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# Large cell anaplastic lymphoma: evaluation of immunophenotype on paraffin and frozen sections in comparison with ultrastructural features

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**Summary.** Eleven cases of large cell anaplastic lymphoma (T type $n=5$, B type $n=4$, 0 type $n=2$) were investigated using electron microscopy and immunophenotyping on formalin-fixed paraffin sections and frozen sections of fresh tissue, to determine whether morphological criteria exist for the discrimination of T, B, and 0 phenotypes. Tumour cell lineage could not be established from ultrastructural features. On paraffin material monoclonal B-cell markers Ki-B5 and L-26 served as reliable tools for recognizing the B phenotype of large cell anaplastic lymphomas (previously determined on fresh material), whereas monoclonal antibodies MT1 (CD43) and UCHL1 (CD45RO) were of limited value in lineage determination.

**Key words:** Large cell anaplastic lymphoma – Electron microscopy – Immunophenotyping

## Introduction

The monoclonal antibody (mAb) Ki-1 (CD30; Schwab et al. 1982) detects an antigen on reactive and neoplastic lymphoid cells in the activation stage (Stein et al. 1985). In Hodgkin's disease (HD) these "activated" cells are usually Hodgkin and Sternberg-Reed cells. However, in approximately 5%–10% of non-Hodgkin's lymphoma (NHL) cases, particularly those containing large blasts, some tumour cells react with this mAb (Stein et al. 1985). The mAbs Ki-1 and BerH2 (Schwarting et al. 1988) are especially useful in characterizing a malignant tumour of large-cell type. This tumour was often interpreted in the past as a malignant histiocytosis (Osborne et al. 1980), but is now recognized as a malignant lymphoma classified as large cell anaplastic lymphoma (LCAL) of T, B, or 0 type in the updated Kiel classification (Stansfeld et al. 1988). The entire tumour cell population in these lymphomas shows a positive immunostaining with the CD30 antibodies Ki-1 and BerH2.

The tumour cells in LCAL possess a characteristic cytology with round to irregularly shaped large nuclei, abundant greyish cytoplasm in Giemsa staining, and often an intrasinusoidal growth pattern similar to that of carcinomas (Osborne et al. 1980). While light microscopic morphology and immunohistochemistry of LCAL have been investigated in detail (Gerdes et al. 1986; Stein et al. 1985; Suchi et al. 1987; Agnarsson et al. 1988; Hall et al. 1988; Chan et al. 1989; Chott et al. 1990), only one paper has dealt with its ultrastructural features (Le Tourneau et al. 1988). In that study only four cases of LCAL T type were investigated. Recently, Burns et al. (1989) reported on the ultrastructural features of one further case of Ki-1 LCAL with clonally rearranged T-cell receptor.

In the present study immunohistologically defined types of LCAL were examined. We evaluated the ultrastructural features not only of the T type of LCAL, but also of the B and 0 types in order to identify features which may be used to discriminate between the B, T and 0 types. In addition, the reliability of mAbs in recognizing different phenotypes of LCAL in paraffin sections was investigated.

## Materials and methods

Eleven cases of LCAL were investigated using electron microscopy and immunophenotyping on both fresh and formalin-fixed tissue. The diagnosis was established based on characteristic light microscopic morphology and a positive reaction of the tumour cells with CD30. Six patients had developed primary LCAL without evidence of pre-existing malignant lymphoma of another type. In 2 other patients LCAL had developed from low-grade NHL of T type. Three further patients had a clinical history of HD nodular sclerosis type (case 5) or mixed cellularity type (cases 8 and 10). Paraffin sections were stained with haematoxylin and eosin, Giemsa, periodic acid-Schiff and Gomori's silver impregnation.

For immunohistochemistry 3-μm paraffin sections were deparaffinized in xylol and immunostained according to the APAAP

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**Table 1.** Immunoreactivity and source of monoclonal antibodies

| Monoclonal antibodies | Immunoreactivity | Source |
|---|---|---|
| *Paraffin sections* | | |
| CD30 (BerH2) | Hodgkin cells "Ki1 lymphoma" | Schwarting et al. (1988) |
| Ki-B3 | Small lymphocytes of follicle mantle, a few inter- and intra-follicular lymphocytes, germinal center cells, plasma cells | Hansmann et al. (1986) Feller et al. (1987) |
| Ki-B5 | Pan B cell | Hansmann et al. (1991) |
| L26 | Pan B cell | Dakopatts, Copenhagen, Denmark |
| MT1 (CD43) | Lymphocytes in T-cell area, a few lymphocytes within the follicle center, myeloid cells, macrophages, B-cell subset | Laboserv Diagnostic, Gießen, FRG |
| CD45RO (UCHL1) | T cells, myeloid cells | Dakopatts, Copenhagen, Denmark |
| CD15 (LeuM1) | Myeloid cells, many Hodgkin cells | Becton Dickinson, Mountain View, CA |
| *Frozen sections* | | |
| CD30 (Ki1) | Hodgkin cells "Ki1 lymphoma" | Schwab et al. (1982) |
| CD19 | B cells | Dakopatts |
| CD22 (HD39) | B cells | Moldenhauer et al. (1986) |
| CD2 (OKT11) | T cells | Ortho-Diagnostics, Heidelberg, FRG |
| CD3 (Leu1) | T cells | Becton Dickinson |
| CD4 (Leu3a) | T helper/inducer cells | Becton Dickinson |
| CD8 (Leu2a) | T cytotoxic/suppressor cells | Becton Dickinson |
| Ki67 | Proliferating cells | Dakopatts |

method (Cordell et al. 1984). The immunoperoxidase reaction was applied on 5-μm frozen sections according to Stein et al. (1982). The primary mAbs used in this study are listed in Table 1.

For electron microscopy 1-mm$^3$ blocks of tumour infiltrate were fixed in 4% glutaraldehyde, post-fixed in 1% osmium tetroxide and embedded in araldite. The ultrathin sections were stained with uranyl acetate and lead citrate and investigated with a Siemens Elmiscope 101.

## Results

The age and sex of the patients and the tumour localization are listed in Table 2. Of the 11 patients, 8 were male and 3 were female. The youngest patient was 30 years old and the oldest was 78. Lymph nodes of cervical ($n=3$), supraclavicular ($n=1$), axillary ($n=2$), inguinal ($n=2$) and mesenteric ($n=2$) origin and the spleen ($n=1$) were involved.

The immunohistochemical results on frozen and paraffin sections are listed in Tables 3 and 4.

On frozen sections tumour cells in all 11 cases reacted with mAb Ki-1 (CD30). Four of the 11 cases reacted positively with CD4 and another case reacted positively with CD2. CD3 was not detectable on tumour cells. Four cases exhibited a B phenotype (CD22 positive) and 2 cases were negative for both T- and B-cell markers. The proliferation rate of LCAL detected with mAb Ki-67 varied from 50% to 90%.

In paraffin sections all cases showed a positive reaction with mAb BerH2 (CD30) (Fig. 1). The 5 cases exhibiting a T-cell phenotype in frozen sections also reacted with mAbs UCHL1 (CD45RO) and MT1 (CD43), which chiefly recognize T cells on formalin-fixed material. However, 2 cases presenting as B-cell type in frozen sections also showed a weakly positive reaction with mAb UCHL1 or MT1 in paraffin sections (cases 4 and 9). mAbs L26 and Ki-B5 (Fig. 2) detected the lymphoma cells in only the 4 cases of LCAL with B-cell phenotype. No positive reaction with mAb Ki-B3 was seen. Two cases (nos. 6 and 11) showed a positive reaction of some tumour cells with CD15 (LeuM1).

The morphological and ultramicroscopical features

**Table 2.** Age and sex of patients and lymph node (LN) or tumour localization

| Case no. | Age (years) | Sex | Localization |
|---|---|---|---|
| 1 (s) | 32 | M | LN cervical |
| 2 (p) | 76 | F | LN mesenteric (jejunum) |
| 3 (p) | 49 | M | LN supraclavicular |
| 4 (p) | 62 | M | LN mesenteric |
| 5 (s) | 46 | F | LN axillary |
| 6 (s) | 59 | M | LN cervical |
| 7 (p) | 35 | M | LN inguinal |
| 8 (s) | 78 | M | LN cervical |
| 9 (p) | 50 | M | Spleen |
| 10 (s) | 50 | M | LN axillary |
| 11 (p) | 30 | F | LN inguinal |

p, Primary large cell anaplastic lymphoma (LCAL); s, secondary LCAL (in cases 1 and 6 secondary to pre-existent low-grade T-NHL; in cases 5, 8 and 10 secondary to Hodgkin's disease)

**Table 3.** Immunoreactivity of LCALs in frozen sections

| Case no. | Monoclonal antibodies | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CD30 | CD19 | CD22 | CD2 | CD3 | CD4 | CD8 | Ki-67 |
| 1 | + | − | − | − | − | − | − | NA |
| 2 | + | NA | − | − | − | − | − | 70% |
| 3 | + | NA | + | − | − | − | − | NA |
| 4 | + | + | + | − | − | − | − | 60% |
| 5 | + | NA | − | + | − | + | − | NA |
| 6 | + | NA | − | − | − | + | − | 50% |
| 7 | + | NA | − | − | − | + | − | 70% |
| 8 | + | + | + | − | − | − | − | 60% |
| 9 | + | NA | + | − | − | − | − | 70% |
| 10 | + | NA | − | − | − | + | − | 70% |
| 11 | + | NA | − | + | − | − | − | 90% |

+, Positive (all tumour cells); −, negative; NA, not analysed; %, estimated percentage of tumour cells with granular nuclear Ki-67 positivity

**Table 4.** Immunoreactivity of LCALs on paraffin sections

| Case no. | Frozen section phenotype | Monoclonal antibodies | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | BerH2 (CD30) | Ki-B3 | Ki-B5 | L26 | UCHL1 | MT1 (CD43) | CD15 |
| 1 | 0 | + | − | − | − | − | ± | − |
| 2 | 0 | + | − | − | − | − | − | − |
| 3 | B | + | − | + | + | − | − | − |
| 4 | B | + | − | + | + | (+) | − | − |
| 5 | T | + | − | − | − | ± | ± | − |
| 6 | T | + | − | − | − | ± | ± | ± |
| 7 | T | + | − | − | − | + | (+) | − |
| 8 | B | + | − | + | + | − | + | − |
| 9 | B | + | − | + | + | − | ± | − |
| 10 | T | + | − | − | − | (+) | + | − |
| 11 | T | + | − | − | − | ± | + | ± |

+, Positive (all tumour cells); (+), weak positivity; −, negative; ±, positivity in small number of tumour cells

**Table 5.** Ultrastructural features of the nuclei of LCALs

| Case no. | Type | Nucleus | | Nucleoli | | |
|---|---|---|---|---|---|---|
| | | polymorph | round | at the nuclear membrane | central | large |
| 1 | 0 | + | + | + | + | + |
| 2 | 0 | + | + | − | + | ++ |
| 3 | B | + | − | + | + | ++ |
| 4 | B | (+) | + | − | + | ++ |
| 5 | T | + | − | − | + | ++ |
| 6 | T | + | − | − | + | − |
| 7 | T | + | + | + | + | + |
| 8 | B | + | − | − | − | − |
| 9 | B | + | − | − | + | + |
| 10 | T | + | − | − | + | + |
| 11 | T | + | − | + | + | (+) |

++, Frequent; +, occasional; (+), rare; −, lacking

**Table 6.** Ultrastructural features of the cytoplasm of LCALs

| Case no. | Type | Polyribosomes | Ergastoplasm | Mitochondria | Golgi apparatus | Lysosomes |
|---|---|---|---|---|---|---|
| 1 | 0 | ++ | + | + | + | + |
| 2 | 0 | ++ | (+) | ++ | − | + |
| 3 | B | ++ | (+) | + | ++ | ++ |
| 4 | B | + | + | + | ++ | (+) |
| 5 | T | + | (+) | (+) | ++ | − |
| 6 | T | ++ | + | (+) | − | (+) |
| 7 | T | ++ | (+) | (+) | ++ | (+) |
| 8 | B | + | ++ | (+) | (+) | + |
| 9 | B | ++ | + | (+) | ++ | ++ |
| 10 | T | ++ | ++ | + | + | + |
| 11 | T | + | ++ | ++ | − | + |

++, Frequent; +, occasional; (+), rare; −, lacking

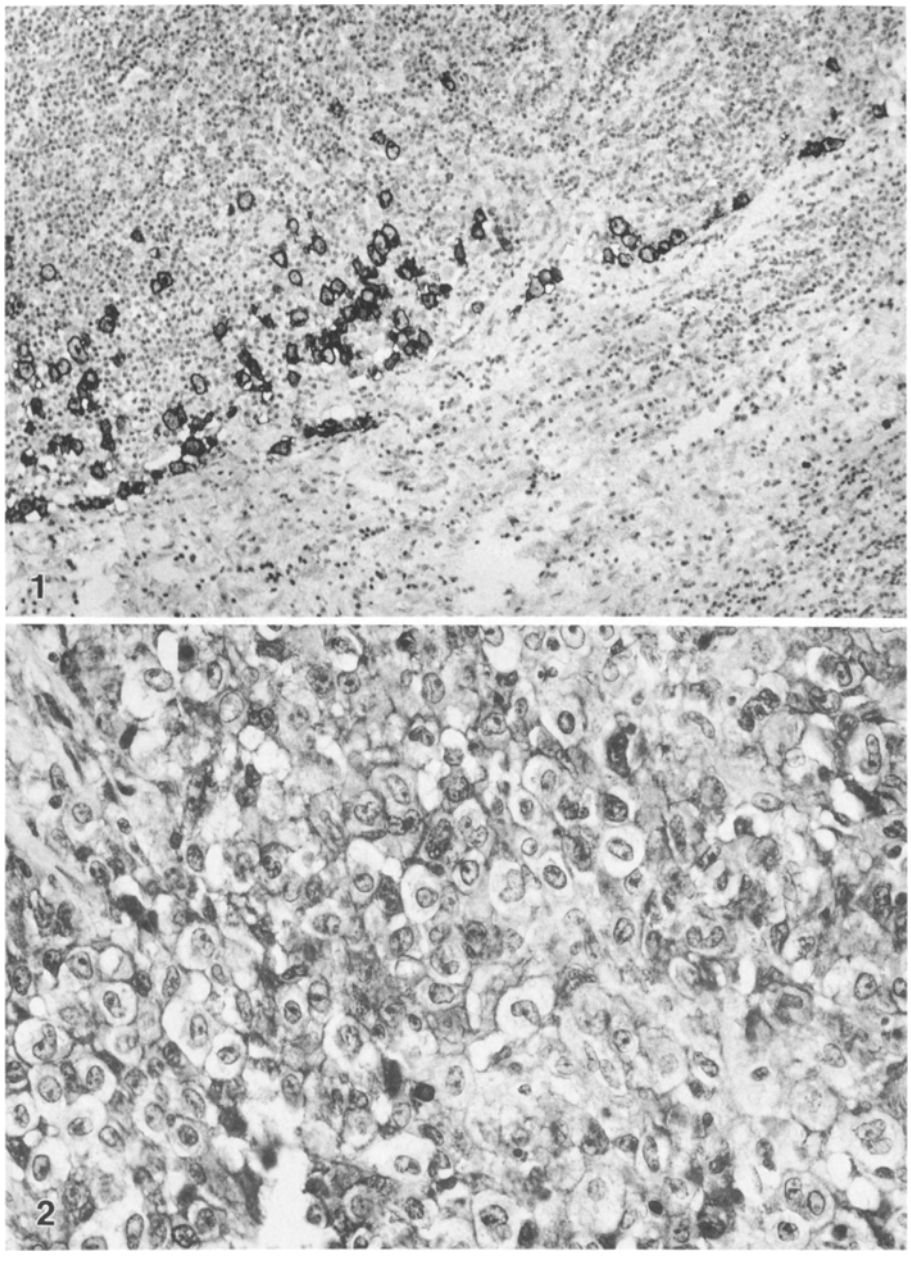


**Fig. 1.** Large cell anaplastic lymphoma (LCAL) positive with monoclonal antibody (mAb), CD30 (BerH2) showing an intrasinusoidal growth pattern. Paraffin section, APAAP, ×180

**Fig. 2.** LCAL of B type positively stained with mAb Ki-B5. Paraffin section, APAAP, ×360

of the tumour cells are summarized in Tables 5 and 6. The nuclei were generally polymorphic and occasionally also round or irregularly shaped. The nucleoli were usually large and centrally located and only occasionally located at the nuclear membrane.

Examination of LCAL-cell cytoplasm revealed variable numbers of polyribosomes in both T-cell and B-cell types (Fig. 3) of LCAL. Relatively high numbers of polyribosomes were found in the 2 cases of O type. The ergastoplasm was usually not well developed in all types of LCAL. Relatively large amounts were present in 2 cases of T type (nos. 10 and 11) (Fig. 4). Moderate numbers of mitochondria were found in all cases of LCAL. The Golgi apparatus was well developed in 5 cases, irrespective of the B- or T-cell phenotype of the tumour cells. Lysosomes were found consistently, usually in small numbers but occasionally also in moderate numbers.

Plasma cells, macrophages with numerous lysosomes and small lymphocytes with irregularly shaped nuclei were often found in the vicinity of the tumour cells.

A differentiation between immunohistochemically predetermined T, B and O types was not possible based on these morphological features.

## Discussion

The cases of LCAL investigated in this study exhibited a broad range of ultrastructural features including high variability in nuclear shape, in localization of the nucleoli and in quantity as well as distribution of the intracellu-

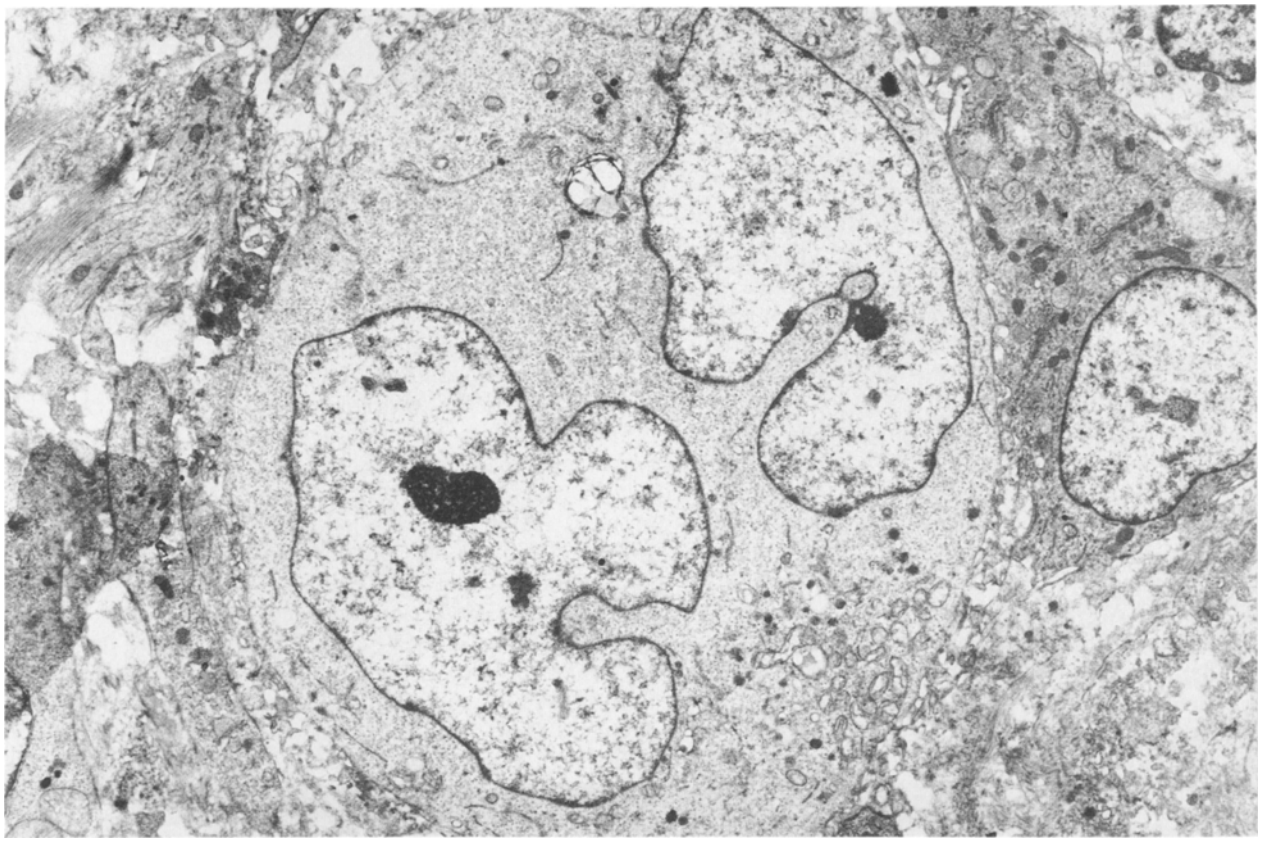

**Fig. 3.** Large tumour cell with features of Reed-Sternberg cell showing two large, irregularly shaped nuclei with two nucleoli and an abundant cytoplasm. Some lysosomes and mitochondria focally arranged (right side of the cell). LCAL of B type. Electron micrograph, ×8000

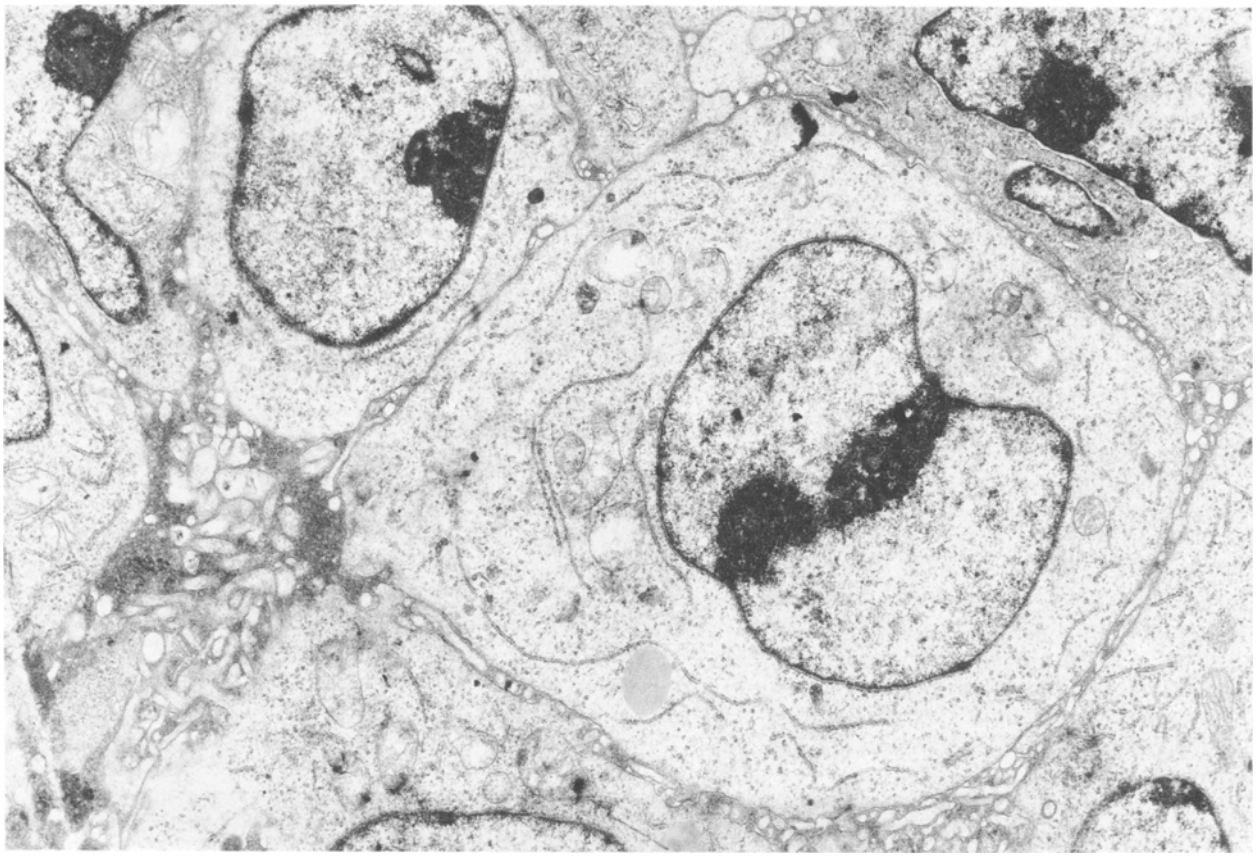

**Fig. 4.** Tumour cells of an LCAL of T type exhibiting a relatively large amount of rough endoplasmic reticulum. Electron micrograph, ×5500

lar organelles. While no distinctive ultrastructural features have been found which permit certain morphological differentiation of T and B lineage of lymphocytes, some features at least suggest T- or B-cell lineage. T cells usually show more irregularly shaped nuclei than B lymphocytes. Furthermore, aggregated lysosomes can often be found in the cytoplasm of T cells, whereas B cells, especially in higher differentiation stages (such as lymphoplasmacytoid cells/plasma cell) exhibit many polyribosomes and well-developed ergastoplasmic profiles (Kaiserling 1977; Müller-Hermelink and Lennert 1978; Peters et al. 1987).

In the cases of LCAL reported by Le Tourneau et al. (1988), all of T-cell phenotype, polyribosomes were found in variable numbers. Although a small number of polyribosomes is a frequent finding in lymphoid cells of T type, the cases examined in the present study showed a variable number of polyribosomes in all types, regardless whether of T or B phenotype. In addition, a large number of polyribosomes was seen in LCAL of 0 type. The ribosomal structures may be interpreted as an indicator of tumour cell lymphokine production. In the majority of cases ergastoplasmic profiles were only found occasionally, but did represent a frequent finding in 3 cases (nos. 8, 10, and 11). Two of these 3 cases were not of B-cell type as one would expect, but expressed T-cell phenotype on frozen sections (Tables 3, 6). Additionally, the number of mitochondria, Golgi apparatus and lysosomes proved to be no indication of any lineage derivation of the tumour cells. Thus, ultrastructural features provided no specific information on the nature of these CD30+ cells. An explanation for this may be that the tumour cells comprising LCAL are stimulated lymphoid cells of a low degree of differentiation (Herbst et al. 1989).

A close relationship between tumour cells of LCAL and Hodgkin cells is postulated (Stein et al. 1985). Both tumour cell types express a similar (but not identical) marker constellation with CD30 positivity and T- or B-cell phenotype (Stein et al. 1985; Falini et al. 1987; Pinkus and Said 1988; Cibull et al. 1989). In our case 8, LCAL of B phenotype developed from HD of mixed cellularity type. The transitional stage between HD and LCAL is synonymous with the term Hodgkin's sarcoma. The diagnosis of HD had been made 2 years earlier, but unfortunately no biopsy material was available for immunohistochemical examination. B phenotype of Hodgkin cells is usually present in the paragranuloma type of HD but is also reported in rare cases of other types (Hall et al. 1988; Pinkus and Said 1988).

The myeloid antigen CD15, originally thought to be a marker for HD, is no longer regarded as a sensitive or specific tool in the diagnosis of HD (Hall and D'Ardenne 1987). Tumour cells from cases of LCAL included in this study were negative for the CD15 antigen in 9 of 11 cases, which is in accordance with other findings in the literature (Agnarsson and Kadin 1988).

According to O'Connor et al. (1987), in determination of LCAL cell lineage, genotypic analysis reveals a discrepancy between genotype and phenotype. Two out of 16 cases with T-cell genotype exhibited B-cell phenotype (CD22+); however, 2 out of 6 LCALs with B-cell genotype showed expression of both B- and T-cell surface markers (CD22+, CD3+, CD4+).

Comparing immunohistochemical results on formalin-fixed, paraffin-embedded material with those of antigen detection on fresh snap-frozen material, the lineage indicated by paraffin and fresh material immunohistochemistry was concordant in 7 of 11 cases. Only the cases of B type, as determined in frozen sections, were recognized by mABs L26 and Ki-B5. mAbs UCHL1 (CD45RO) and MT1 (CD43), which chiefly recognize T cells, exhibited a positive reaction with B types. MT1 also showed a partial positive reaction in 1 case of 0 type (case 1). The limited lineage specificity of these "T-cell markers" on paraffin sections has been reported in the literature (Mason and Gatter 1987; Poppema et al. 1987; Fellbaum et al. 1989; Norton and Isaacson 1989), and of these, UCHL1 (CD45RO) seems to be the more reliable T-cell marker on paraffin sections.

*In conclusion*, only a panel of mAbs applied on paraffin material may provide clues as to the lineage of LCAL. According to our results, the B-cell markers Ki-B5 and L26 are reliable indicators of B-cell phenotypes of LCAL. Electron microscopy does not facilitate the determination of LCAL derivation.

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**Note added in proof.** After submitting this paper an ultrastructural study of 26 cases of Ki-1 lymphomas was published by Rivas et al. (1990) (Ultrastruct Pathol 14:381–397)

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