Peripheral T Cell Lymphoma: Immunologic and Cell-Kinetic Observations Associated With Morphological Progression

Per Carl D. Winberg, Khalil Sheibani, Robert Krance, and Henry Rappaport

Peripheral T cell lymphomas (PTCLs) form a morphologically heterogeneous group of non-Hodgkin's lymphomas that are generally considered to have immunophenotypes associated with mature T cells, usually those of helper T cells. We now describe and correlate the clinical, morphological, immunological, and cell-kinetic findings based on the evaluation of eight tissue samples obtained at various times from a 13-year-old girl with PTCL. The early morphological expressions of this patient's PTCL were those of diffuse mixed-cell lymphoma and focal large-cell lymphoma (LCL) evolving from the histologic picture of an atypical immune response (AIR). These morphological findings were associated with an immature T cell immunophenotype associated with cortical thymocytes—namely, sheep erythrocyte rosette (sER), T11, Leu-2a, Leu-3a, HLA-DR, OKT6, OKT9, OKT10—and with cell-kinetic findings that showed no evidence of aneuploidy and few cells in S phase. Diffuse pleomorphic LCL developed, which was associated with further dedifferentiation of the neoplastic T cells to the immunophenotype sER, T11, Leu-2a, Leu-3a, HLA-DR, OKT6, OKT9, OKT10 and with cell-kinetic findings that demonstrated a distinct aneuploid population and a dramatic increase in the percentage of cells in the S phase. The immunophenotype of the PTCL at the time of the patient's death was T11, Leu-2a, Leu-3a, HLA-DR, OKT6, OKT9, OKT10, an immunophenotype indistinguishable from that of a non-B non-T cell lymphoma. The immunologic findings in this case also suggest that an AIR in some cases may represent a prelymphomatous state or may be a morphological expression of PTCL. These observations indicate that PTCLs may be characterized by rapidly changing clinical, morphological, immunological, and cell kinetic findings which are best evaluated by multidisciplinary studies.
IMMUNOLOGIC PROGRESSION OF PTCL

Table 1. Pathologic Specimens and Morphological Diagnoses From an Adolescent Patient With Peripheral T Cell Lymphoma on Which Immunologic Studies Were Done

| Specimen | Tissue                | Site                  | Date Specimen Obtained | Morphological Diagnoses*
|----------|-----------------------|-----------------------|------------------------|--------------------------
| A        | Lymph node            | Right inguinal        | 12/9/82                | AIR                      |
| B        | Lymph node            | Right cervical        | 12/9/82                | AIR                      |
| C        | Lymph node            | Right axillary        | 12/9/82                | AIR, with development of LCL |
| D        | Skin                  | Posterior cervical    | 12/9/82                | DMEH                     |
| E        | Skin                  | Back                  | 12/9/82                | DMEH                     |
| F        | Lymph node            | Retroperitoneum       | 1/13/83                | Diffuse LCL              |
| G        | Lymph node            | Retroperitoneum       | 1/13/83                | Diffuse LCL              |
| H        | Lung (open biopsy)    | Left lower lobe       | 2/24/83                | Diffuse LCL              |

Abbreviation: DMEH, DM lymphoma with an epithelioid histiocytic reaction. (For other abbreviations, see text.)

*When non-Hodgkin’s lymphoma was present, the histologic features were classified according to the “modified” Rappaport classification.18

(B), and right axillary (C) lymph nodes, and skin from the posterior neck (D) and back (E) were obtained on Dec 9, 1982, and submitted for both morphological and immunologic study. The right inguinal (A) and cervical (B) lymph nodes were interpreted as showing AIRs, whereas the axillary lymph node (C) contained LCL in the presence of an AIR. The skin biopsy specimens were characteristic of DM lymphoma with an epithelioid histiocytic reaction. Because her disease regressed spontaneously without clinical evidence of tumor, chemotherapy was not instituted, and she was discharged on Dec 14, 1982.

The patient was readmitted on Jan 10, 1983, to the SBCH, where an abdominal computed tomography (CT) scan demonstrated a 5-cm mass in the left iliac fossa. She was transferred to the COH on Jan 12, 1983, and an abdominal laparotomy with biopsy of enlarged retroperitoneal lymph nodes (F and G) was performed on Jan 13, 1983. Following the diagnosis of diffuse LCL involving the retroperitoneum, chemotherapy was begun with cyclophosphamide, Adriamycin, vincristine, and prednisone. There was clinical regression of disease; further chemotherapy included cytosine arabinoside and L-asparaginase.

Because of fever, left leg pain, and shortness of breath, the patient was readmitted to SBCH on Feb 15, 1983. Subsequently, on Feb 19, 1983 she was transferred to the COH, where chest radiographs demonstrated bilateral interstitial infiltrates and a left pleural effusion. On Feb 24, 1983, the patient underwent an open lung biopsy (H) which showed diffuse LCL; treatment with Adriamycin, vincristine, and prednisone. Pathologic findings suggestive of metabolic (lytic) bone disease during the course of her disease.

MATERIALS AND METHODS

Histopathology studies. Initial histopathologic material was received in consultation at the James Irvine Center for the Study of Leukemia and Lymphoma at the COH. All subsequent histologic material except for the autopsy specimens was processed in the Sylvia Cowan Surgical Pathology Laboratory at the COH.

Reagents for immunologic studies. Peroxidase- and fluorescein-conjugated F(ab')2 goat anti-human antisera for IgG, IgA, IgM, and IgD heavy chains, and for s and λ light chains (Tago, Burlingame, Calif) were used for detection of surface immunoglobulins. The samples were studied further with a panel of monoclonal antibodies, including: anti-T11 (E rosette-forming T cells) and anti-B1 (B cell-restricted antigen) from Coulter Immunology, Hialeah, Fla; anti-Leu-1 (T cells, some B cells in lymphoproliferative disorders), anti-Leu-2a (T suppressor/cytotoxic lymphocytes), anti-Leu-3a (T helper lymphocytes, some histiocytes), and anti-HLA-DR (B cells, monocytes, and activated T cells) from Becton Dickinson Laboratories, Sunnyvale, Calif; T-29/33 (hematopoietic cells) from Hybritech, San Diego; and OKT6 (most thymocytes), OKT9 (transferrin receptor-bearing cells), and OKT10 (primarily hematopoietic stem cells) from Ortho Diagnostics, Raritan, NJ.

Immunologic studies on cells in suspension. The preparation of cell suspensions from solid tissues, the separation of mononuclear cells by Ficoll-Hypaque density gradient centrifugation, and the immunologic study of the cell suspension samples were done as previously described.21,22 Neuraminidase-treated fresh sheep erythrocytes were used for the quantitation of spontaneous sheep erythrocyte rosette (ser) formation.

Immunohistochemical studies on frozen sections. Portions of solid tissues were frozen in isopentane precooled to −120 °C in liquid nitrogen, sectioned at 6-μm thickness, and stored at −70 °C until they were immunostained as previously described.21 Immunoglobulin heavy and light chains were evaluated with the direct technique.23 For evaluation of other surface membrane-associated antigens, we used a modification of the avidin–biotin complex technique.24 Primary antibody was not added to one of the two sections on each slide; this section served as a control for endogenous peroxidase activity. An additional control included substitution of primary antibody by nonimmune serum or ascites fluid. Sections of normal tonsil were used as a positive control.

Flow cytofluorometric analysis. The DNA content of cells in suspension was analyzed using a FACS IV flow cytometer equipped with a 50-μm diameter nozzle (Becton Dickinson FACS Systems, Mountain View, Calif). A 488-nm argon laser line at 400 mW was used for excitation, and the total fluorescence emission above 620 nm was measured. Cells were prepared and stained for DNA content according to previously described techniques.25 Nuclei isolated from chicken erythrocyte nuclei (CENs) were used as an internal standard. The percentage of cells in the S phase of the cell cycle was determined according to model I of the methods of Baish et al.26 The DNA content (degree of ploidy) was indicated by the ratio between the mean channel of the human G0-G1 peak and the CEN peak, as described previously.25

RESULTS

Histopathology findings. Histologic material from 11 samples was obtained during the patient’s eight-month clinical course; the morphologic findings for each of the specimens are described in detail in another report.18 We now briefly summarize the morphologic findings from the eight
tissue samples obtained at the COH and subjected to both morphological and immunologic study (Table 1).

Histologic evaluation of the right inguinal (A) and cervical (B) lymph nodes biopsied on Dec 9, 1982, revealed a spectrum of morphological findings which we interpreted as being consistent with an AIR. The nodal architecture was partially retained, with moderate fibrosis of the capsule and medullary areas. The medullary areas also showed pronounced plasma cell infiltration, vascular proliferation, and depletion of small lymphocytes (Fig 1). In cortical areas, lymphoid aggregates composed of small mature-appearing lymphocytes, with scattered histiocytes and occasional immunoblasts admixed, were present. None of the morphological features indicated the presence of a neoplastic process.

The right axillary lymph node (C) also biopsied on Dec 9, 1982, showed LCL arising in the presence of an AIR, which histologically resembled but did not fulfill all of the histologic criteria of AILD. The normal nodal architecture was partially preserved, with sinus hyperplasia and occasional residual germinal centers present. Focally, however, there was a proliferation of plasma cells, large plasmacytoid

Fig 1. Lymph node (A) involvement by an AIR. Medullary areas are depleted of small lymphoid cells and contain increased numbers of plasma cells and proliferating blood vessels lined by plump endothelial cells. The immunophenotype of the predominant mononuclear cell population was sER", T11", Leu-2a", Leu-3a", HLA-DR", OKT6", OKT9", OKT10" (hematoxylin-eosin stain; original magnification x500, current magnification x500).

Fig 2. Lymph node (C) showing LCL arising in the presence of an AIR. Large lymphoid cells, cytologically different from adjacent plasma cells and plasmacytoid large cells, occur in clusters near proliferating blood vessels. The immunophenotype of the predominant mononuclear cell population, as in lymph node specimen A, was sER", T11", Leu-2a", Leu-3a", HLA-DR", OKT6", OKT9", OKT10" (hematoxylin-eosin stain; original magnification x500, current magnification x500).
lymphoid cells, and vascular channels in an arborizing pattern. Clusters of large lymphoid cells, which had large vesicular nuclei, one to three prominent nucleoli, and moderate amounts of pale cytoplasm, were identified within the plasma cell infiltrates (Fig 2). The atypical large lymphoid cells differed cytologically from the large plasmacytoid cells. The presence of the large cells in clusters and islands was interpreted as indicating the development of LCL, according to criteria similar to those previously described for identifying the evolution of LCL within the histologic picture of AILD.28

The skin specimens from the posterior neck (D) and back (E), also biopsied on Dec 9, 1982, resembled one another and showed involvement by a DM lymphoma with a prominent epithelioid histiocytic reaction (Fig 3). Whereas individual and small clusters of neoplastic lymphoid cells were identified in the epidermis and lymphoid infiltrates were present in perivascular locations in the dermis, the primary site of lymphomatous involvement was the superficial subcutaneous tissue.

The two retroperitoneal lymph nodes (F and G) biopsied during an abdominal laparotomy performed on Jan 13, 1983,
showed diffuse LCL characterized by considerable nuclear pleomorphism (Fig 4). Most cells had large vesicular nuclei of varying shapes, including bilobed nuclei that resembled those observed in Sternberg-Reed cells, as well as hyperlobated, cerebriform, and convoluted forms. Atypical mitotic figures and pyknotic debris were abundant. Neoplastic cells showing erythroagocytosis were also identified.

The lung biopsy specimen (H) obtained on Feb 24, 1983, showed extensive involvement by LCL (Fig 5). The lymphomatous infiltrate was present in the alveolar septa, peribronchial tissues, and pleura. The neoplastic lymphoid cells had vesicular nuclei, an open chromatin pattern, and multiple nucleoli. Occasional bizarre large cells with atypical mitotic figures were admixed. Because of the moderate-to-abundant pale-to-clear cytoplasm, many of the neoplastic cells resembled atypical histiocytes.

Immunopathology findings. Eight tissue samples (A through H) obtained on three different dates were studied by immunohistochemistry on cryostat-cut fresh-frozen sections (CFFS). Immunologic studies were done on cells in suspension (CS) prepared from three lymph node specimens (C, F, and G). The results of the immunologic studies are summarized in Tables 2 and 3.

The immunologic studies done on CS and CFFS from the right axillary lymph node (C), showing the evolution of LCL from the histologic picture of AIR, demonstrated that the immunophenotype of the predominant lymphoid cell population was sER, T11, Leu-1, Leu-2a, Leu-3a, HLA-DR, OKT6, OKT9, OKT10 (hematoxylin-eosin stain; original magnification × 500, current magnification × 500).

**Table 2. Immunologic Characterization of the Predominant Lymphocyte Population Determined by Frozen Section Studies**

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Abbreviations: ++++, positive, but membrane staining increased over normal positivity; ++, normal membrane positivity; +, positive, but quantitatively less than normal membrane positivity; -, no positive staining.
stratified in the studies of CFFS, whereas fewer lymphoid cells in the CS were positive. In the interpretation of the immunologic results, one should consider that the only morphological evidence of malignant lymphoma in this node was the focal presence of small clusters of large lymphoid cells. Nonetheless, the immunologic results were interpreted as indicating the presence of an atypical, if not neoplastic, T cell lymphoproliferative disease.

The predominant cell population in the right inguinal (A) and cervical (B) lymph nodes, the histologic features of which were interpreted as an AIR without morphological evidence of evolution into LCL, had the atypical T cell immunophenotype T11+, Leu-1-, Leu-2a-, Leu-3a-, HLA-DR*, OKT6-, OKT9+, OKT10-. The diffuse pleomorphic LCL involving the left lung (H) studied on Feb 24, 1983, had the immunophenotype T11+, Leu-1-, Leu-2a-, Leu-3a-, HLA-DR+, OKT6+, OKT9+, OKT10-. In contrast to the findings in previous specimens, T11 positivity was not detected. The absence of OKT10 positivity, which was first noted in the retroperitoneal lymph nodes (F and G), was also observed in the lung. The determination of the immunophenotype in this specimen was not difficult, because the neoplastic infiltrate was monomorphous and few residual non-neoplastic lymphoid cells remained.

Table 3. Immunologic Characterization of Lymphocytes in Cell Suspensions Prepared From Biopsied Lymph Nodes

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Abbreviations: + + +, markedly intense; ++, moderately intense; +, faint; NA, not applicable.

* Atypical cells formed sER.

Immunologic studies done on the two skin biopsies (D and E) obtained on Dec 9, 1982, and showing DM lymphoma were limited to CFFS; the CS contained insufficient numbers of cells for analysis. The neoplastic T cell population in the skin expressed the immunophenotype T11+, Leu-2a-, Leu-3a-, HLA-DR*, OKT6-, OKT9+, OKT10-, which was similar to the immunophenotype of the predominant cell populations in the lymph nodes (A through C) studied on the same day, except that the majority of cells in both skin biopsies also expressed OKT9 positivity. The two morphological differences between the lymph nodes (A through C) and the biopsied skin (D and E) were: (1) the lymph nodes showed extensive involvement by an AIR, whereas the skin specimens showed extensive involvement by DM lymphoma and no evidence of an AIR; and (2) diffuse epithelioid histiocytic reactions were present in the skin but absent in the lymph nodes. Because there were few residual nonneoplastic lymphocytes in the skin, we believe that the immunophenotype observed was clearly that of the neoplastic lymphoid cells.

The neoplastic lymphoid populations in the two retroperitoneal lymph nodes (F and G) studied on Jan 13, 1983, had the immunophenotype sER+, T11+, Leu-1+, Leu-2a+, Leu-3a-, HLA-DR+, OKT6-, OKT9+, OKT10-. The percentages of sER+ cells in the retroperitoneal lymph nodes (16% and 19%) were markedly reduced compared with those in the axillary lymph node (80%). Review of the cytospin preparations indicated that only small lymphocytes formed E rosettes, a finding which suggested that the sER+ cells were residual non-neoplastic T cells. Although the majority of the neoplastic cells were T11+, the immunofluorescence intensity in the CS was less than that observed in the earlier study of the axillary lymph node (C). Unlike the skin biopsy specimens, the neoplastic large lymphoid cells in both retroperitoneal lymph nodes did not express the antigens detected by anti-Leu-1, anti-Leu-2a, anti-Leu-3a, or the OKT10 monoclonal antibody.

The diffuse pleomorphic LCL involving the left lung (H) studied on Feb 24, 1983, had the immunophenotype T11+, Leu-1-, Leu-2a-, Leu-3a-, HLA-DR+, OKT6+, OKT9+, OKT10-. In contrast to the findings in previous specimens, T11 positivity was not detected. The absence of OKT10 positivity, which was first noted in the retroperitoneal lymph nodes (F and G), was also observed in the lung. The determination of the immunophenotype in this specimen was not difficult, because the neoplastic infiltrate was monomorphous and few residual non-neoplastic lymphoid cells remained.

Fig 6. DNA analysis of cells obtained from the right axillary lymph node (C). The tallest peak in this histogram corresponds to the tumor G0–G1 cells, and the smaller peak to the left represents CEN, which served as an internal standard for the measurement of the ploidy level. The G0–G1 tumor cells are in a diploid position. No abnormal peaks were noted, and the S fraction was relatively low (3.5%).
**Cell-kinetic findings.** The DNA analysis of cells from the right axillary lymph node (C) showed no evidence of aneuploidy (Fig 6). Most cells were in the G0–G1 phase of the cell cycle and the S fraction was relatively low (3.5%). In contrast, the DNA analysis of cells obtained from the retroperitoneal lymph node (F) revealed a completely different pattern (Fig 7). The DNA distribution showed a distinct aneuploid population positioned at a hypotetraploid level and the fraction of aneuploid cells that were in the S phase of the cell cycle was much larger than that of the supraclavicular lymph node, indicating a higher proliferative activity.

**DISCUSSION**

**Morphological progression of PTCL.** The morphological progression of non-Hodgkin's lymphomas has been well documented. Most reports, however, have described the histologic conversion of low-grade B cell lymphomas (diffuse well-differentiated lymphocytic lymphoma, chronic lymphocytic leukemia [CLL] and follicular lymphomas of the poorly differentiated type), to diffuse LCL, which has a more aggressive clinical behavior. The development of diffuse LCL has been reported to occur in 29% to 44% of adult patients with follicular lymphoma, and it occurs with a high frequency in the rare pediatric patients who have follicular lymphoma. A similar histologic conversion to diffuse LCL has been reported in about 10% of cases with CLL (Richter's syndrome).

Histologic progression in PTCL has been less well studied. For non-Hodgkin's lymphomas with diffuse epithelioid histiocytic reactions (MLEH), which are generally presumed to be a variant of PTCL, the development of diffuse LCL and the loss of epithelioid histiocytic reactions in the course of a patient's illness have been reported for a small number of cases in which immunologic studies were not done or yielded limited results. Conditions resembling AIR and AILD have been associated with some cases of MLEH. To our knowledge, the occurrence of all of these morphologic findings in the same patient was described and documented in a separate report on this 13-year-old patient with PTCL.

We evaluated histologic material from 11 biopsy specimens obtained during the course of our patient's disease; the morphological findings in eight of these specimens are summarized in this report. Based on these findings, we described a variety of morphologic expressions of PTCL in a single patient and suggested that this heterogeneity may be a reflection of the natural biologic course of the lymphoma. The biopsy specimens from our patient demonstrated histologic progression, beginning with AIR and DM lymphoma involving different anatomic sites during early stages of the disease, to pleomorphic diffuse LCL with erythrophagocytic tumor cells near the time of her death. These observations suggest that morphologic transformation of PTCL is expressed by a progressive cellular pleomorphism with the appearance of large often bizarre lymphoid cells, and by the gradual diminution and disappearance of residual B cell areas and of epithelioid histiocytic reactions, which were present initially. We concluded that diffuse pleomorphic LCL represents the final stage of histologic progression in PTCL.

In almost all cases of low-grade B cell lymphomas that were characterized by morphologic progression to higher-grade lymphomas and in which immunologic studies were done, the neoplastic large cells were of the same immunophenotype as the original neoplastic small-cell proliferation, a finding which suggests that the immunophenotype of the neoplastic B cells remains relatively constant during the morphologic progression. Recently, however, switches in light-chain expression have been described in low-grade B cell lymphomas in which clonal evolution and morphologic progression have occurred. In contrast to these studies on B cells, few investigators thus far have focused on the evaluation of the stability of the immunophenotype of neoplastic T cells in PTCL.

**Immunologic observations.** Based on our immunologic studies done on the right axillary lymph node (C) and on skin biopsy specimens (D and E), we believe that sER+, T11+, Leu-2a+, Leu-3a+, HLA-DR+, OKT6−, OKT9+, OKT10+ was the initial immunophenotype of our patient's PTCL. This immunophenotype is abnormal because of the co-expression of Leu-2a and Leu-3a and because of the high HLA-DR and OKT10 positivity. Simultaneous expression of Leu-2a and Leu-3a has been associated with an intermediate level of T cell differentiation corresponding to that of a common thymocyte, a finding that is not expected in a normal lymph node. This co-expression has been identified in cases of neoplastic T cell lymphoproliferative disorders, including T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma and T cell prolymphocytic leukemia, as well as in rare cases of Japanese adult T cell leukemia/lymphoma syndrome and cutaneous T cell lymphoma. The expression of both Leu-2a and Leu-3a has been noted in

![Fig 7](Image) DNA analysis of cells obtained from the retroperitoneal lymph node (F). The first peak corresponds to CEN. The second peak represents diploid G0–G1 cells, and the tallest peak corresponds to aneuploid (hypotetraploid) tumor cells. The S fraction for the tumor cells was high. The diploid cells are non-neoplastic elements and/or diploid tumor cells.
several cases of PTCL previously reported from North America.17

The prominent HLA-DR positivity and the expression of OKT10 were other unusual immunologic findings. Positivity for HLA-DR has been associated with T cells in activated states40,47 and in PTCL.17,31,32 Positivity for OKT10 is associated with immature hematopoietic cells and activated lymphocytes.33,50 Because the morphological findings in the skin clearly indicated involvement by lymphoma and not a reactive process, we concluded that sER+, T11+, Leu-2a+, Leu-3a+, HLA-DR+, OKT6+, OKT9+, OKT10+ was the initial immunophenotype of our patient’s PTCL. This interpretation is in agreement with the concepts of others who have suggested that an unusual immunophenotype (in this case, the co-expression of the Leu-2a and Leu-3a antigens and the expression of antigens associated with T cell activation [HLA-DR, OKT9, OKT10]) may be indicative of T cell neoplasia.3,17,51

Immunologic studies done on samples obtained from subsequent biopsies, however, revealed that sER+, T11+, Leu-2a+, Leu-3a+, HLA-DR+, OKT6+, OKT9+, OKT10+ was not a stable immunophenotype and there were several significant changes in immunologic expression during the course of the patient’s disease. Regarding the evaluation of the lung biopsy (H), the natural histologic progression and immunologic dedifferentiation of this patient’s PTCL cannot be fully assessed, since multi-agent aggressive chemotherapy was initiated after the retroperitoneal biopsies (F and G) had been performed. However, we believe that the morphological and immunologic findings described for samples studied prior to Jan 15, 1983, represented natural expressions of PTCL.

Immunologic studies done on the two retroperitoneal lymph nodes (F and G) biopsied one month after the skin biopsies (D and E) revealed a change in the immunophenotype of the PTCL. The marked reduction in the number of sER+ cells and the continued presence of T11+ positivity suggest the presence of a nonfunctioning E rosette receptor site. The inability of the neoplastic T cells in PTCL to form E rosettes has also been observed by others.24 The loss of the co-expression of the Leu-2a and Leu-3a antigens is consistent with dedifferentiation of the neoplastic T cells to a more immature thymocyte stage.33,54 The markedly reduced number of sER+ cells and the loss of Leu-2a and Leu-3a positivity did not indicate conversion to a “null” or “non-B non-T” immunophenotype, since the neoplastic cells continued to be T11+. The increased HLA-DR and OKT9 positivity in these samples was correlated with an increased percentage of neoplastic large T cells.

In the lung biopsy specimen (H), expression of the T11 antigen was lost, leaving only HLA-DR and OKT9 positivity; this immunophenotype is consistent with cells showing little evidence of lymphoid differentiation. If this had been the only tissue obtained for immunologic study, there would have been no immunologic evidence that this was a T cell lymphoma, and the immunophenotype would have been consistent with a non-B non-T (null) cell lymphoma, or a true histiocytic malignancy.2,31,53 The loss of T11 positivity may have resulted from aggressive multi-agent chemotherapy, or it may indicate that the neoplastic lymphoid cell population again shifted to a more immature stage of differentiation. A similar loss of pan-T cell antigens over time was recently reported in rare patients with PTCL,17,51 and in three patients with adult T cell leukemia from whom specimens were studied at relapse.47

**Atypical immune reactions and PTCL.** The presence of lymph nodes (A and B) with the morphological features of AIR in a patient with PTCL may have several interpretations: (1) the presence of AIR was coincidental and was not related to the patient’s PTCL; (2) AIR may represent a prelymphomatous state; and (3) AIR may represent a morphological expression of PTCL.19 If AIR is a morphological expression of PTCL, we know of no current criteria for establishing its neoplastic nature on the basis of histologic material alone. However, the presence of atypical large lymphoid cells in clusters within the morphological picture of an AIR involving the axillary lymph node (C) indicated evolution into LCL. We base this interpretation on: (1) our previous experience with AILD and the development of LCL25; (2) the fact that malignant lymphoma was evident in several other anatomic sites biopsied at the same time; and (3) the results of immunologic analysis.

The observation that the predominant cell population in the two lymph nodes (A and B) showing AIR only had the same immunophenotype as the lymph node (C) with the histologic picture of LCL evolving in AIR, and the fact that this immunophenotype was similar to that of the DM lymphoma involving the skin (D and E) has important implications. In this case, the AIR may represent early forms of PTCL that cannot be recognized on the basis of morphological criteria alone. Alternatively, the AIR may be similar to AILD and may represent an altered immunologic “microenvironment” which may (1) lead to the evolution of PTCL34 or (2) accompany or represent PTCL.8,17,28,52 The findings that the predominant lymphoid population expressed the HLA-DR and OKT10 antigens and that there was an apparent dedifferentiation of the lymphoid cells to the cortical thymocyte level as indicated by the coexpression of the Leu-2a and Leu-3a antigens are compatible with either a hyperreactive regenerative state of the immune system49 or with T cell neoplasia.17,52 The present patient had no clinical or morphological evidence of immune system reconstitution, and the immunophenotypes of the predominant cell populations in the lymph nodes (A and B) showing AIR only, and in the lymph node (C) showing AIR and LCL, were essentially identical to that of the DM lymphoma involving the skin (D and E). Therefore, we believe that the AIR was either a morphological manifestation of PTCL or an immune microenvironment representing a prelymphomatous state.

**Biologic progression of PTCL.** Our observations in this case indicate that PTCL may show rapidly changing clinical, morphological, immunologic, and cell-kinetic findings that are best appreciated and evaluated by multidisciplinary studies. The morphological findings from multiple sequential biopsies enabled us to follow the natural biological progression of this patient’s PTCL. The early morphological expressions of the PTCL (DM lymphoma with a bland cytologic appearance and focal LCL evolving in an AIR)
were associated with (1) an immature T cell immunophenotype corresponding to cortical thymocytes, and (2) cell-kinetic findings that showed few cells in the S phase and no evidence of aneuploidy. During the early phase of her disease, the patient received only intermittent low-dose steroid therapy.

The development of diffuse LCL with pleomorphism in the retroperitoneal lymph nodes was accompanied by further dedifferentiation of the neoplastic T cells to a stage in which the only T cell marker expressed was T11. Moreover, cell-kinetic studies clearly demonstrated the presence of a distinct aneuploid population of cells which was positioned at the hypotetraploid level. There was also a dramatic increase in the percentage of cells in the S phase to a level associated with high-grade lymphomas. During this phase, the patient developed disseminated and bulky disease which responded to a limited extent to aggressive chemotherapy. Following the institution of aggressive chemotherapy and during the patient’s terminal phase, the PTCL expressed a null cell immunophenotype.

The immunologic findings in this case, which we attribute to the biological progression of PTCL, have important implications for diagnosis and treatment. The demonstration of an atypical T cell immunophenotype in a lymph node which has the morphological features of AIR should raise the suspicion of PTCL. Atypical T cell immunophenotypes include: (1) co-expression of Leu-2a and Leu-3a antigens, (2) high expression of HLA-DR, OKT9, and OKT10 antigens, and (3) loss of expression of one or more pan-T cell antigens. The immunophenotype of the neoplastic T cells of PTCL may be subject to rapid changes; thus, detection of minimal or recurrent lymphoma may be missed if immunologic studies are based on one or only a few immunologic markers. This contrasts with the relative sensitivity and reliability of following B cell lymphomas according to the criteria of monoclonality, or of following certain acute lymphoblastic leukemias by using specific markers (terminal deoxynucleotidyl transferase, common acute lymphocytic leukemia antigen, etc.). Because there was no immunologic evidence of T cell differentiation in our patient’s lung biopsy specimen, which showed involvement by PTCL, it appears that, as a result of either chemotherapy or biological progression, the T cell nature of the lymphoma is not always demonstrable immunologically. Finally, the potential instability of the immunophenotype of the neoplastic T cells may limit the successful treatment of PTCL with monoclonal antibodies.

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Peripheral T cell lymphoma: immunologic and cell-kinetic observations associated with morphological progression

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