Lymphomatoid Papulosis

A Cutaneous Proliferation of Activated Helper T Cells Expressing Hodgkin's Disease-Associated Antigens

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A distinctive immunologic phenotype was demonstrated for the characteristic large atypical cells in skin lesions of 9 patients with lymphomatoid papulosis (LP). Co-expression of Hodgkin's disease (HD)-associated antigen(s) Ki-1, and often Leu-M1, with helper T-cell antigens T11, T4, and T3 and cellular activation antigens Tac, Ia, and T9 was the most common phenotype, observed in 6 of 9 cases. In 2 cases T-cell-specific antigens were not detected, and the phenotype was indistinguishable from Reed-Sternberg (RS) cells of HD. Numerous Ki-1 positive cells and infrequent expression of Leu-1 antigen by large atypical cells in LP cases facilitated the differential diagnosis between LP and mycosis fungoides. A possible transition between small, medium, and large cells expressing only T-cell antigens and large transformed RS-like cells expressing both T-cell and HD-associated antigens was shown by immunoelectron microscopy. These immunologic findings should prove useful for the diagnosis of LP and may help to explain the unexpectedly frequent clinical associations of LP, mycosis fungoides, and HD. (Am J Pathol 1985, 119:315–325)

LYMPHOMATOID papulosis (LP) has been defined as a continuing self-healing skin eruption that is clinically benign but histologically malignant.[1] The malignant appearance is due to a predominance of large atypical cells with convoluted nuclei, sometimes resembling Reed–Sternberg (RS) cells of Hodgkin's disease (HD).[2–4] The origin of these RS-like cells has been controversial. They are claimed to be derived from either a T cell[5–6] or a nonlymphoid cell in the Langerhans/interdigitating reticulum cell series.[7] In the present study of skin lesions from 9 patients with LP we describe a distinctive immunologic phenotype for the large atypical cells in most cases expressing both helper T cell and HD-associated antigens. This finding should prove useful for the histologic diagnosis of LP and may help to explain the apparent biologic relationship of LP to mycosis fungoides and HD.

Materials and Methods

Nine patients with recurrent, self-healing papular, nodular, or plaque lesions and numerous large atypical cells in histologic sections were selected for this study. The clinical characteristics and morphology of skin lesions of the 9 patients are given in Table 1.

Four-millimeter punch biopsies of skin were obtained from all patients. Specimens from 4 patients (4, 5, 6, and 8) were directly snap-frozen. Specimens from patients 1, 2, 3, 8, and 9 were fixed in periodate-lysine-paraformaldehyde (PLP) fixative for 4–6 hours at 4 C according to the method of McLean and Nakane[8] and sent to us before freezing. These PLP-fixed specimens were transferred through increasing concentrations of sucrose (7%, 15%, and 25% plus 10% glycerol) in 0.05 M phosphate buffer (pH 7.4) and then snap-frozen. Each specimen was cut at approximately 6 μ thickness and placed in acetone or PLP at 4 C for 5 minutes.

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Table 1—Clinical Characteristics and Morphologic Features of Skin Lesions of 9 Patients With Lymphomatoid Papulosis

Patient	Sex	Age of onset	Duration (years)	Clinical course	Morphology of lesions*			Distribution of infiltrate	Cellular composition of infiltrate
					Papules	Nodules	Plaques		
1	F	22	4	No treatment, still getting new lesions	+	–	–	Superficial and deep perivascular	Admixture or spectrum of CMC† and large atypical cells
2	M	48	8	Poor control on multiple therapies	+	+	–	Deep interstitial	Sheets of large atypical cells
3	M	27	<1	Partial response on tetracycline	+	+	–	Extensive perivascular and interstitial	Numerous eosinophils, neutrophils and large atypical cells
4	M	41	13	Lost to follow-up	+	–	–	Superficial perivascular	Mixture of small lymphocytes and large atypical cells
5	F	42	20	Good control on methotrexate	+	–	–	Superficial perivascular and interstitial. Epidermotropism	Large atypical cells sharply demarcated from CMCs in epidermis, perivascular small lymphocytes
6	F	61	14	Good control on methotrexate	+	–	–	Superficial perivascular	Mixture of small lymphocytes and large atypical cells
7	M	15	23	Minor response on UVB phototherapy	+	–	+	Superficial perivascular and interstitial	Mixture of small lymphocytes and large atypical cells
8	M	32	13	Still getting new lesions; 5-year remission from Stage II-A Hodgkin's disease	–	+	+	Deep interstitial	Sheets of large atypical cells, numerous eosinophils, some neutrophils
9	M	75	1	Developed mycosis fungoides	–	+	+	Superficial perivascular and interstitial	Predominance of CMCs

* Papules, <2 cm, nodules, >2 cm in diameter.
† CMC, cerebriform mononuclear cells.

Cryostat sections were then washed in PBS for 15 minutes. Horse serum was used to block nonspecific binding of antibodies. Sections were then allowed to react with various murine monoclonal antibodies, listed in Table 2.

Reaction of primary antibodies was localized with the avidin–biotinylated peroxidase complex according to the method of Hsu et al.[23] The reaction product was darkened with 1% Osmium. For light microscopy, the immunoperoxidase-labeled frozen sections were covered with glycerol mounting medium and a coverslip. For electron microscopy, frozen sections prepared and antibody-labeled in the same manner as above were fixed in 3% glutaraldehyde before the diaminobenzidine reaction, dehydrated in a graded series of alcohols, and embedded in Epon (Ted Pella, Inc., Tustin, Calif) by rapidly inverting gelatin embedding capsules filled with the epoxy resin. The Epon was allowed to harden overnight at 60 C. Detachment of the capsule from the glass slide was accomplished by gentle heating. Ultrathin sections were cut from the face of the Epon block with a diamond knife on an LKB ultramicrotome and examined either unstained or stained with uranyl acetate under a JEOL electron microscope. Cell reactivity with monoclonal antibodies was detected by a continuous layer of granular electron-dense reaction product outlining the cell membrane and cell processes between adjacent cells. No reaction product was observed within the cytoplasm, overlying the nucleus, or in the interstitium. Control sections stained with an irrelevant antibody were examined ultrastructurally in all cases and revealed no staining.

Results

There was a good correlation between the gross morphology and histologic appearance of skin lesions in the 9 patients with LP (Table 1). Nodular lesions were

Table 2—Monoclonal Antibodies and Their Reactivity

Antibody clone(s)	Antigen recognized	Reference	Reactive cells
9.6 (OKT11)	E-rosette receptor p45	9	All E-rosetting T-cells
Leu 1 (10.2)	p65	10	Thymocytes, all T cells except some cytotoxic/suppressor T cells
Leu 4 (OKT3)	p19	11	Mature thymocytes, peripheral T cells
Leu 3a (OKT4)	p62	12	Thymocyte subpopulations, helper T cells
Leu 2a (OKT8)	p32–33 p70 (unreduced)	13	Thymocyte subpopulations, cytotoxic/suppressor T cells
3A1	p40	14	Thymocytes, all T cells except some helper T cells
Tac	Interleukin-2 receptor	15	Activated and functionally mature T cells
T9	p94 reduced p190 (unreduced)	16	Transferrin receptor on proliferating cells
T10	p45	17	Thymocytes and activated T cells
HB10a	Framework region of Ia p29–34	18	B cells, dendritic cells, macrophages, activated T cells
HLB-3	p168–34	19	Pan-B (except plasma cell)
OKT6	p49	20	Cortical thymocytes, Langerhans cells
Ki-1	unknown	21	Hodgkin (Reed–Sternberg) cells and unidentified smaller cells in lymph node, tonsil
Leu M1	unknown	22	Monocytes, granulocytes, Hodgkin (Reed–Sternberg) cells

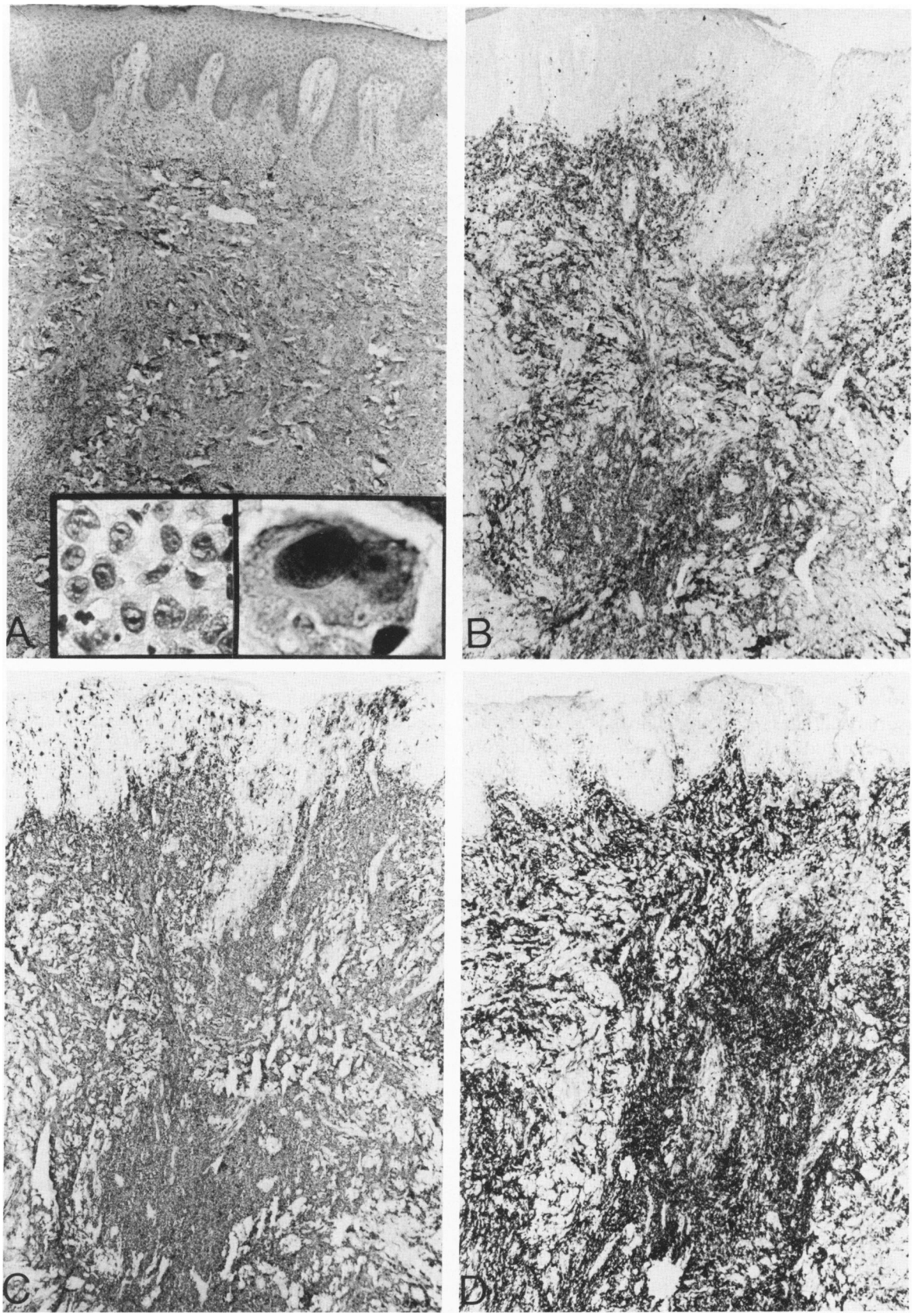
most often associated with deep perivascular and diffuse interstitial infiltrates with a predominance of large atypical cells, including RS-like cells with multilobated or multiple nuclei (Figure 1). Papules and plaque lesions were usually associated with superficial and perivascular infiltrates containing an admixture of small lymphocytes and inflammatory and large atypical cells (Figure 2). In 3 such cases (1, 5, and 9) there were also a number of small and medium-sized cerebriform mononuclear cells (CMC) with hyperchromatic nuclei; these CMCs infiltrated the basal and parabasilar layers of the epidermis in Case 5.

Immunoperoxidase stains of frozen sections showed that the large atypical cells expressed HD-associated antigen Ki-1 in all cases and Leu-M1 in 4 of 9 cases (Table 3). In 7 of these 9 cases immunoperoxidase staining of consecutive sections revealed that the majority of Ki-1–positive cells also expressed T-cell–specific antigens (Figure 1 and Table 3). In 6 cases, the pattern of antigen expression conformed to a helper T-cell phenotype $T11^+$, $T3^+$, $T4^+$; whereas in one case (7), a predominance of cytotoxic/suppressor $T8^+$ cells was found.

A state of T-cell activation was shown by the expression of Tac and Ia antigens by tumor cells in all cases (Figure 1 and Table 3). A varying number of cells in each case also expressed the T9 antigen, corresponding to the transferrin receptor found on proliferating cells. B-cell markers, including surface immunoglobulin (sIg) and a "pan"-B cell antigen (HLB-3), were never found. The T6 antigen, a marker of Langerhans cells, was confined to dendritic cells in the epidermis and in some cases the dermis but was not expressed by large atypical cells or CMCs.

Expression of "pan"-T cell antigens Leu-1 and 3A1 was confined to small lymphocytes and CMCs in most cases (Figure 2). In only 3 cases (1, 4, and 6) did some of the large atypical cells appear to express Leu-1 antigen (Table 3). In 2 cases (5 and 8) no T-cell–specific antigens were detected on large atypical cells (Figure 2). In these cases, the phenotype of large atypical cells conformed to that of RS cells in most cases of HD.

Immunoelectronmicroscopy was done to confirm the light-microscopic immunoperoxidase findings. Figure 3A confirms the absence of Leu-1 (10.2) antigen on large atypical cells in Case 3. Figures 3B and C confirm the expression of both HD-associated antigen Ki-1 and T-cell–specific antigen 9.6 (T11) by large atypical cells in Case 3. Figure 4 shows a spectrum of cells from classic cerebriform cells through large atypical cells resembling transformed lymphocytes expressing T4 antigen and HD-associated antigens Ki-1 and Leu-M1 in a plaque lesion of LP from Case 9.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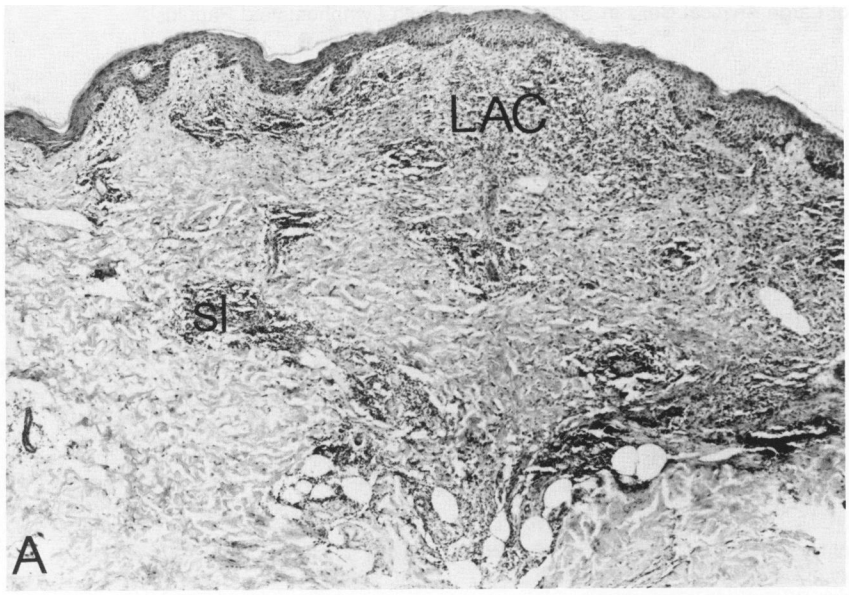
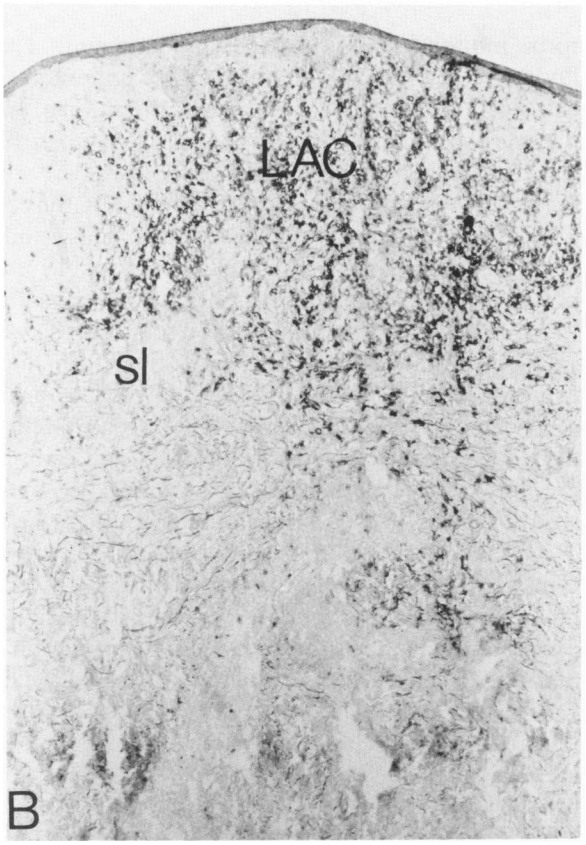




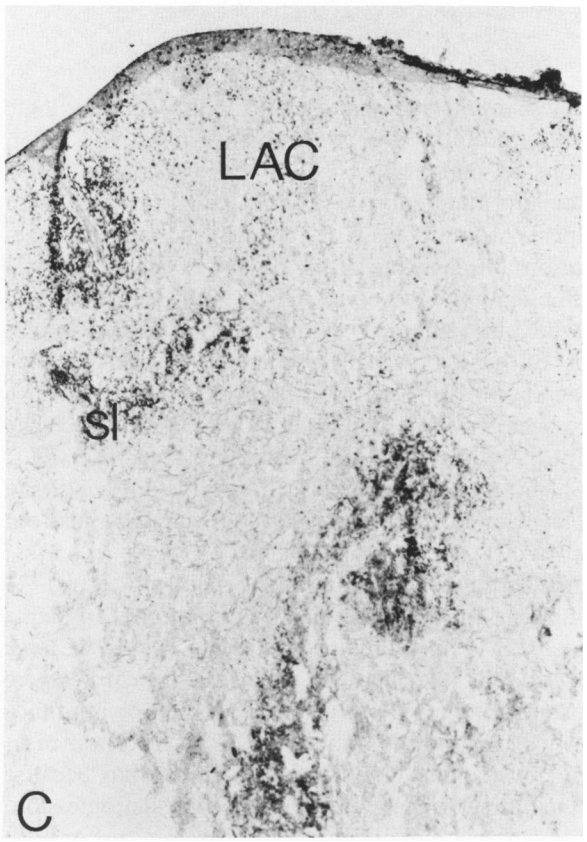


Figure 2A—Superficial infiltrate of large atypical cells (*LAC*) and perivascular small lymphocytes (*sl*) in a frozen section of skin from Patient 5 in a papular lesion of LP. (H&E, ×40) **B**—Large atypical cells stained with antibody Ki-1. (×40) **C**—Small lymphocyte stained with antibody Leu-1 (10.2). (×40)

Figure 1—Extensive dermal lymphoid infiltrate in a frozen section of skin from Patient 3 with nodular lesions of LP. **A**—H&E-stained (×40), with insets of large atypical cells (×160) and an RS-like cell (×1000). Comparable immunoperoxidase staining of consecutive sections with monoclonal antibodies: **B**, Ki-1; **C**, HB10a (Ia); **D**, Leu 3a (T4). (All ×40)

Table 3—Phenotype of Large Atypical Cells in Skin of Patients with Lymphomatoid Papulosis

Immunologic markers		Case*								
		1	2	3	4	5	6	7	8	9
Hodgkin's diseased associated	Ki-1	+	+	+	+	+	+†	+	+	+
	Leu-M1	0	+‡	0	+	0	0	+†	+†	+
T-cell–specific	9.6 (T11)	+	+	+	+	0	ND	+	0	+
	Leu-1 (10.2)	+	0	0	+†	0	+	0	0	0
	Leu-4 (OKT3)	0	+	0	+	0	+	+	0	+
	Leu-3a (OKT4)	+	+	+	+	0	+	0	0	+
	Leu-2a (OKT8)	0	0	0	0	0	0	+	0	0
	3A1	0	0	0	0	0	ND	0	0	0
Activation antigens	Tac	+	+‡	+	+‡	+	+	+	+	+†
	OKT9	+‡	+‡	+‡	+†	+	+	+†	+	+†
	OKT10	0	0	0	0	0	0	0	0	ND
	HB10a (anti-Ia)	+	+	+	+	+	+	+	+	+
B-cell–specific	HLB-3	0	0	0	0	0	0	0	ND	0
	sIg	ND	ND	ND	ND	ND	ND	0	0	ND
Other	T6	0	0	0	0	0	0	0	0	0

* +, more than 50% of large atypical cells positive; ND, not done; 0, negative.
† Twenty to fifty percent of large atypical cells are positive.
‡ Less than 10% of large atypical cells are positive.

Discussion

These results demonstrate a distinctive immunologic phenotype for the large atypical cells infiltrating the skin lesions of patients with LP. Co-expression of HD-associated antigen(s) Ki-1, and often Leu-M1, with helper T-cell antigens T11, T3, and T4 and cellular activation antigens Tac, Ia, and T9 was the most common phenotype, observed in 6 of 9 cases. In 1 case (7) in which immunoelectronmicroscopy was performed, most of the atypical cells appeared to have a $T8^+$ cytotoxic/suppressor T-cell phenotype. Rare $T8^+$ cases have also been reported in mycosis fungoides, in which the helper T-cell phenotype is more commonly observed.[24] In 2 of our LP cases, no T-cell–specific antigens were detected and the phenotype was indistinguishable from that of RS cells in most cases of HD.[25,26]

In a comparative immunohistochemical study of 27 cutaneous T-cell lymphomas we found only 2 patients whose skin lesions contained frequent Ki-1 positive large atypical cells.[27] In each case the histologic features were those of a nonepidermotropic large cell or immunoblastic lymphoma containing RS-like cells. These cases were considered to be malignant lymphomas because of their invasive characteristics and clinical progression, leading to death in one instance. However, one or both of these cases may have been the result of progression of lymphomatoid papulosis to a T-cell–immunoblastic lymphoma (T-IBL), as reported in an earlier case by Tucker et al.[28] Ki-1–positive cells were infrequent or absent in 25 other cutaneous T-cell lymphomas, including 12 cases of mycosis fungoides and 6 cases of the Sézary syndrome; in these cases Leu-1–positive cerebriform mononuclear cells were predominant. These findings suggest that in some instances immunohistochemical staining may facilitate the distinction of lymphomatoid papulosis (and T-IBL) from mycosis fungoides and the Sézary syndrome.

In most cases of lymphomatoid papulosis, the combined electron-microscopic immunoperoxidase studies confirmed that large atypical cells were capable of expressing both T-cell and HD-associated antigens. In at least 1 case (9) there appeared to be a transition between small, medium, and large cells with cerebriform nuclei expressing only T-cell antigens and large transformed cells, including RS-like cells expressing both T-cell antigens and HD-associated antigens. These observations are consistent with the results of a recent experimental study in which the Ki-1 antigen was expressed by helper T cells activated by autologous or allogeneic lymphocytes and transformed to blast cells *in vitro*.[29] We suggest that a similar mechanism may be operative in lymphomatoid papulosis during the transformation of Sézary-like helper T cells to Ki-1–positive RS-like cells.

Willemze et al demonstrated two major histologic types of LP, type A lesions, in which large atypical cells are the principal cellular component, and type B lesions, in which CMCs predominate.[4,7] These authors proposed a nonlymphoid origin for the large atypical cells in LP, possibly related to the Langerhans/interdigitating reticulum cell series, because of the presence of C3 and IgGFc-receptors, strong expression of Ia-like antigens, and absence of T-cell antigens in 8 of 10 cases.[7] These cases may correspond to our Cases 5 and 8, in which only Ia, Tac, T9, and HD-associated antigens were found. We found no T6 antigen, characteristic of Lan-

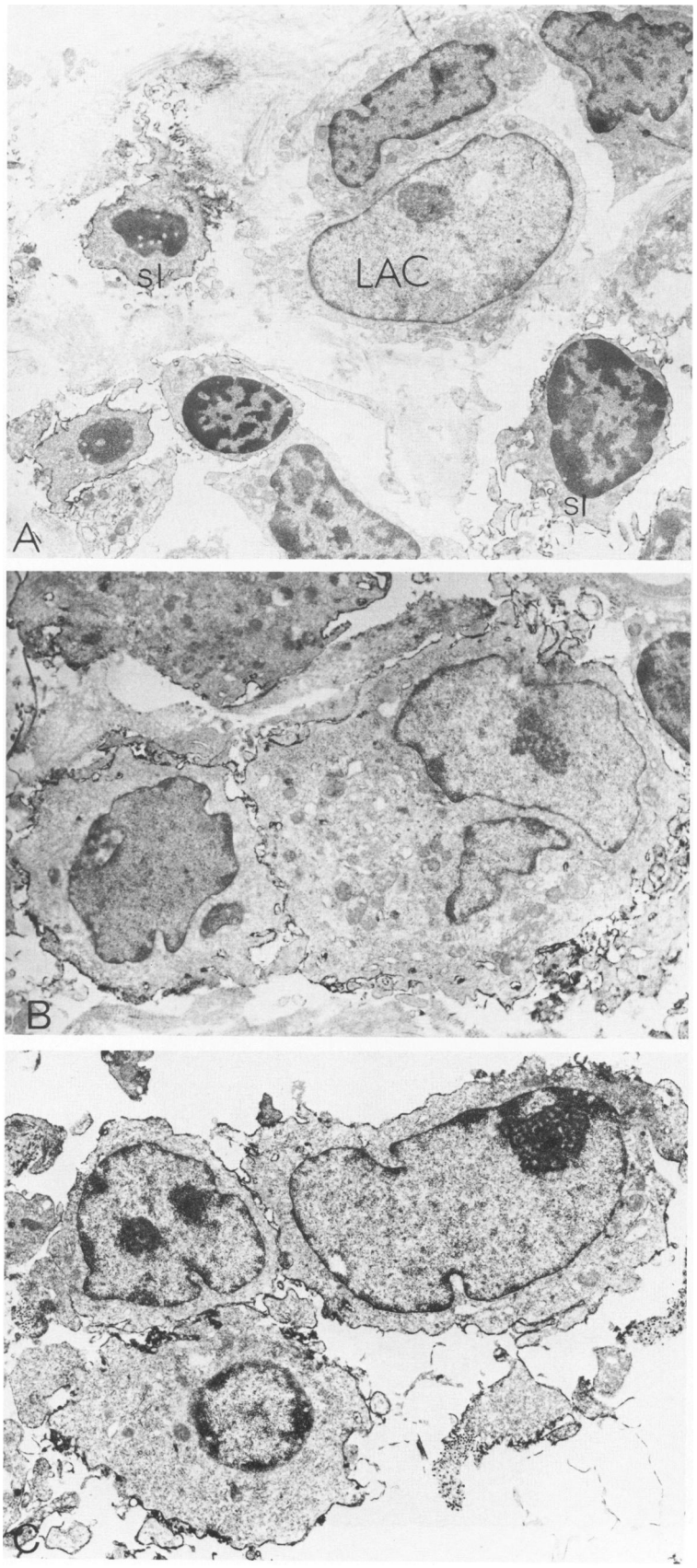
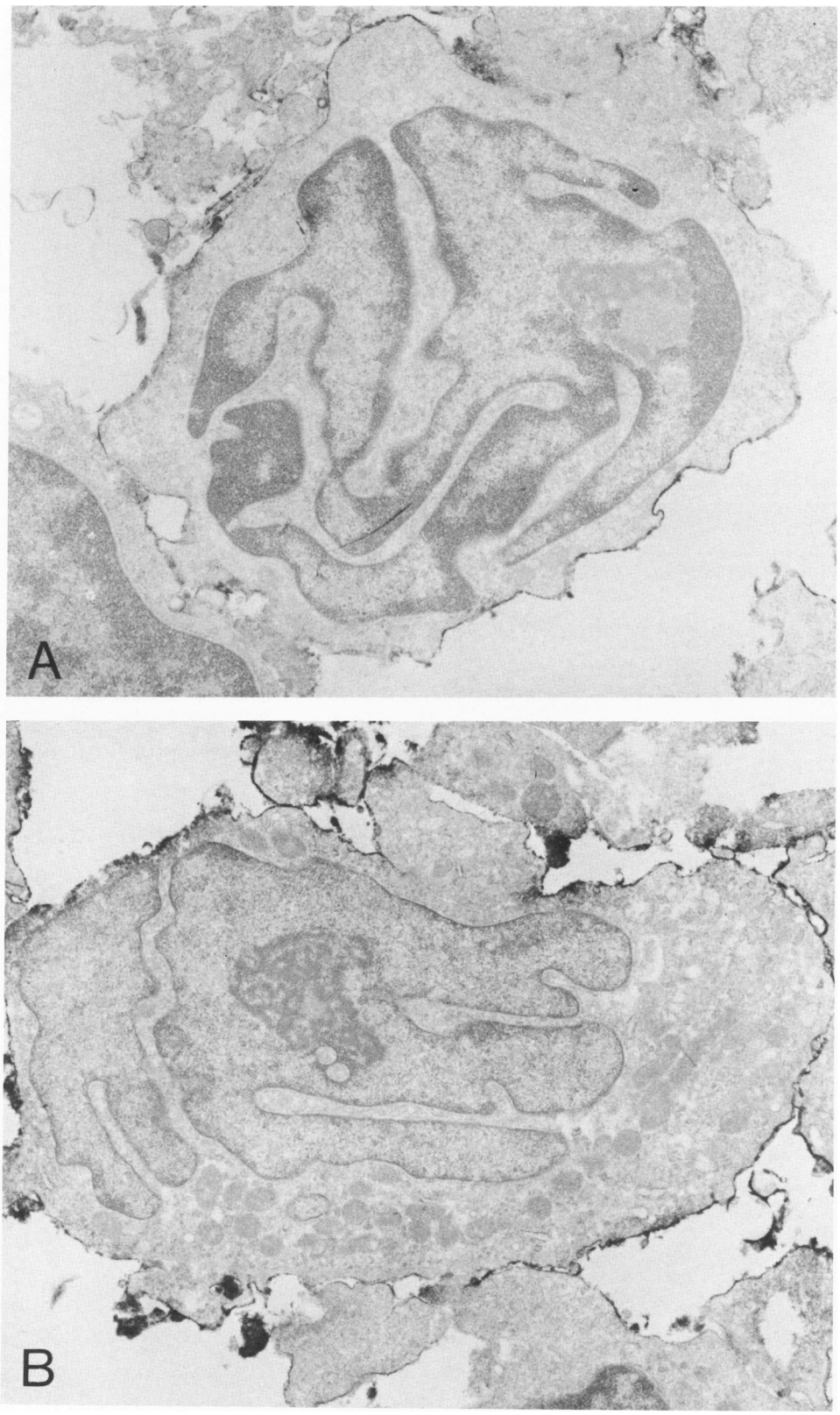


Figure 3A—Electron micrograph showing dark surface staining of lymphocytes (*sl*) but not large atypical cells (*LAC*) with antibody Leu-1 (10.2). (×5333) **B**—Surface staining of large atypical cells with antibody Ki-1. (×6333) **C**—Surface staining of large atypical cells with antibody 9.6 (T11). (×6700).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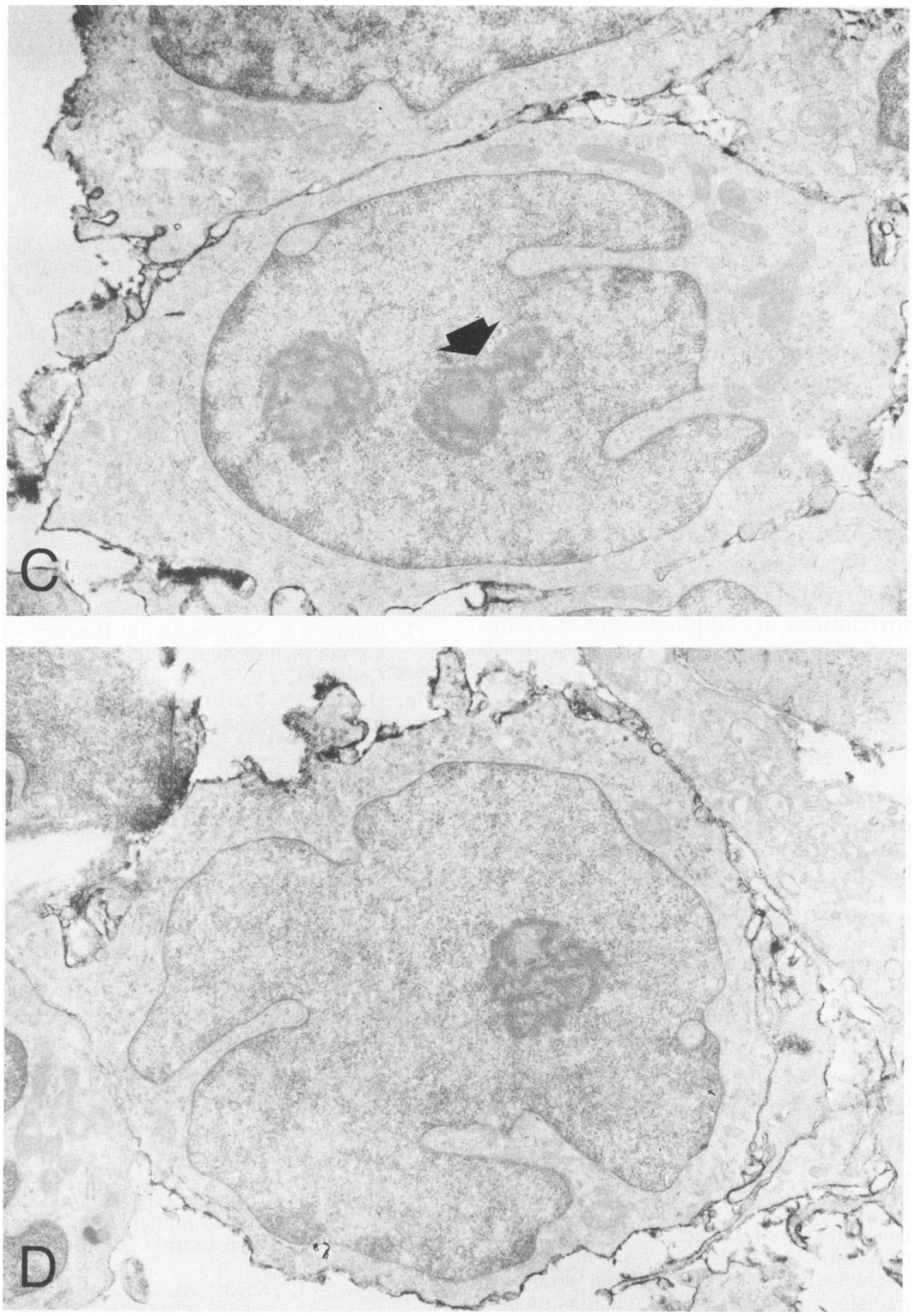

Figure 4A–D—Electron micrographs of a plaque lesion from Patient 9. Spectrum of cells with highly convoluted nuclei (**A** and **B**) and transformed-appearing nuclei (**C** and **D**) showing surface staining of helper-cell antigen Leu 3a (T4) in **A** and **C**, and HD-associated antigens Leu-M1 (**B**) and Ki-1 (**D**). The *arrow* points to a prominent nucleolus in **C**. (**A**, ×15,833; **B**, ×12,667; **C**, ×9500; **D**, ×15,833)

gerhans cells,[20] on large atypical cells. Willemze et al also recognized that the large atypical cells in LP type A lesions are morphologically and immunologically similar to true RS cells of HD.

Lymphomatoid papulosis has been considered to be the lesion responsible for some cases of benign self-healing Hodgkin's disease confined to the skin that were previously reported as primary cutaneous HD.[30] Secondary involvement of the skin in HD is usually a late preterminal manifestation associated with retrograde spread of tumor cells in lymphatics.[31] Therefore, we considered the spontaneously regressing skin nodules of

Patient 8 to be lymphomatoid papulosis separate from, although possibly related to his HD in abdominal lymph nodes, which had been treated to complete remission 5 years earlier. In fact, biopsy of his axillary and inguinal lymph nodes at the time of the most recent skin lesions revealed only dermatopathic lymphadenopathy without evidence of HD. As shown in this case, the distinction of LP from cutaneous HD will usually require clinical correlation, because the large atypical cells can be morphologically and immunologically similar in both LP and HD. However, from the present study it appears that the expression of mature helper T-cell antigens T3 and T4 by large atypical cells in most cases of LP distinguishes them from true RS cells in most examples of HD.

The current study provides an explanation for the clinically observed progression of some cases of LP to mycosis fungoides or HD.[32-36] The cell lineage of large atypical cells in LP may be similar or identical to that of tumor cells in mycosis fungoides and some types of HD. Further correlations of cell phenotype and clinical course may help to predict which patients with LP will eventually develop mycosis fungoides or HD.

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