Virchows Arch [Pathol Anat] (1985) 405:439–452

Virchows Archiv A

The blood microvasculature in T-cell lymphomas

A morphological, ultrastructural and immunohistochemical study

C. Kittas[1], M.-L. Hansmann[2], Bettina Borisch[2], A.C. Feller[2], and K. Lennert[2]

[1] Department of Pathology, University of Athens, Medical School, Ampelokipi – Goudi 11527, Athens, Greece
[2] Institut für Pathologie, Klinikum der Christian-Albrechts-Universität, Hospitalstr. 42, D-2300 Kiel 1, FRG

Summary. The microvasculature of lymph nodes of 55 cases of T-cell lymphoma was studied by light microscopy, immunohistochemistry and electron microscopy. A modified peroxidase-antiperoxidase (PAP) method was used for staining paraffin sections with lectin I of Ulex europaeus (UEA-I), which is a specific marker for vascular endothelial cells. The T-cell nature of each case was proven by immunohistochemistry, including immunoperoxidase staining of frozen sections with monoclonal T-cell antibodies. The cases were subclassified according to previously established criteria, but with the addition of a separate group showing a high content of clear cells. For the purpose of the present study, the small blood vessels were separated into two main variants, viz.: high endothelial venules (HEV) and all other types of vessels with flat endothelium (SVFE). The development of each of these variants and the extent of lymphocyte migration through the vascular wall were assessed semiquantitatively.

The findings suggest that the blood microvasculature, as a whole, is similar in all types of T-cell lymphoma. There were distinct differences, however, in the development of the two main categories of small vessels between the various types. Chronic lymphocytic leukaemia of T-type (T-CLL) and Sézary's syndrome were poor in SVFE and rich in HEV, and there was considerable lymphocyte traffic through the latter. In contrast, T-immunoblastic and especially T-lymphoblastic lymphomas showed numerous SVFE, only a few or no HEV and minimal lymphocyte traffic. The appearance of the microvasculature varied markedly in the various subtypes of "pleomorphic T-cell lymphoma". In the small cell subtype HEV predominated and SVFE represented only a small or moderate fraction of the microvasculature. As the size of the neoplastic lymphoid cells increased towards the medium-sized and large cell

Offprint requests to: K. Lennert at the above address

subtype, there was a decrease in the number of HEV and an increase in the number of SVFE accompanied by a decrease in lymphocyte migration. In T-cell lymphoma of the clear cell type the microvasculature showed features between those of T-CLL and the small cell subtype of pleomorphic T-cell lymphoma.

Electron microscopy confirmed the light microscopic findings and revealed many similarities in vascular changes between "pleomorphic T-cell lymphomas" and lymphogranulomatosis X.

Key words: T-cell lymphoma – Microvasculature – Ultrastructure – Immunohistochemistry – Ulex europaeus lectin I

Introduction

The lymph node blood microvasculature consists of arterioles, metarterioles, arcades of anastomosing capillaries, small venules and the so-called epithelioid or high endothelial "postcapillary" venules (HEV), which finally merge into collecting venules and small veins lined with flat endothelium. There are also numerous arteriovenous communications (Anderson et al. 1975). HEV are generally thought to be the most important route of lymphocyte recirculation from the blood into lymphoid tissues (Gowans and Knight 1964; Marchesi and Gowans 1964). Thus, in the past two decades, there have been a large number of publications concerning the structural, histochemical and metabolic characteristics of HEV in normal and stimulated mammalian lymph nodes (Krüger 1968; Röpke et al. 1972; Anderson et al. 1973; Kittas and Henry 1980; Kittas and Henry 1981; Kittas et al. 1981). In addition, since HEV are a unique vascular site for the selective passage not only of T-(Syrjänen 1978 and 1979), but also of B-lymphocytes (Kotani et al. 1974; Chin et al. 1982), many authors were prompted to study the mechanism of the specific interaction between the endothelial cells HEV and lymphocytes (Andrews et al. 1980; Chin et al. 1982).

Alterations of other parts of the lymph node blood microvasculature under the influence of various antigenic stimuli have also been described (Herman et al. 1972 and 1979; Anderson et al. 1975), but their morphology, ultrastructure and histochemistry have been studied less extensively than those of HEV.

Knowledge of the vascular changes in lymphomas is fragmentary, with the exception of the pathogenically controversial entity called lymphogranulomatosis X (or angioimmunoblastic lymphadenopathy) (Frizzera et al. 1975; Lukes and Tindle 1975; Neiman et al. 1978; Knecht and Lennert 1981). HEV have been reported to be numerous in T-zone lymphoma and pleomorphic T-cell lymphoma, in which they represent a characteristic feature of the tumour (Lennert 1981; Lennert et al. 1982). HEV have also been observed in chronic lymphocytic leukaemia of T type (T-CLL), mycosis fungoides and Sézary's syndrome (Lennert 1981; Robb-Smith and Taylor 1981), and they may be very prominent in some cases of immunocytoma (Lennert and Mohri 1978). Other parts of the lymph node blood microvascu-

lature are mentioned less often, if ever, in the various descriptions of malignant lymphomas.

It is often impossible to type lymphomas, especially T-cell lymphomas, by morphological criteria alone. Studies using a combination of morphological and highly sophisticated cytochemical and immunohistochemical methods, however, not only enable us to classify a neoplasm according to the cell of origin, but also provide data for a further subclassification of the tumour. Recently, T-cell lymphomas and leukaemias were classified on the basis of results obtained in such a multi-variable study (Lennert et al. 1982). But this was a very beginning. the category "pleomorphic T-cell lymphoma", especially, has to be subdivided into some further types (Lennert et al. 1985).

Here we report the light microscopic, ultrastructural and immunohistochemical features of the blood microvasculature in the various subgroups of T-cell lymphoma defined by the primitive classification of 1982. Any differences seen in the microangioarchitecture could the used as additional criteria for such subclassification. This was the main scope of our work and that is why the present study deals only with lymphomas of T-lymphocytic origin and not with other lymphomas or non-malignant lymph node diseases. Since lectin I of Ulex europaeus (UEA-I) has been found to be a marker for human endothelial cells (Holthöfer et al. 1982; Yonezawa et al. 1982), paraffin sections were also stained with a modified peroxidase-antiperoxidase (PAP) method, using a commercially available UEA-I and the corresponding anti-lectin, for a more detailed analysis of the vessels.

Material and methods

Fifty-five cases of malignant non-Hodgkin's lymphoma were examined. The T-cell origin of the neoplastic cells was proven by immunohistochemistry in all cases. Frozen sections were stained with an immunoperoxidase method described in detail elsewhere (Stein et al. 1982). Briefly, cryostat sections were fixed in acetone and incubated for 30 min with the panel of monoclonal antibodies to T-cell subpopulations used in the previous study (Lennert et al. 1982). The sections were then treated with peroxidase-conjugated rabbit anti-mouse Ig (DAKO Immunoglobulins, Copenhagen, Denmark) and goat anti-rabbit IgG antibody (Medac, Hamburg, FRG). Peroxidase activity was demonstrated with diaminobenzidine (0.6 mg/ml) and hydrogen peroxide (0.01%).

Paraffin sections of formalin-fixed tissue were stained with Giemsa, haematoxylin and eosin (H&E), silver impregnation (Gomori) and periodic acid Schiff (PAS).

For the specific demonstration of vascular endothelium with UEA-I (Holthöfer et al. 1982), paraffin sections were stained by the PAP method (Graham and Karnovsky 1966; Sternberger et al. 1970; Taylor and Burns 1974) with the following modification. After blocking of endogenous peroxidase, the sections were rinsed in phosphate-buffered saline (PBS) and then incubated with commercially available UEA-I (E.Y. Lab., San Mateo, CA, USA), diluted 1:50 in PBS, pH 7.4, at room temperature in a moist chamber for 30 min. After being washed in PBS, the sections were treated with primary antibody (rabbit anti-UEA-I from E.Y. Lab.) diluted 1:100. Swine anti-rabbit antibody and rabbit PAP complex (DAKO Immunoglobulins) were used as linking and labelling antibody, respectively. The peroxidase reaction was visualized with 3,3-diaminobenzidine (Walter, Kiel, FRG) as chromogen. The sections were counterstained with Meyer's haemalum, dehydrated and mounted with Eukitt (Kindler, Freiburg, FRG).

In 13 cases (see Table 1) tissue blocks were also available for electron microscopy. The tissue was fixed in 5% glutaraldehyde (0.1 M sodium cacodylate buffer, pH 7.4) and 1% OsO_4 and embedded in Araldite. Semithin sections were stained with azure II methylene

blue. Ultrathin sections were stained with uranyl acetate and lead citrate. The electron microscope used was a Siemens Elmiskop 101 (80 kV).

For better assessment of the changes in the blood microvasculature in T-cell lymphomas, we separated the different types of small blood vessels into two main variants, viz: high endothelial venules (HEV) and all other types of small vessels with flat endothelium (SVFE), including arterioles, metarterioles, capillaries, venules and small veins. The sinus system was not included in the present study. The endothelium of the sinuses has been reported to be usually negative for UEA-I in the normal state and variably positive in various types of Hodgkin's disease (Möller and Lennert 1984). Although we also found occasional UEA-I positive endothelial cells in the sinuses of various types of T-cell lymphomas, their description is beyond the scope of the present work.

On the basis of light microscopic examination of paraffin sections either stained with Giemsa, H and E, Gomori and PAS or immunostained for UEA-I, HEV were readily distinguished from SVFE by the structure of their walls, the lymphocyte traffic and mainly their voluminous endothelial cells. We must underline that in the vast number of the 55 cases of T-cell lymphomas in our study, there was a complete replacement of the normal lymphoid tissue by neoplastic elements. Limited areas with remnants of lymphoid follicles were seen in very few cases. After surveying the neoplastic tissue in all the available paraffin sections from each case of T-cell lymphoma, the number of HEV and, separately, the number of SVFE, whether longitudinally or transversely cut, was counted in 30 random optical fields. Finally, the number of each type of blood vessel per optical field (o.f.) $\times 250$ was estimated for each case. Converting the numerical to a plus grading system a semiquantitative value can be assigned as follows: $-$ = no detectable HEV or SVFE; $+$, $++$, $+++$, $++++$ = small, moderate, large and very large number of HEV or SVFE respectively, where small = 1 vessel, moderate = 2–3 vessels, large = 4–5 vessels, and very large = > 5 vessels per o.f. $\times 250$. The lymphocyte traffic through HEV walls was also semiquantitatively assessed on the same plus grading system: $-$ = no detectable lymphocytes; $+$, $++$, $+++$, $++++$ = small, moderate, large and very large number of migrating lymphocytes respectively (slightly modified system of Kittas and Henry 1979a).

Results

The 55 cases of T-cell lymphoma were subclassified (Table 1) according to their morphological and immunological features (Lennert et al. 1982). In three cases originally interpreted as pleomorphic T-cell lymphoma, a

Table 1. Types of T-cell lymphoma examined in this study

Morphological type	No. of cases	No. of cases examined by electron microscopy
T-CLL	15	3
Sézary's syndrome	3	1
Pleomorphic T-cell lymphoma	13	6
Small cell subtype	5	2
Medium-sized cell subtype	4	3
Large cell subtype	4	1
T-cell lymphoma of clear cell type	3	–
T-immunoblastic lymphoma	6	1
T-lymphoblastic lymphoma	15	2
Total	55	13

Table 2. Occurrence of high endothelial venules (HEV) and small vessels with flat endothelium (SVFE) in relation to the different types of T-cell lymphoma ($n=55$)

	No. of cases	Content of HEV					Content of SVFE				
		−	+	++	+++	++++	−	+	++	+++	++++
T-CLL	15	0	0	0	7	8	0	12	3	0	0
Sézary's syndrome	3	0	0	0	2	1	0	3	0	0	0
Pleomorphic T-cell lymphoma	13	0	4	6	2	1	0	1	5	5	2
Small cell subtype	5	0	0	2	2	1	0	1	3	1	0
Medium-sized cell subtype	4	0	2	2	0	0	0	0	2	2	0
Large cell subtype	4	0	2	2	0	0	0	0	0	2	2
T-cell lymphoma of clear cell type	3	0	0	0	3	0	0	3	0	0	0
T-immunoblastic lymphoma	6	0	3	3	0	0	0	0	1	4	1
T-lymphoblastic lymphoma	15	11	3	1	0	0	0	0	1	2	10

− = no detectable vessels; + = small, ++ = moderate, +++ = large, ++++ = very large number of vessels

Table 3. Degree of lymphocyte traffic through walls of high endothelial venules in relation to the different types of T-cell lymphoma ($n=55$)

	No. of cases	Degree of lymphocyte traffic				
		−	+	++	+++	++++
T-CLL	15	0	0	4	6	5
Sézary's syndrome	3	0	0	0	2	1
Pleomorphic T-cell lymphoma	13	0	8	5	0	0
Small cell subtype	5	0	2	3	0	0
Medium-sized cell subtype	4	0	3	1	0	0
Large cell subtype	4	0	3	1	0	0
T-cell lymphoma of clear cell type	3	0	0	2	1	0
T-immunoblastic lymphoma	6	2	4	0	0	0
T-lymphoblastic lymphoma	15	10	5	0	0	0

− = no detectable migrating lymphocytes; + = small, ++ = moderate, +++ = large, ++++ = very large number of migrating lymphocytes

vast number of cells with clear cytoplasm was found. These cases were grouped together in a separate subtype, the "clear cell type". We must mention, however, that the list of subtypes in Table 1 is not intended as a new classification.

In general, PAP immunostaining with UEA-I proved to be the most useful method for vascular demonstration, since the endothelium of arteries,

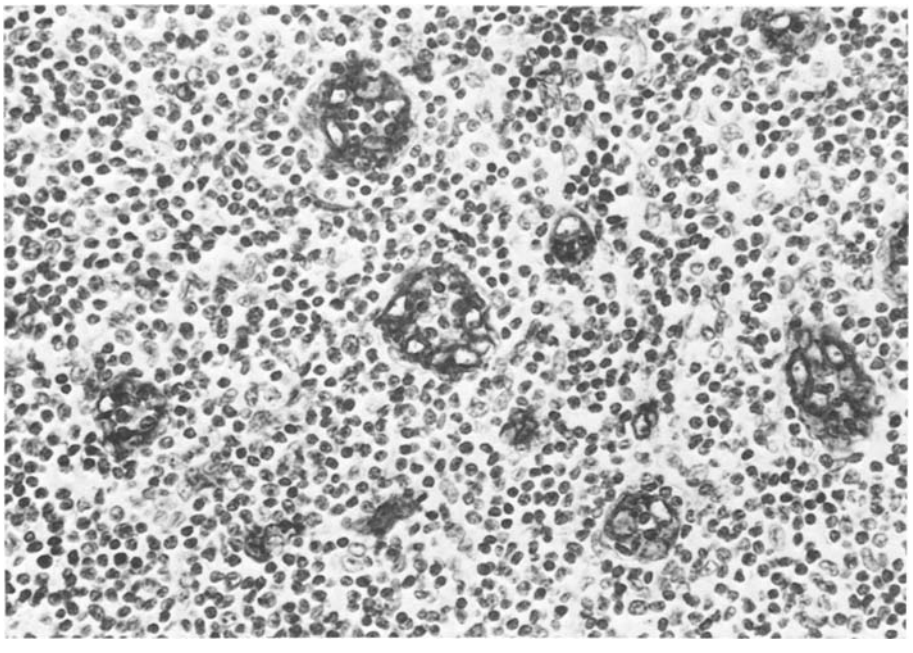

Fig. 1. T-CLL. Transversely cut high endothelial venules showing numerous migrating lymphocytes. The endothelial cells are strongly positive for UEA-I. × 250

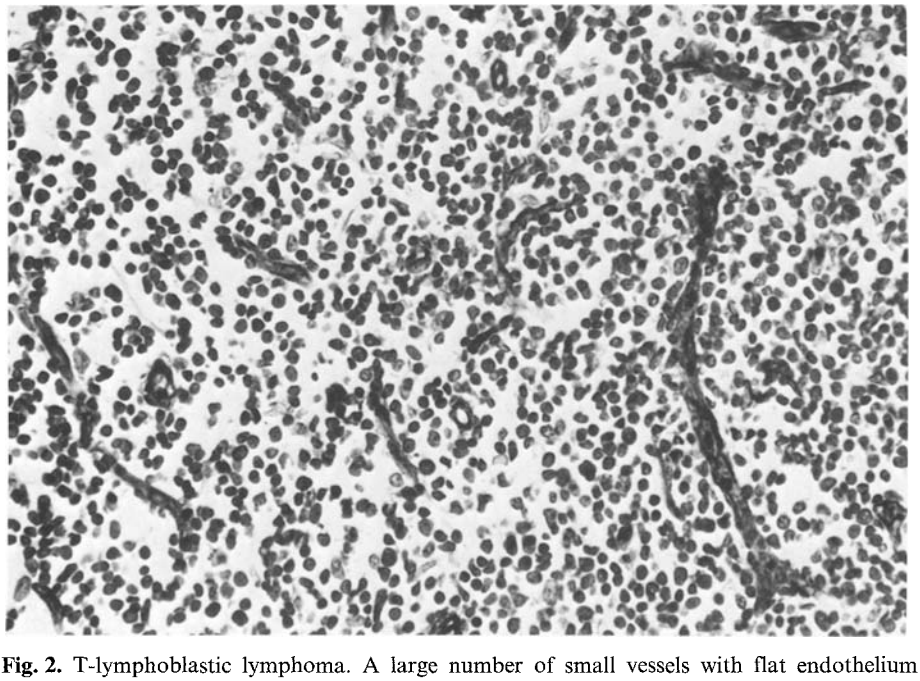

Fig. 2. T-lymphoblastic lymphoma. A large number of small vessels with flat endothelium are seen. The endothelial cells are strongly positive for UEA-I. High endothelial venules are missing. × 250

metarterioles, capillaries, HEV, venules and small veins showed a strong reaction. Our findings regarding the blood microvasculature in the various subtypes of T-cell lymphoma are as follows:

Light microscopic examination of paraffin sections either stained with conventional methods or immunostained for UEA-I revealed large or very large numbers of HEV in all cases of T-CLL (Table 2). These vessels were widely distributed throughout the neoplastic tissue and were most often seen in transverse section (Fig. 1). Mitotic figures of endothelial cells were extremely rare. In the great majority of cases SVFE were found in small numbers; only in three cases was there a moderate number of SVFE (Table 2). Another prominent feature was the moderate, large, or very large number of lymphocytes passing through HEV walls (Fig. 1, Table 3).

The microvasculature of the involved areas of lymph nodes with Sézary's syndrome was similar to that seen in T-CLL (Tables 2 and 3).

By contrast, the development of the two main categories of small blood vessels in T-immunoblastic and T-lymphoblastic lymphomas was significantly different from that seen in T-CLL and Sézary's syndrome. In each, the angioarchitecture was not easily recognizable with conventional stains because it was overriden by a large number of immunoblasts or lymphoblasts respectively. PAP-immunostaining with UEA-I, however, revealed, on the whole, a well-developed blood microvasculature such as is seen in T-CLL and Sézary's syndrome but with different numbers of SVFE and HEV. Thus, a large or very large number of SVFE was seen randomly dispersed throughout the neoplastic tissue in T-immunoblastic and, most frequently, in T-lymphoblastic lymphomas (Fig. 2). Only a small to moderate number of HEV was seen in T-immunoblastic and this figure was even less in T-lymphoblastic lymphomas. Migration of lymphocytes was absent or minimal (Tables 2 and 3).

There was one remarkable exception, namely, a case of lymphoblastic lymphoma (showing a focal acid phosphatase reaction) in which many HEV could be recognized on light and electron microscopy. Many of the tumour cells showed some rough endoplasmic reticulum and other features that were consistent with those of plasmacytoid T cells (Kaiserling 1978). In reactive lymph nodes plasmacytoid T cells are usually seen near HEV (Vollenweider and Lennert 1983). In this case the lymphoma had developed in a patient with ataxia telangiectasia.

When the 13 cases of pleomorphic T-cell lymphoma were considered as a unified entity the content of their blood microvasculature in HEV and SVFE appeared to vary markedly (Table 2).

Analysis of the microangioarchitecture in the three subtypes of pleomorphic T-cell lymphoma revealed the following: In one case of small cell subtype the pattern of blood microvasculature was very similar to that seen in T-CLL. The other four cases showed a moderate to large number of HEV which were seen in transverse or longitudinal section and a small or moderate number of SVFE. Lymphocyte traffic was slight to moderate (Fig. 3, Tables 2 and 3). In most cases of medium-sized cell subtype the number of HEV was further decreased while an increase in the number

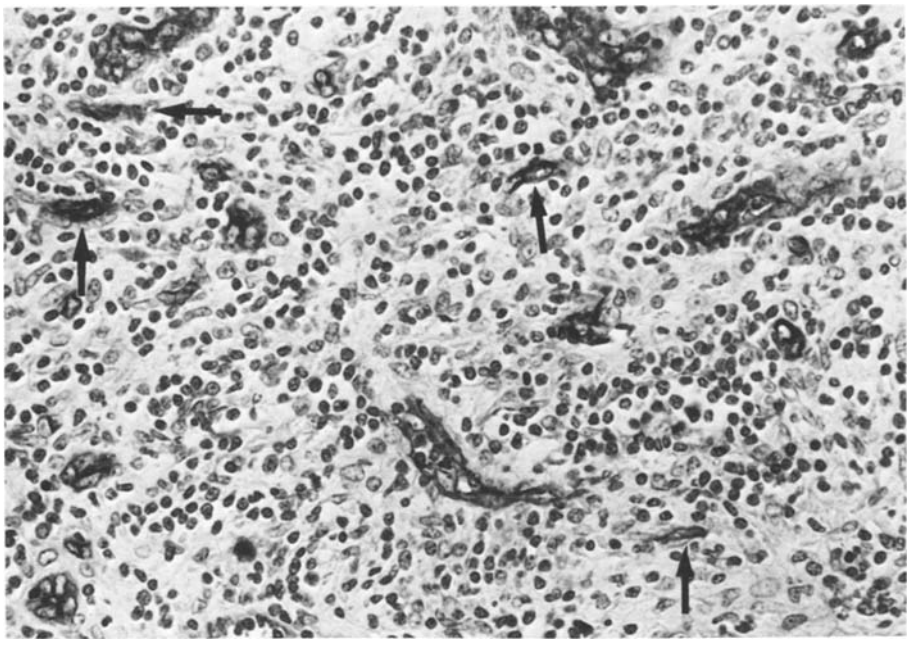

Fig. 3. Small cell subtype of pleomorphic T-cell lymphoma. Several high endothelial venules, mostly in longitudinal section, and small vessels with flat endothelium (*arrows*). Lymphocyte traffic is slight. PAP immunostaining with UEA-I, ×250

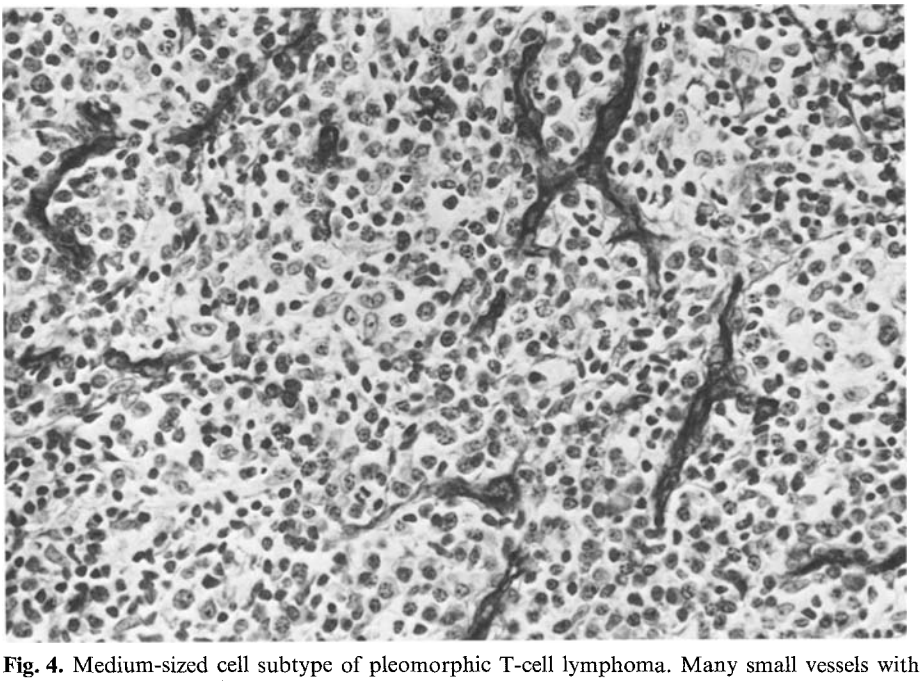

Fig. 4. Medium-sized cell subtype of pleomorphic T-cell lymphoma. Many small vessels with flat endothelium in longitudinal section. These vessels show arborization. PAP immunostaining with UEA-I, ×250

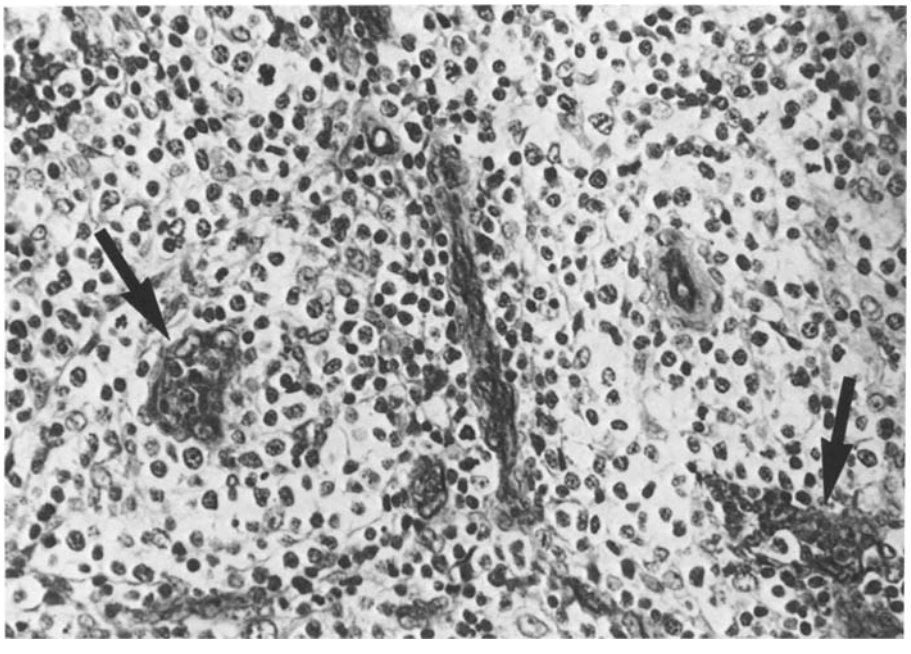

Fig. 5. Clear cell type of T-cell lymphoma. Numerous neoplastic lymphoid cells showing clear cytoplasm. High endothelial venules with moderate to large degree of lymphocyte traffic (arrows). Small vessels with flat endothelium are also evident. PAP immunostaining with UEA-I, ×250

of SVFE was seen as compared to the number of these vessels in T-CLL and the small cell subtype of pleomorphic T-cell lymphoma (Table 2). The SVFE were often seen in longitudinal section and several of them showed arborization (Fig. 4). More often only small numbers of lymphocytes migrated through the HEV walls (Table 3). The four cases of the large cell subtype showed a small to moderate number of HEV and usually only a few migrating lymphocytes. By contrast, there was a large or very large number of SVFE (Tables 2 and 3).

In the three cases showing numerous neoplastic clear cells the microvasculature had an appearance between that of T-CLL and that of the small cell subtype of pleomorphic T-cell lymphoma. The clear cell type showed a large number of HEV, a moderate or large number of migrating lymphocytes and few SVFE (Fig. 5, Tables 2 and 3).

The electron microscopic examination of the blood microvasculature generally supported the light microscopic findings in all types of T-cell lymphoma and added some new ones. Thus, in T-CLL and Sézary's syndrome the HEV showed the ultrastructural features previously described by other authors (Marchesi and Gowans 1964; Kittas et al. 1981) but their basement membrane was significantly split in many places. A further interesting observation was the presence of high endothelial cells in other types of small vessels usually lined by flat endothelium, e.g. fenestrated capillaries

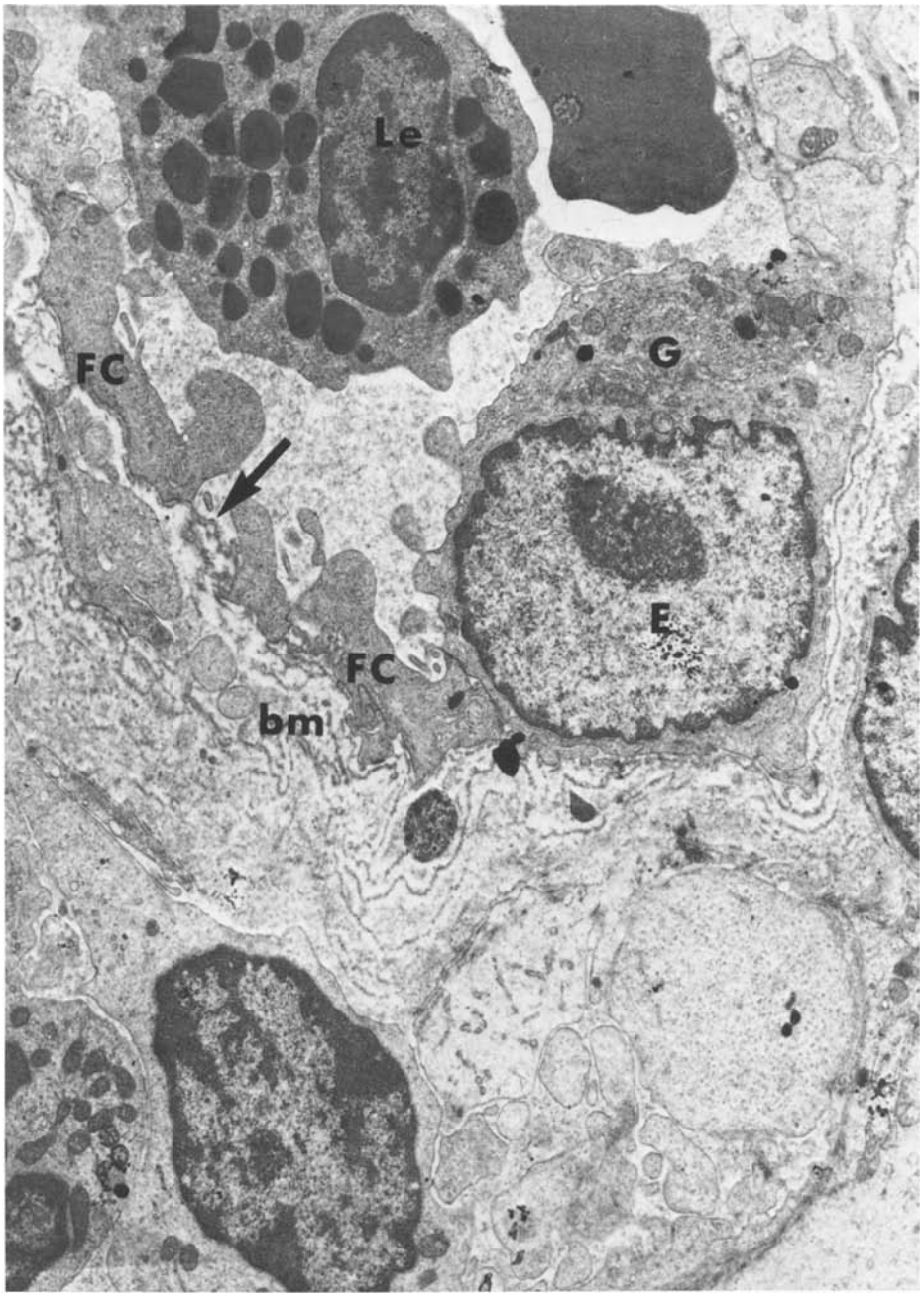

Fig. 6. T-CLL. Fenestrated capillary showing flat endothelial cells (*FC*) with a fenestra (*arrow*) and one typical high endothelial cell (*E*). Basement membrane (*bm*). Leukocyte (*Le*). Golgi apparatus (*G*). Ultrathin section. ×7,200

(Fig. 6). Electron microscopy in the various subtypes of pleomorphic T-cell lymphoma revealed that the basement membrane, mainly of the HEV, was often split and its normal structure was occasionally replaced by a thick electron-dense layer. Apposition of collagenous fibrils on a usually normal basement membrane was observed more often in HEV of the medium-sized cell subtype of pleomorphic T-cell lymphoma.

Discussion

The angioarchitecture of mammalian lymph nodes under normal and various pathological or experimental conditions has been amply described (Marchesi and Gowans 1964; Krüger 1968; Herman et al. 1972; Anderson et al. 1975; Syrjänen 1978). In addition, changes in the microvasculature of lymph nodes have been reported in various hyperimmune and abnormal hyperimmune reactions, including lymphogranulomatosis X (Frizzera et al. 1975; Gleichmann et al. 1978; Knecht and Lennert 1981). Most authors were impressed by the HEV and made no comment on the other small vessels with flat endothelium (SVFE). In malignant lymphomas the vessels were of only marginal interest to most investigators and this interest was focussed on HEV. The latter have been mentioned, for example, in descriptions of pleomorphic T-cell lymphoma (T-zone lymphoma), T-CLL, Sézary's syndrome, mycosis fungoides and immunocytoma (Lennert and Mohri 1978; Lennert 1981; Robb-Smith and Taylor 1981; Lennert et al. 1982).

The present study of T-cell lymphomas takes into consideration the whole lymph node microvasculature, including HEV and other types of small vessels, such as arterioles, metarterioles, capillaries, venules and veins. Our findings indicate that in all variants of T-cell lymphoma there is relatively stable development of the microvasculature, irrespective of the differences seen in its content in HEV and SVFE. PAP immunostaining with UEA-I proved to be the most useful method for studying vessels (cf., Holthöfer et al. 1982). This technique "unmasked" small vessels that could not be recognized with conventional stains in T-immunoblastic and T-lymphoblastic lymphomas, which showed a very high cell content. Thus the relatively stable vascular development when compared with the one of the other types of T-cell lymphomas became obvious. This observation is in agreement with that of Herman et al. (1979), who found the vascularization of antigenically challenged lymph nodes to be remarkably constant.

Some types of T-cell lymphoma showed a predominance of HEV, others of SVFE. In a few T-cell lymphomas the numbers of HEV and SVFE were approximately equal. T-CLL and Sezary's syndrome were rich in HEV and were thus placed at one extreme. T-immunoblastic and T-lymphoblastic lymphomas were rich in SVFE and were placed at the other extreme. T-CLL and Sézary's syndrome showed a large number of lymphocytes passing through the walls of HEV, whilst the latter two types exhibited minimal lymphocyte traffic through vascular walls. These findings support the theory that the development of HEV depends, at least in part, on the extent of lymphocyte migration from the blood into lymphoid tissues (De Sousa et al.

1969; Miller 1969; Nightingale and Hurley 1978), although other reports implicate different factors in the morphological peculiarities of high endothelial cells (Van Deurs and Röpke 1975; Kittas and Henry 1979b).

Another interesting finding was the presence of endothelial cells with the ultrastructural characteristics of high endothelium in other types of small vessels that are normally lined with flat endothelium. This was noticed on electron microscopy only in cases with marked or very marked lymphocyte traffic, such as T-CLL and Sézary's syndrome, and supports the theory of "high" or so-called epithelioid transformation of the vascular endothelium as an expression of its variably stimulated functional activation (Baldwin 1982). Our observation of relatively stable blood vascular development but morphologically variable angioarchitecture in the various types of T-cell lymphomas might thus be explained in part by "epithelioid" transformation of the flat vascular and endothelium in cases with increased lymphocyte migration.

The cases of pleomorphic T-cell lymphoma showed the whole spectrum of microvascular changes seen in the other types of T-cell lymphoma. On analysis of the microvasculature in the three subgroups of pleomorphic T-cell lymphomas, the small cell subtype appeared to contain a large number of HEV and fewer SVFE and mainly exhibited moderate lymphocyte traffic. As the size of the neoplastic lymphoid cells increased, there was a gradual increase in the number of SVFE and a decrease in the number of HEV and the lymphocyte traffic diminished.

This observation is in agreement with the data given by Nanba and Hanaoka (1982) in their study concerning the interrelationship between malignant lymphoma and leukemia. These authors report that T or B, normal or neoplastic lymphocytes migrating through the HEV wall are morphologically small, while their migratory properties decrease as they become larger.

The clear cell type represented a separate variant of T-cell lymphoma. In this type the vascular features were between those of T-CLL and those of the small cell subtype of pleomorphic T-cell lymphoma.

The ultrastructural features of the vessels in pleomorphic T-cell lymphomas often resembled those described in lymphogranulomatosis X. Several cases of pleomorphic T-cell lymphoma showed all three types of vascular alterations reported by Knecht and Lennert (1981) in lymphogranulomatosis X, viz.: a thick electron-dense layer in place of the normal basement membrane (type A), a splintered basement membrane (type B) and a normally structured basement membrane surrounded by material containing collagenous fibrils (type C). This suggests that there might be a relation between at least some cases of pleomorphic T-cell lymphoma and lymphogranulomatosis X.

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Accepted November 19, 1984