	4/85	5/85	Solitary tumor	3 × 3	Lymph-adenopathy	MF	MF	Prednimustin	Further progression; died of lymphoma
15	67/F	4/87	6/87	Multiple tumors	8 × 5; 4 × 3; 2 × 3	Lymph-adenopathy	MF	MF	COPBLAM	Regression of skin lesions and lymph-adenopathy

LyP, lymphomatoid papulosis; MF, mycosis fungoides.

Table 2. *Monoclonal and Polyclonal Antibodies Used in this Study*

Cluster	Antibody	Source/reference	Specificity
CD2	T9-10	DAKOPATTS	T cells (E-rosette-associated antigen)
CD3	UCHT-1	DAKOPATTS	TCR-associated antigen
CD4	T3-10	Dr. P. Rieber DAKOPATTS	T helper/inducer cells, macrophages
CD5	DK23	DAKOPATTS	T cells, B cell subset
CD8	DK25	DAKOPATTS	Suppressor T cells
CD11c	S-HCL3/KB90	Becton Dickinson DAKOPATTS	All monocytes and macrophages
CD22	To15	DAKOPATTS	B cells
CD25	ACT-1	Own laboratory	IL-2R
CD30	Ki-1	Own laboratory/ DAKOPATTS[3,4]	Reed-Sternberg cell-associated antigen
CD30	Ber-H2	Own laboratory[29] DAKOPATTS	
CD43	DF-T1	Dr. D. Flavell/DAKOPATTS	T cells in paraffin sections
	β-F1	Dr. M. Brenner[30] T Cell Science	TCR β-chain
	Ki-M6/EMB11	Behring/DAKOPATTS	Macrophages
	Ber-MAC3	Own laboratory	Macrophages
	Antilysozyme (polyclonal)	DAKOPATTS	Macrophages
	KL1	Immunotech Dianova	Cytokeratin
	Ki-67	DAKOPATTS[15]	Proliferating cells
	Tü35	Dr. A. Ziegler[31]	HLA-DR

than on infiltrating reactive lymphocytes (Figure 5A). In paraffin sections from most cases, a positive reaction with β-F1 could be detected on only some of the anaplastic large tumor cells (Figure 5B). Most atypical cells also expressed HLA-DR antigens and receptors for interleukin-2 (IL-2). They did not react with B cell (CD22) or monocyte-macrophage-associated antibodies (CD11c, Ber-MAC3), and were negative for lysozyme and cytokeratin. A high percentage of tumor cells showed nuclear staining with the proliferation-associated antibody Ki-67.[15] In Ki-67-stained sections that were additionally labeled with Ber-H2, S-HCL-3, or KB90 (CD11c), the Ki-1 (CD30) antigen in all instances was found to be coexpressed with the nuclear Ki-67 antigen, but not with CD11c (Figure 6). In some areas, the stromal infiltrate contained many macrophages (CD11c-, Ber-MAC3-, and lysozyme-positive cells) and, occasionally, $CD8^+$ T cells.

Discussion

Histologically, the cutaneous ALC tumors in our study were composed of large and sometimes multinucleated cells with rounded or, more often, irregular nuclei containing nucleoli ranging from a large single nucleolus to small multiple nucleoli; the cytoplasm was usually abundant. This morphology led in the past to the erroneous categorization of identical or similar lesions as true histiocytic malignancies, ie, malignant histiocytosis (MH) or regressive atypical histiocytosis (RAH), or LyP of "histiocytic" type (type A) or anaplastic carcinoma.[11–13] This interpretation of the morphology was understandable because cutaneous ALC lymphoma cells often resemble tumor cells of anaplastic carcinoma with criteria corresponding to that published for so-called "histiocytic" neoplasms.[16,17] Accordingly, one of our cases was prediagnosed as squamous cell carcinoma, two cases as histiocytic lymphoma, and one as reticulum cell sarcoma. In two cases of malignant anaplastic tumors, the differential diagnosis of an anaplastic carcinoma was discussed.

Due to immunohistologic findings, however, it is now evident that MH of the lymph node, RAH, and LyP of histiocytic (A) type are not histiocytic, but lymphocytic in origin.[3,18] For our cases, a carcinomatous or histiocytic nature could be excluded because the tumor cells constantly lacked epithelial and histiocytic markers, but expressed T cell antigens. A proof of the T cell nature was provided by the demonstration of the T cell receptor (TCR) β-chain on the tumor cells. In line with the large size and irregular shape of the tumor cells in our cases was demonstration of the CD30 and CD25 activation antigens in the tumor cells, which relates these tumor cells to acti-

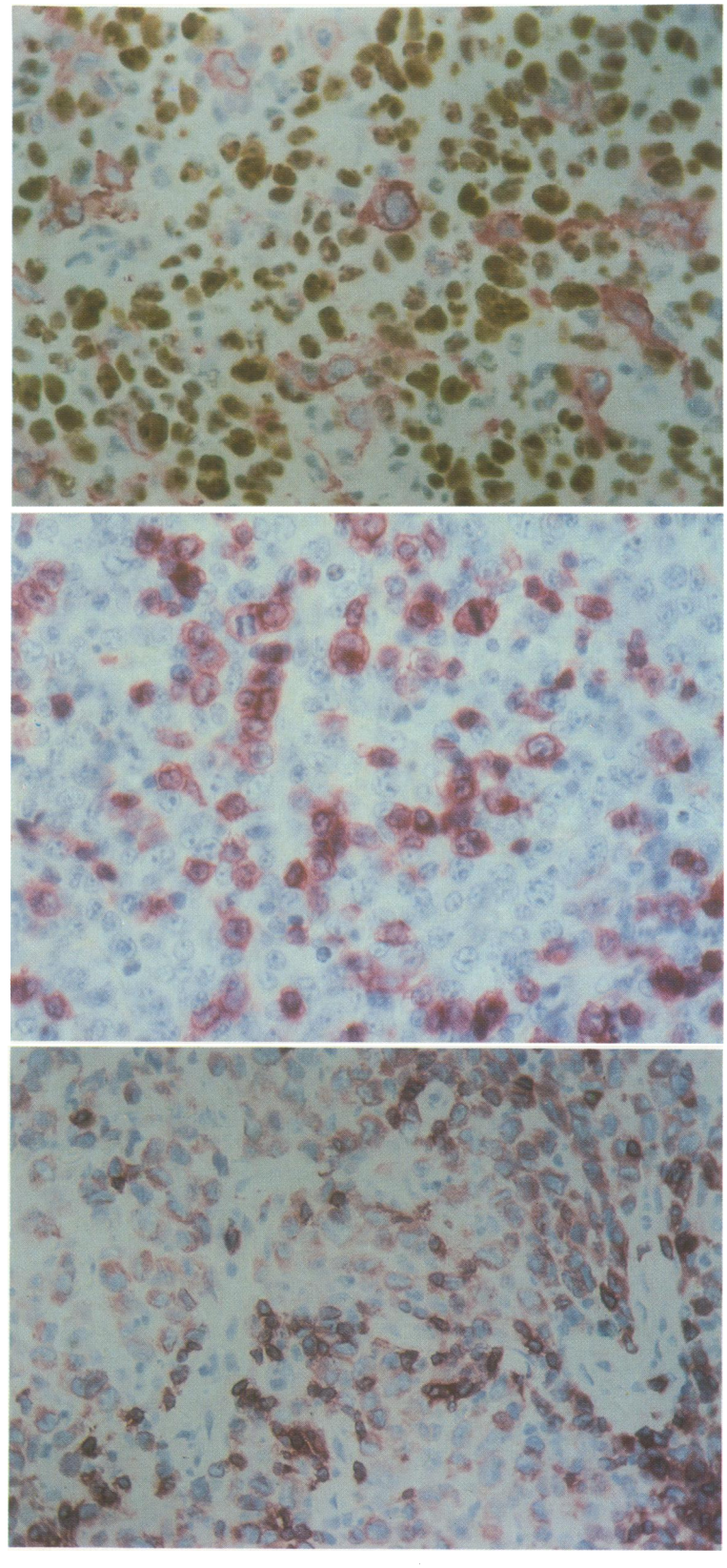

Figure 2 (top). *Paraffin section. Note the predominance of large anaplastic tumor cells, which are more densely packed here than in other areas, and their similarity to Hodgkin and Reed-Sternberg cells (H&E, ×450).* **Figure 3 (center).** *Paraffin section stained with Ber-H2 (CD30). Almost all tumor cells show an intense labeling of the Golgi region, the surface membrane, or both and comprise most of the infiltrating cells (×450).* **Figure 4 (bottom).** *Paraffin section stained with DF-T1 (CD43). Most of the neoplastic cells are positive. Note the strongly stained HSR-like tumor cells (×450).*

Table 3. *Antibody Reactivity of the Tumor Cells in Cutaneous ALC Lymphomas*

Antibody	Case 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CD2 (F)	++	+	++	+	+	++	+	+	+	+	+	+	+	−	−
CD3 (F)	++	++	+	++	+	+	+	+	+	+	+	+	+	−	−
CD4 (F)	++	+	−	+	−	+	++	−	+	−	+	−	+	+	−
CD5 (F)	+	++	−	++	+	−	−	+	+	+	−	−	+	−	−
CD8 (F)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CD11c (F)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CD22 (F)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CD25 (F)	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	++	++	++	++	++
CD30 (F/P)	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
CD43 (F/P)	++	++	+	++	+	+	+	+	++	++	+	+	+	+	++
Ki-67 (F)	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
HLA-DR (F)	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	++	++	++	++	++
Ber-MAC3 (F)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
β-F1 (F)	+	++	++	+	++	ND	+	ND	ND	ND	ND	+	+	ND	+
Lysozyme (F/P)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Cytokerain (F)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

F, frozen material; P, paraffin sections; +, weakly stained, ++, moderately stained (as compared with reactive CD8 lymphocytes); +++, strongly stained; −, negative; ND, not done; Ki-67 ++, 25% to 50% tumor cells positive.

vated T cells. *In vitro*-activated T cells expressing both CD30 and CD25 are cytologically very similar to the tumor cells of the skin lesions under discussion.[19]

Demonstration of the CD30 and CD25 antigens on tumor cells of LyP type A and RAH,[20–23] however, implies further the close relationship of these tumors to our cases of cutaneous Ki-1$^+$ ALC lymphomas. According to the literature, the only difference between the lesions under discussion seems to lie in the density of the atypical cells and the abundance of admixed nonmalignant cells.[24] In RAH and typical cutaneous ALC lymphomas, the malignant cells form cohesive sheets, whereas in LyP type A they are less dense and more variable due to varying amounts of admixed nonmalignant cells of different types. Clinically, LyP type A presents most often with multiple papular lesions,[25] but ulcerating tumors are also reported to occur.[12] The clinical features of RAH are not clearly defined because only five cases have been reported so far. These patients had solitary or multiple tumors that developed within a short period and resolved spontaneously.[6] Spontaneous regression could not be observed in our cases. Immediate therapy after development of these lesions, however, may have interfered with such a clinical course. At this point, the question arises whether the above-mentioned clinical differences really justify a nosologic separation of LyP, RAH, and cutaneous Ki-1$^+$ ALC lymphomas. It is more likely that these lesions represent only variants of the same disease entity and that the clinical differences reflect the variability of the biological behavior of this tumor entity.

As mentioned, the cutaneous Ki-1$^+$ ALC lesions described here are morphologically and immunophenotypically identical to the lymphonodal Ki-1$^+$ ALC lymphomas of T cell type. Despite this similarity, it is relevant to recognize that there are clinical differences between primary cutaneous and lymphonodal Ki-1$^+$ ALC lymphomas. Primary lymphonodal Ki-1$^+$ ALC lymphomas usually show a rapid spread into other lymph node regions and nonlymphoid organs including skin.[6,8,9,26] In contrast, our cutaneous Ki-1$^+$ ALC lymphomas tend to remain localized in the skin for a long time. This indicates that the localization of primary Ki-1$^+$ ALC lymphomas is clinically relevant.

The development of specific lymphadenopathy in two of our patients with primary cutaneous Ki-1$^+$ ALC lymphomas and a fatal course in one of these cases, however, indicate a possibly unfavorable prognosis for this cutaneous lymphoma category. It is important to note that cutaneous Ki-1$^+$ ALC lymphomas do not only occur primarily, but also arise secondarily from other types of lymphomas such as MF, pleomorphic T cell lymphoma, T cell lymphoma of angioimmunoblastic type, and Lennert's lymphoma, as well as Hodgkin's disease.[8,9,19] Cases 14 and 15, in whom Ki-1$^+$ ALC lymphoma developed in preceding and concomitant MF, are examples of this phenome-

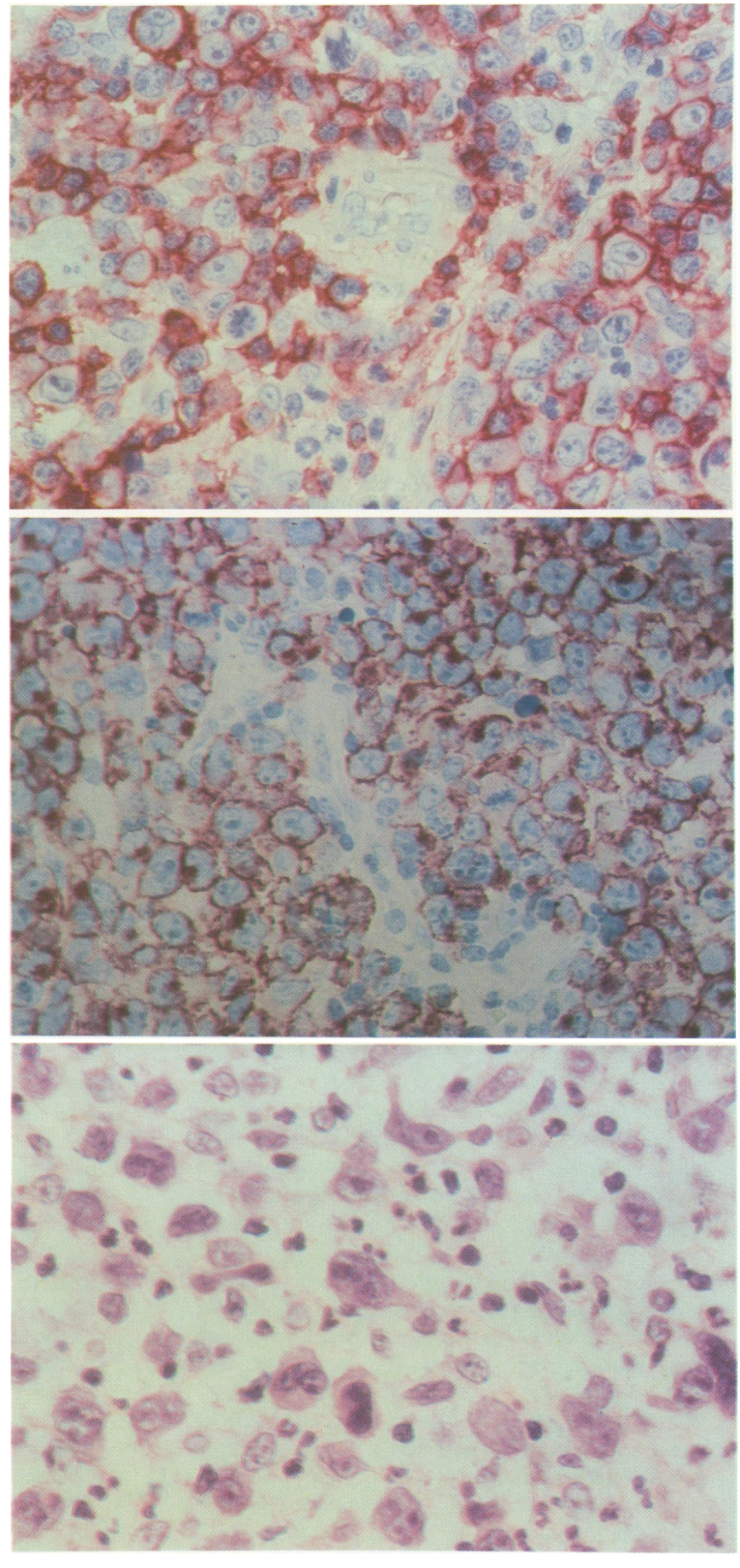

Figure 5. **A** *(top): Cryostat section stained with β-F1; most of the tumor cells are labeled, although less intensively than reactive perivascular T lymphocytes (×300).* **B** *(center): Paraffin section stained with β-F1; only some of the neoplastic cells (mitotic figures) are positive (×450).* **Figure 6 (bottom).** *Cryostat section with double labeling with Ki-67 and S-HCL3 (CD11c). Ki-67$^+$ cells (proliferating cells) are negative for macrophage-associated antigen (CD11c) (×450).*

non. Presence of an atypical small-cell component with hyperconvoluted nuclei in the infiltrate supports the notion that development of Ki-1$^+$ ALC lymphoma in these patients is a transformational event rather than second *de novo* lymphoma. Both the secondary cutaneous and lymphonodal Ki-1$^+$ ALC lymphomas have a much worse prognosis compared with the corresponding primary cutaneous Ki-1$^+$ ALC lymphomas and with the preceding cutaneous T cell lymphoma.[9,26,27] Based on the abovementioned reports and history of our two secondary ALC lymphomas, the subsequent large-cell transformation with appearance of Ki-1 antigen during the course of a lymphoma appears to be a bad prognostic sign.

Because of their cytomorphology and large growth fraction, primary cutaneous Ki-1 ALC lymphomas are grouped among cutaneous lymphomas of high-grade malignancy by the EORTC Cutaneous Lymphoma Study Group.[28] Such a grouping has prompted clinicians to treat these lymphomas with aggressive therapeutic protocols. Our observations, however, do not justify such measures because some patients are certainly overtreated. More information is needed on the biological properties of primary Ki-1 ALC lymphoma to establish adequate therapy for all cases. The aim of this communication is to increase awareness of the existence of primary cutaneous Ki-1$^+$ ALC lymphomas and to initiate further studies on their clinical course.

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