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Morphological characteristics of malignant T-cell lymphomas in baboons

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Abstract. Fifteen cases of generalized peripheral T-cell non-Hodgkin's lymphoma in baboons were phenotyped immunologically and morphologically. Using the updated Kiel classification the cases included low-grade and high-grade lymphomas and low-grade lymphomas that had transformed into high-grade lymphomas. In the low-grade group there were seven cases of lymphocytic type, partly corresponding to chronic lymphocytic leukaemia of T type and to T-zone lymphoma in man. In addition there were four cases of prolymphocytic-lymphocytic type, which show large nodules ("proliferation centres") and which have no equivalent in the Kiel classification. In four cases there was a progression to an immunoblastic lymphoma and in one case to a large cell anaplastic lymphoma. In addition, three cases of large cell anaplastic lymphoma without a low-grade component were found. Both the immunoblastic lymphomas and the large cell anaplastic lymphomas corresponded well with the same types in the Kiel classification. The cases of large cell anaplastic lymphoma were also CD30 positive. Most of these lymphomas were CD4 positive, but there were rare cases that were either CD8 positive, showed both CD4 and CD8 positivity or had lost both antigens. Antigens associated with cell activation were often revealed. All but one baboon had antibodies in the blood against the retrovirus STLV-1 (simian T-cell leukaemia virus 1), which is very similar to human T-cell leukaemia virus 1 (HTLV-1) in man. Despite this virological resemblance, the morphology of these T-cell lymphomas does not resemble that of the HTLV-1-positive Japanese T-cell lymphomas but is like that of the HTLV-1-negative European cases.

Key words: Baboon malignant lymphoma – Peripheral T-cell lymphoma – Simian T-cell leukaemia virus

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Introduction

An outbreak of malignant lymphoma started about 20 years ago among adult baboons (*Papio hamadryas*) in the main stock of the Sukhumi monkey colony, causing the death of more than 300 monkeys (Lapin et al. 1980; Lapin 1985). In the high-risk group, 0.75–1.73% of adult baboons die annually of malignant lymphoma. All baboon lymphoid tumours are, as far as we know, non-Hodgkin's malignant lymphomas (NHL). From immunological typing, these NHL may be of both B-cell and T-cell type, similar to those seen in man. Previous morphological studies of baboon lymphomas (Lapin et al. 1980; Yakovleva et al. 1985, 1987, 1990) were based on the Kiel classification, which was developed for human NHL (Gérard-Marchant et al. 1974; Lennert and Mohri 1978; Stansfeld et al. 1988). They revealed considerable similarities between malignant lymphomas found in baboons and those that develop in humans.

Similarities between baboon lymphomas and analogous human forms manifested themselves in the association of this disease with B- and T-lymphotropic viruses. B-lymphotropic herpes virus papio, isolated from lymphomatous animals (Lapin et al. 1975) in 1974–1975, belongs to the subfamily of B-lymphotropic Epstein-Barr virus (EBV)-like herpes viruses. It is transmitted horizontally and is widely distributed among the adult baboons in the Sukhumi monkey colony (Lapin 1988). C-type retrovirus of baboons, which had been detected in lymphomatous baboons in the late 1970s, was identified as simian T-cell leukaemia virus 1 (STLV-1; Saxinger et al. 1984) after isolation of oncogenic retrovirus human T-cell leukaemia virus-1 (HTLV-1) from lymphomatous human patients (Poiesz et al. 1980; Miyoshi et al. 1981). HTLV-1 and STLV-1 are closely related antigenically (Saxinger et al. 1984; Voevodin et al. 1987). The prevalence of STLV-1 in the baboons in the high risk stock (Voevodin et al. 1985; Lapin 1988) resembles the situation in the endemic areas of Japan and the Caribbean basin, where a high rate of occurrence of HTLV-1 infection is associated with human T-cell malignant lymphomas (Gallo et al. 1984; Watanabe 1986).

In humans, HTLV-1 is mainly associated with peripheral T-cell lymphomas of pleomorphic type and also with T-immunoblastic lymphomas (Lennert et al. 1985; Suchi et al. 1987; Watanabe et al. 1988). In our immunohistological investigations of baboon NHL we were unable to establish a correlation between malignant lymphomas of various cell types and the percentage of carriers of B- or T-lymphotropic viruses, assessed by indirect-antiviral antibodies in blood sera of examined baboons (Yakovleva et al. 1986). Clinically, NHL is a long-term disease in baboons, chronic in character with relapses and spontaneous remissions. The final stage of the disease is characterized by pronounced lymphadenopathy, splenomegaly and involvement of various organs (Lapin et al. 1980; Yakovleva et al. 1987).

We previously performed immunological phenotyping of baboon lymphoma cells on suspensions of tumour cells. At first we used polyclonal immune sera against immunoglobulins and determined general T-lymphocyte markers, but recently we have worked with a panel of monoclonal antibodies (mAbs) for various leucocyte antigens of men and monkeys (Indzhiia et al. 1990).

In this study we have carried out morphological and immunohistochemical investigations of T-cell NHL in paraffin sections. Our aim was to determine both the differences and the similarities between these types of lymphoma in baboons and man. Our immunohistochemical study of baboon NHL was facilitated by the fact that most baboon tissue antigens react positively with similar antihuman mAbs (Indzhiia et al. 1990, in press). This paper describes mainly the lymphoid organs.

Materials and methods

Fifteen baboons (*P. hamadryas*), aged 5 to 19 years, dying with malignant T-cell lymphomas, were sacrificed in the last stage of disease under ketamin anaesthesia by total bleeding via arterial catheter. One animal died within the period of spontaneous remission, but 9 months before death a biopsy of an enlarged axillary lymph node was taken. Specimens of fresh lymphoid organs taken from dead animals were immunophenotyped in tumour cell suspension with the indirect immunofluorescence test using a panel of mAbs against leucocyte antigens of man and monkeys and polyclonal anti-immunoglobulin sera (Table 1), as described previously (Indzhiia et al. 1990). At autopsy, specimens of tumour material (approx. 0.5×0.5 cm) were frozen in liquid nitrogen and brought to Germany on dry ice. Cryostat sections 5 µm thick were made just prior to the immunohistochemical reactions.

For morphological investigations specimens of lymphoid and extralymphatic organs were fixed in 10% formalin and embedded in paraffin. Histological sections were stained with haematoxylin and eosin, Giemsa, periodic acid-Schiff (PAS) and silver impregnation according to Gomori. Immunohistochemical tests with some

Table 1. List of monoclonal antibodies used in the investigation

Antibody	CD material	Specificity	Source
Monoclonal			
9.6	CD2 suspension	Sheep erythrocyte receptor	E. Clark[a]
T11	CD2 frozen section	Sheep erythrocyte receptor	E. Clark[a]
FN18	CD3 suspension	Pan-T-cell	E. Clark[a]
Leu3a	CD4 suspension/frozen section	T-helper/inducer	Becton Dickinson
G17-2	CD4 suspension	T-helper/inducer	E. Clark[a]
G10-1	CD8 suspension	T-suppressor/ cytotoxic	E. Clark[a]
HD37	CD19 suspension	Pan-B-cell	E. Clark[a]
1F5	CD20 suspension	Pan-B-cell	E. Clark[a]
2A3	CD25 suspension	IL-2 receptor	Becton Dickinson
Ber-H2	CD30 paraffin section	Activated T, B, Sternberg-Reed cells	Stein, Berlin
UCHL1	CD45RO paraffin section	T-subset, B-cells, granulocytes, monocytes	DAKO
LN2	CD74 frozen section	B-cells, monocytes	
2C3	anti-γ chain suspension	B-cells	E. Clark[a]
HB 10a	suspension	HLA-DR	E. Clark[a]
L26	CD20-like, paraffin sections	B-cells	DAKO
Ki-B3	? paraffin sections	Some B-cells	Wacker, Kiel
Ki-B5	? paraffin sections	Some B-cells	Parwaresch, Kiel
Polyclonal			
IgG	Anti-heavy chain suspension/frozen section	B-cells	DAKO
	Anti-light chain suspension/frozen section	B-cells	DAKO
	Anti-light chain suspension/frozen section	B-cells	DAKO

[a] Monoclonal antibodies were kindly presented by Dr. E. Clark (Washington Regional Primate Research Center, USA) during our joint research. Their characteristics were published in Clark and Draves (1987)

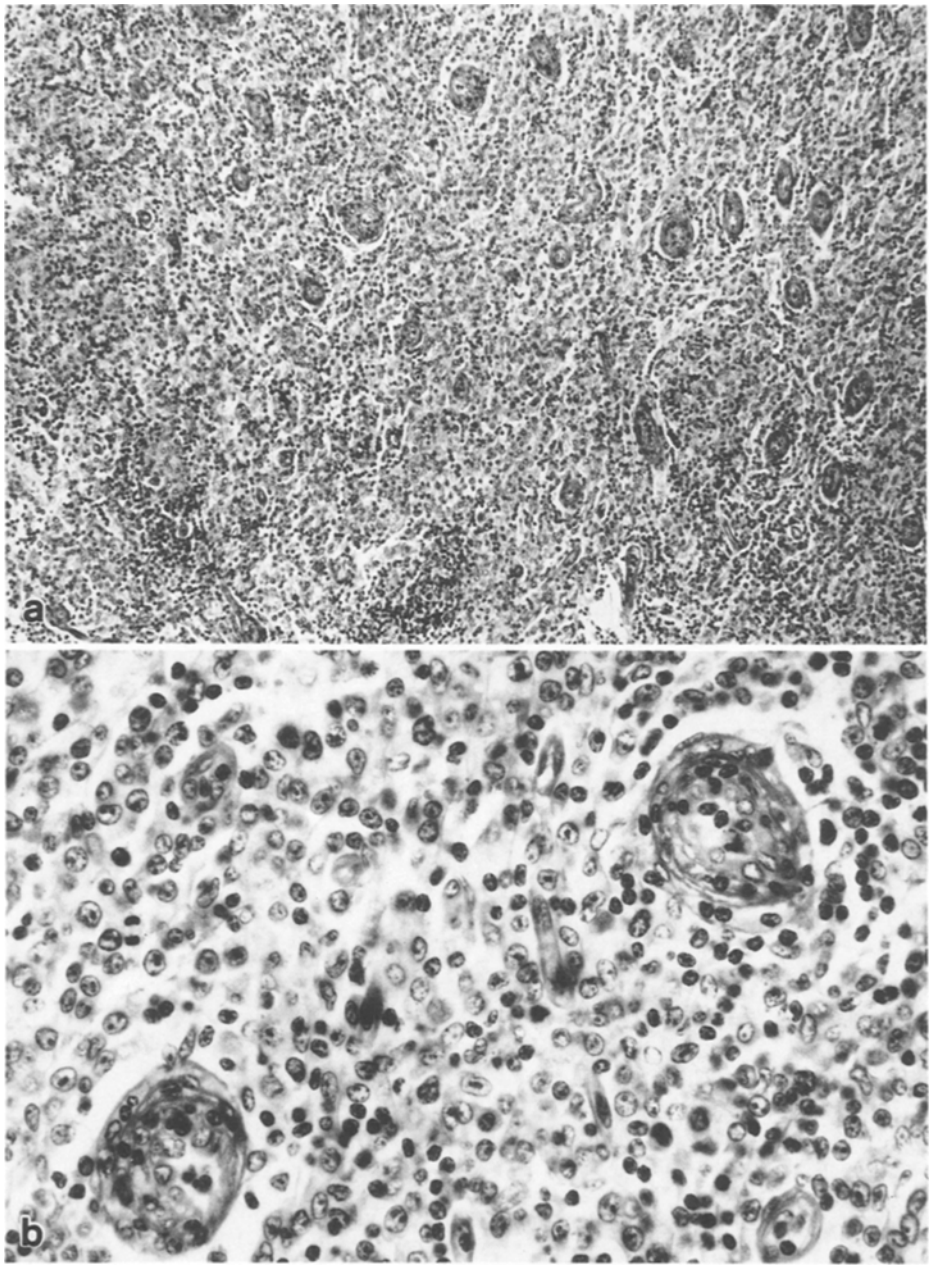

Fig. 1 a, b. Lymphocytic type with high numbers of high endothelial venules, which are filled and permeated by lymphocytes. Blood picture leukaemic. PAS, **a** ×110, **b** ×441

mAbs and polyclonal sera were conducted on paraffin sections. Not all of the polyclonal antisera and mAbs for human differential leucocyte antigens reacted with paraffin-embedded baboon lymphoid tissues. Variants of the indirect peroxidase-antiperoxidase test and the alkaline phosphatase-antialkaline phosphatase method were used to reveal differential leucocyte antigens on cryostat and paraffin sections (Johnstone and Thorpe 1982).

Baboon sera were tested for the presence of antibodies against STLV-1 by Western blotting on nitrocellulose film with the standard electrophoretic method (Laemmli 1970). Baboon sera were kept frozen at −20° C and then used in a dilution of 1:20 with HTLV-1-positive antigen isolated from tissue culture C-10. Negative sera were obtained from healthy adult animals of separate stock. A positive reaction was evaluated according to the intensity of the lines for two antigens: p24CA (cytoplasmic antigen) and gp21TM (transmembrane antigen).

These tumours of the baboon lymphoid system were NHLs. They were classified according to the updated Kiel classification (Stansfeld et al. 1988; Lennert and Feller 1992).

Results

Lymph nodes of various groups were involved by malignant lymphoma: peripheral lymph nodes, including the cervical group, together with mediastinal and abdominal lymph nodes. In general, the spleen and some parenchymatous organs were affected.

The affected lymph nodes were enlarged (Table 2) and formed irregular conglomerates up to 5 cm in diameter. Cytologically and histologically we were able to distinguish four types of lymphoma according to the characteristics of the dominant tumour cells: lymphocytic, prolymphocytic-lymphocytic, immunoblastic and large cell anaplastic. The lymphocytic and prolymphocytic-lymphocytic types were classified as low-grade malignant lymphomas and the immunoblastic and large cell anaplastic types as high-grade malignant lymphomas. In six

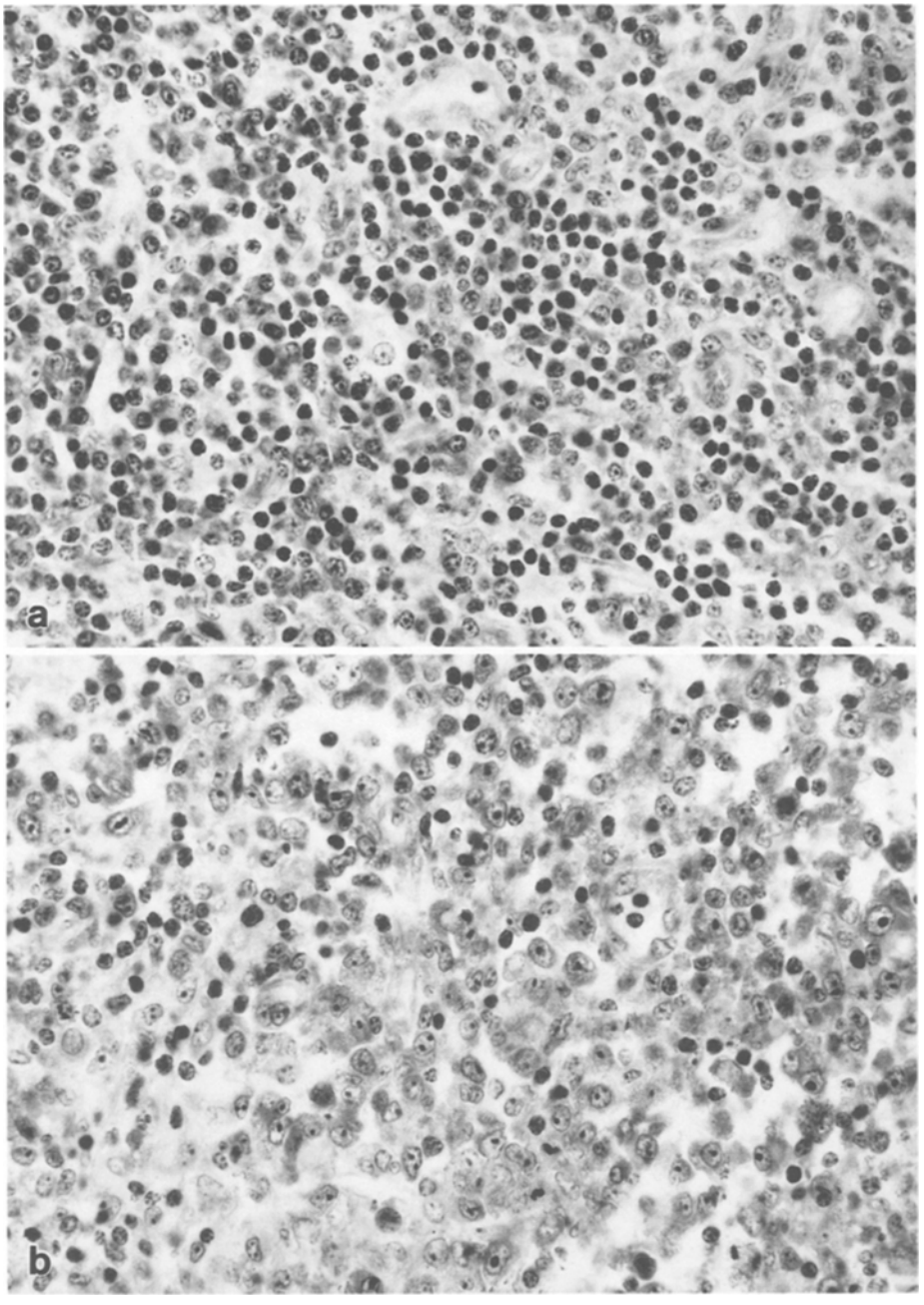

Fig. 2a, b. Lymphocytic type, transition into an immunoblastic lymphoma. **a** Low-grade lymphoma, **b** high-grade lymphoma. Giemsa, ×441

cases all areas of the lymphoma investigated could be classified as low-grade (four cases of the lymphocytic type and two of the prolymphocytic-lymphocytic type); in three cases the lymphoma was high-grade (large cell anaplastic lymphoma) without a low-grade component. In six cases the tumour consisted of a low-grade component with more or less extensive high-grade portions. The low-grade component could be lymphocytic (four cases) or prolymphocytic (two cases) in nature. The high-grade component was usually immunoblastic (in five cases), and only once of large cell anaplastic type.

Lymphocytic lymphoma of T-cell type was diagnosed in 7 of the 15 cases studied. In all cases the tumours were characterized by diffuse growth and complete or almost complete replacement of the normal lymphoid tissue of the lymph node. The general appearance of the tumour was rather monomorphic, though cell diameters varied somewhat. The majority of the lymphoid cells consisted of small lymphocytes with round or slightly convoluted nuclei, condensed chromatin and sparse cytoplasm that stains grey with Giemsa. Some lymphomas in this group had notably pleomorphic nuclei. Among the lymphocytes a few prolymphocytes and immunoblasts were found, the latter varying in number from case to case. Few mitotic figures were found, and were mainly in the large cells. Prolymphocytes differ from lymphocytes mainly in that they have a somewhat larger nucleus with a slightly finer chromatin structure and one or two small nucleoli. In some cases the prolymphocytes and immunoblasts were arranged in the form of

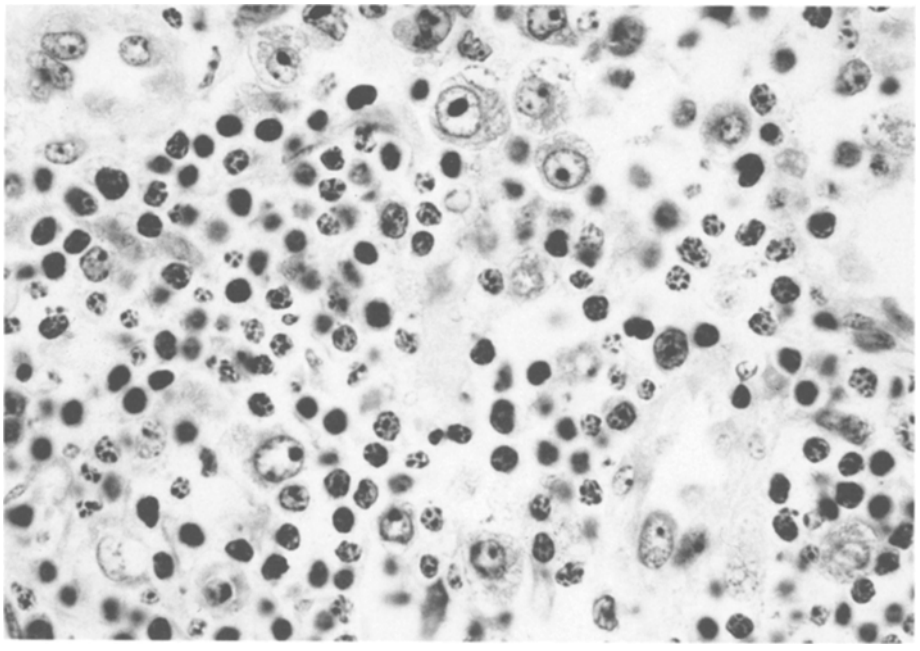

Fig. 3. Lymphocytic type with some large cells resembling Hodgkin cells. Giemsa, × 700

Table 2. Cytological type of lymphoma and involvement of lymphoid organs

Case no.	No. of baboon	Cytological types of lymphoma		Intensity of lymph node involvement		Degree of splenomegaly (weight in g[a])	Involvement of tonsils
		Low-grade component	High-grade component	Peripheral	Thoracic and abdominal		
1	15600	Lymphocytic	+ Immunoblastic	+	+	360	+
2	13845	Lymphocytic	−	+	+	400	−
3	20555	Lymphocytic	−	+−	+	58	−
4	14799	Lymphocytic	−	+	+	143	−
5[b]	17930	Lymphocytic	−	+−	+−	28	−
6	13373	Lymphocytic	+ Immunoblastic	++	+−	220	−
7	19780	Lymphocytic	+ Large cell anaplastic	++	+	61	+
8	12931	Prolymphocytic-lymphocytic	+immunoblastic	++	+	100	−
9	14596	Prolymphocytic-lymphocytic	−	+	+	100	−
10	17912	Prolymphocytic-lymphocytic	−	+	+	130	−
11	17539	Prolymphocytic-lymphocytic	+immunoblastic	++	++	36	−
12	13593	Prolymphocytic-lymphocytic	+immunoblastic	+++	++	73	+
13	13977	−	Large-cell anaplastic	+++	+++	230	−
14	18658	−	Large-cell anaplastic	+++	++	400	+
15	15614	−	Large-cell anaplastic	+++[c]	−	18	−

[a] Spleen weight of a healthy adult baboon is about 30 g
[b] The animal died during a period of remission; the cytological type was established on a biopsy obtained at the onset of the disease
[c] Mainly involvement of submaxillary lymph nodes
+− = minimally enlarged; ++ = moderately enlarged; + = slightly enlarged; +++ = highly enlarged

light areas corresponding to the proliferation centres in human chronic lymphocytic leukaemia of B type.

High endothelial venules were seen in all cases in this group. In two cases accumulations of various sized lymphocytes were detected in the lumen of the venules (Fig. 1). Most cases exhibited bundles of fibres spreading from the capsule toward internal parts of the affected node, occasionally inducing the impression of a Hodgkin's lymphoma of nodular sclerosing type. The marginal sinus was sometimes almost fully or partly preserved.

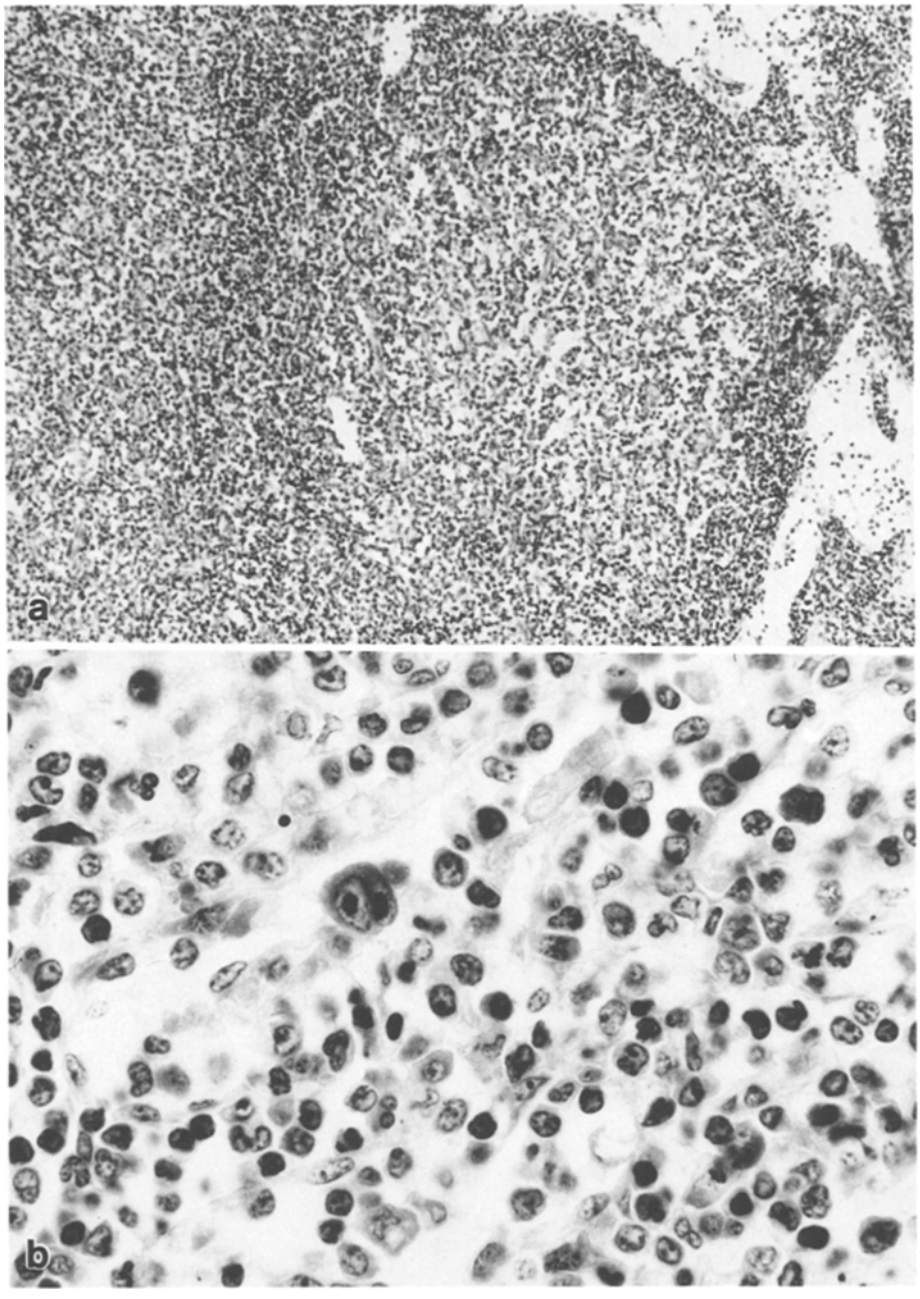

Fig. 4a, b. Prolymphocytic type. **a** Nodular pattern. H & E, ×140. **b** Pleomorphic prolymphocytes and a binucleated giant cell like a Sternberg-Reed cell. Giemsa, ×700

In most cases only solitary hypoplastic lymphoid follicles were seen. Clinically there was a leukaemic blood picture.

In two cases (nos. 1, 6) the number of immunoblasts in some lymph nodes was highly increased, and large sheets or clusters of pure populations of immunoblasts even developed (Fig. 2). This signalizes the development of a high-grade lymphoma of immunoblastic type. Occasionally single very large cells (resembling Hodgkin cells) were seen, or groups of such cells, or even binucleated cells (resembling Sternberg-Reed cells) (Fig. 3). In case 7 there was a gradual transition from small cells via medium-sized pleomorphic cells to large anaplastic cells, consistent with the development of a large cell anaplastic lymphoma (cf. below).

Two cases of lymphocytic lymphoma (nos. 4 and 7) contained large numbers of epithelioid cells with abundant cytoplasm that had large oval and irregularly stretched nuclei with small nucleoli. These cells were either solitary or formed separate clusters. Rarely, small perivascular granulomas with aggregations of histiocytes were formed. In the PAS reaction the cytoplasm of epithelioid cells generally stained very weakly and diffusely; only some showed circumscribed stronger perinuclear positivity (corresponding to the Golgi body). As a rule, neither necrosis nor granulocytic infiltration was observed to any great extent in the affected nodes of investigated monkeys.

There were five cases of *prolymphocytic-lymphocytic lymphoma* (Table 2). The infiltration consisted mainly

Table 3. Results of immunophenotyping of baboon lymphomas[a]

Case no.	Suspensions[c]						Cryostat sections			Phenotype
	CD2	CD3	CD4	CD8	CD25	MHC II-DR	CD2	CD4	CD30	
1	80	78	68	33	40	35	+	+	ND	$CD4^+$
2	40	ND	12	51	7	18	+	+ (in some cells)	ND	$CD8^+$
3	58	59	37	24	23	14	+	+	−	$CD4^+$ $CD8^+$
4	42	28	84	15	30	32	+	+	ND	$CD4^+$
5	52	90	70	22	34	22	++	++	−	$CD4^+$
6	77	67	75	20	40	5	+	+	+ (in some large cells)	$CD4^+$
7	76	79	42	39	35	25	+	+	++ (in groups of large cells)	$CD4^+$ $CD8^+$
8	82[c]	ND	ND	ND	ND	14	ND	ND	ND	ND
9	86	74	84	16	20	57	ND	ND	ND	$CD4^+$
10	ND	26	67	20	20	3	+	+	ND	$CD4^+$
11	52	49	23	15	37	24	+−	−	−	$CD4^-$ $CD8^-$
12	70	68	33	54	3	44	+	+−	+ (in single large cells)	$CD8^+$
13	54	ND	31	38	22	49	+	−	+++	$CD4^+$ $CD8^+$
14	57	ND	19	16	10	9	ND	ND	++[d]	$CD4^-$ $CD8^-$
15	48	26	44	10	27	40	+	+	++	$CD4^+$

[a] The table includes only positive results for tumour cells
[b] Percentage of antigen-positive cells
[c] Percentage of E-rosette-forming cells at +4° C
[d] Tumour cells were investigated in suspension and on paraffin section
ND, No data

of so-called prolymphocytes, a moderate number of small lymphocytes and some immunoblasts. Pleomorphic nuclei were sometimes found. Mitotic figures were rare. In the affected lymph nodes the normal structure was completely replaced by tumour infiltration, mainly diffuse in character. In all cases, however, compartmentalization of tumour cells was observed, but at low magnification we recognized that the prolymphocytic infiltration was mainly seen in large, not very sharply demarcated nodules in the T regions of the lymph node (Fig. 4a). The nodules also contained immunoblasts and lymphocytes, and were surrounded by small lymphocytes. In all cases of prolymphocytic lymphoma there were large numbers of high endothelial venules and small vessels with flattened endothelium. A moderate increase in fibres and thickening of the capsule were seen. Giant cells were rarely observed and mostly resembled Sternberg-Reed cells (Fig. 4b). Mostly there was a moderate number of immunoblasts in the lymphoid tissue. In cases 8, 11 and 12 parts of lymph nodes or even entire lymph nodes were infiltrated by immunoblasts, consistent with the development of a high-grade malignant lymphoma of immunoblastic type.

T-cell immunoblastic lymphomas were seen secondarily, in two cases of lymphocytic and two cases of prolymphocytic-lymphocytic lymphoma (Table 2, Fig. 2). The nodes were diffusely infiltrated by immunoblasts, sometimes with incomplete compartmentalization and total replacement of the normal structure of the node and partial (or complete) disappearance of sinuses. The tumour cells varied in size. They contained pale nuclei with one or two large nucleoli and asymmetrical, rather abundant, basophilic cytoplasm (light to dark blue when stained with Giemsa). Multiple mitoses were seen in cells of various sizes. The immunoblasts were occasionally intermingled with mononuclear and multinucleated giant cells, some of which resembled Sternberg-Reed cells. Thickening and fibrosis of the lymph node capsule was either moderate or absent, though in some areas the capsule was infiltrated by immunoblasts. Vessels were mainly thin and tended to have flattened endothelium. Accumulations of immunoblasts and lymphocytes were often seen in vascular lumens. Remnants of hypoplastic lymphoid follicles were sometimes found. In one of the nodes (no. 12) single tumour cells reacted positively with the mAb Ber-H2 (Table 3) and tended to grow in the lumen of sinuses.

Large-cell anaplastic lymphomas were found in four cases (Table 2). Three cases appeared to be primary, because there was no low-grade component. In one case (no. 7), however, in addition to a small cell lymphoma we found areas in which medium-sized pleomorphic cells proliferated and gave rise to large CD30-positive anaplastic cells.

In the three cases of primary large cell anaplastic lymphoma (Fig. 5a, b) the normal structure of the affected nodes was completely destroyed. The tumour tissue was homogeneous and the cells larger than in immunoblastic lymphoma. Cell nuclei were pleomorphic, often eccentrically located and blue to violet in Giemsa-stained slides. The nuclear chromatin was delicate and reticular. The nucleoli were very large, often solitary and both eccentrically and centrally located. The nucleus was round, oval or irregular in shape, sometimes showing deep indentations on one side. A wide, asymmetrical rim of cytoplasm was mostly grey-blue or even intensely blue in some cells. Giant cells with two, three or more nuclei were observed. Some giant cells resembled Sternberg-Reed cells. In tumour cells, including giant cells, mitotic figures were often found, and they were sometimes atypical. Numerous capillaries were observed in tumour tissue but there were few high endothelial venules. The tumour was characterized by its unusual growth there were aggregations of tumour cells in the sinuses and the vessel

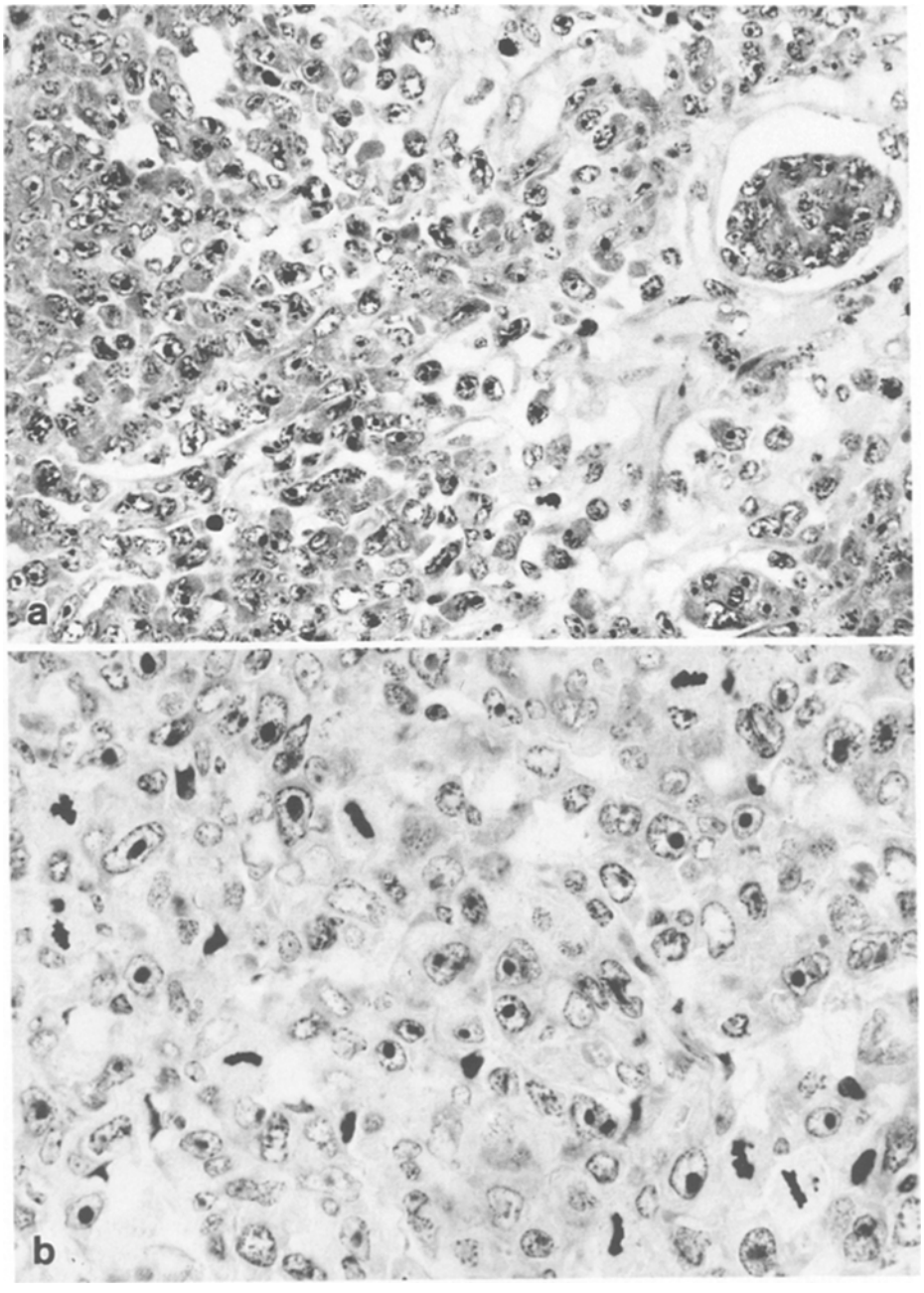

Fig. 5a, b. Large-cell anaplastic lymphoma. **a** Basophilic large cells, also intravascular growth. Giemsa, ×400. **b** Very large cells with solitary large nucleoli. Giemsa, ×700

walls were infiltrated. Slight or moderate fibrosis could be seen along the vessels in different areas. Areas of necrosis with a mild leucocytic reaction around their periphery were observed.

Various degrees of splenomegaly were observed in 12 of 15 cases (Table 2). Lymphocytic and prolymphocytic NHL with pronounced splenomegaly tended to form a thick splenic capsule, which was infiltrated by lymphocytes and a few immunoblasts in several cases. In all cases numerous tumour infiltrates were observed in the T-cell perivascular lymphocytic sheath, infiltrating the area around lymphoid follicles, and here mainly the marginal zones. In all cases of secondary immunoblastic lymphoma spleen infiltration was mainly immunoblastic. Lymphoid follicles were sometimes hypoplastic.

In two of three cases of large cell anaplastic lymphoma splenomegaly was pronounced. Numerous large, irregular nodules involved T zones and perifollicular areas. Follicles were completely or almost completely replaced by tumour cells. Case 15 with mainly local involvement of lymph nodes was an exception. In this case the spleen was hypoplastic, but some isolated anaplastic large cells were found. Among other lymphoid organs, the tonsils were affected in 4 of 15 cases (Table 2). Macroscopically the organ was not enlarged, though histologically there was a diffuse, lymphocytic or prolymphocytic-lymphocytic infiltration together with hypoplastic lymphoid follicles. In one case of large cell anaplastic lymphoma (14) there was a proliferation of anaplastic cells.

Table 4. Involvement of extralymphatic organs

Case no.	Liver	Kidneys	Lungs	Adrenal glands	Heart	Salivary glands (submaxillary)	Skin	Extranodal tumours
1	+	+−	+++	+−	+−	−	++	−
2	++	+−	+−	−	−	+−	−	−
3	+−	−	−	−	+++	−	−	+ (heart)
4	+−	+−	−	−	−	−	−	−
5[a]	−	−	−	−	−	−	−	−
6	+−	+	+−	+−	−	−	−	−
7	+−	+	−	−	−	+−	−	−
8	+−	+−	−	++	−	+	++	−
9	+	+	+++	−	+−	−	−	−
10	+	+++	+++	−	+−	++	−	−
11	+−	+−	−	−	−	+−	−	−
12	−	++	+++	−	−	−	−	+ (subcutaneous tissue)
13	−	+−	−	+	−	ND	−	−
14	+−	+++	+−	+−	−	ND	−	−
15	−	−	+−	−	−	+	−	−

[a] Animal died during a period of remission
ND, No data

Table 5. Lymphoid cell content in the peripheral blood and bone marrow of baboons with T-cell non-Hodgkin's lymphomas

Case no.	Number of leucocytes (10^9/l)	Number of lymphocytes		Percentage of lymphocytes in bone marrow	Presence of tumour cells in bone marrow[a]	Presence of lymphocytes in vessels of tumours
		%	absolute (10^9/l)			
1	12.4	40	4.96	18.6	+−	+
2	14.10	45.3	6.39	24.2	−	−
3	82.00	90	73.80	16.8	−	++
4	5.70	32	1.82	ND	−	−
5	12.00	43	5.16	22	−	−
6	14.00	63	9.10	ND	−	−
7	10.30	33	3.81	ND	−	+
8	17.00	48	8.66	ND	+−	+
9	18.00	10	1.8	20.4	−	−
10	16.00	17	2.72	ND	+−	−
11	37.20	5	1.86	ND	++	−
12	32.00	45	14.81	22.2	+	+
13	25.00	13	3.25	6.8	+	+
14	28.00	12	3.36	21.6	++	+
15	24.00	9	2.16	14	+−	+
Control[b]	11.62±4.81	20–35	4.47	11.4	−	−

[a] In the bone marrow smears of baboons nos. 1, 8, 10, 11 and 12 immunoblasts were found; in nos. 13, 14 and 15, large anaplastic cells were found
[b] Control: average data on healthy baboons 9–10 years old (13)
ND, No data

Parenchymatous extralymphatic organs and the skin were affected differently (Table 4). In some cases kidneys, lungs and liver were especially involved. Rarely, tumour infiltration was detected in the adrenals and salivary glands. In the liver the process tended to spread mainly periportally. In kidneys infiltration occurred in the cortical layer; in the adrenal glands the medulla was sometimes slightly or moderately infiltrated. Where the lungs were involved, the tumour showed a peculiar pattern because of the development of pronounced fibrosis. In case 3 a large lymphoid tumour occurred in the heart. In case 12 some small tumours were observed in subcutaneous tissues of the trunk (Table 4).

The *skin* was macroscopically affected in two cases (nos. 1 and 8, Table 4). This manifested itself in the appearance of patches with a desquamating surface. Histologically, the patches exhibited irregular sheets of massive diffuse dermal infiltration without involvement of the epidermis. Cell accumulations were mainly composed of small lymphocytes. Mitotic figures were rare. Parakeratosis and hyperkeratosis were observed in the epidermis.

The type of lymphoma and the organ involvement did not correlate with the level of bone marrow infiltration or with the state of the peripheral blood. In all cases investigated quantitatively (Table 5) bone marrow smears had a higher content of lymphocytes than the norm for the age. Moreover, in some baboons with immunoblastic and large cell anaplastic lymphomas single large tumour cells or small clusters were seen in the bone marrow. In the peripheral blood an increase in the total number of blood leucocytes was seen in most cases, but an increase in the absolute number of lymphocytes occurred only in some cases. In two cases (nos. 3 and 12) the peripheral blood had a clear-cut leukaemic picture.

Immunological phenotyping of tumour cells (Table 3) in cell suspensions showed that all 15 cases investigated were peripheral T-cell lymphomas, mainly with helper (CD4+) phenotype. Five cases had an unusual phenotype with co-expression of CD4 and CD8 antigens or loss of both accompanied by high expression of pan-T-cell antigens. Antigens associated with cell activation [IL-2 receptors (IL-2R) and Ia antigen] were frequently expressed by lymphoma cells. In cryostat sections (Table 3) tumour cells of all cases reacted with the mAb T11 (anti-CD2) and in most cases with Leu3a (anti-CD4). The tumour cells of all cases of anaplastic large cell lymphoma reacted positively with the mAb Ber-H2 (CD30). Varying amounts of CD30-positive cells were also detected among the tumour cells of two cases of secondary immunoblastic lymphoma (nos. 6 and 12). A considerable admixture of B-cells was found in some cases but with no light chain restriction in any of the cases. On cryostat and paraffin sections the cells did not react with anti-immunoglobulin antisera, but some cells of residual lymphoid follicles, B-immunoblasts and plasma cells showed positive reactions. In paraffin sections, positive reactions with the mAb L26 (CD20) and Ki-B3 (CD45R) were seen in the same cells.

In almost all cases (except no. 7) blood sera from baboons with NHL were positive for retrovirus STLV-1. This reaction was generally moderate; only in three cases of highly progressive lymphoma (nos. 11, 14, 15) was the antibody reaction intense.

Discussion

We have compared baboon T-cell malignant lymphomas with analogous entities in humans, especially with the HTLV-1-positive T-cell leukaemia/lymphoma (ATLL), which is endemic in Japan and in the Caribbean basin. Morphologically and immunologically all 15 cases of baboon NHL described here were regarded as generalized peripheral T-cell malignant lymphomas. They originated from the peripheral T-cell areas of the lymph node and developed various tumour types defined according to the proliferating T-cell variants. All baboons with NHL investigated in this study except one contained in their serum antibodies for T-lymphotropic retrovirus STLV-1, which is related to human HTLV-1 (Voevodin et al. 1987). It is known that ATLL has helper (CD4-positive) phenotype (Popovic et al. 1983; Gallo et al. 1984; Watanabe et al. 1988). The T-cell lymphomas in the Sukhumi monkey colony are also mostly of helper phenotype.

ATLL is characterized by pronounced cell pleomorphism (Popovic et al. 1983; Gallo et al. 1984; Watanabe et al. 1988). Baboon lymphomas, in contrast, were only slightly or moderately pleomorphic, irrespective of the presence of antibodies for STLV-1. The low level of cell pleomorphism in baboon T-cell lymphomas makes them similar to human peripheral T-cell lymphomas in Europe (Lennert et al. 1985) and China (Liang et al. 1986), but European and Chinese cases of T-cell malignancy are apparently not associated with T-lymphotropic retrovirus. In addition to lymphocytic NHL some T-immunoblastic lymphomas in humans can be associated with HTLV-1 in endemic areas (Suchi et al. 1987). Cases of large cell anaplastic Ki-1-positive lymphoma of T type in Europe did not contain HTLV-1 (Stansfeld et al. 1988) if they were localized in lymph nodes, but HTLV-1 (DNA provirus copy) has recently been reported in cells of cutaneous CD30-positive T-cell lymphoma in Europe (Anagnostopoulos et al. 1990).

There is some difference between skin involvement in virus-associated peripheral T-cell baboon and human lymphomas. According to the observations of Watanabe and others (Van der Valk et al. 1986; Watanabe 1986; Watanabe et al. 1988) in ATLL the skin is often affected, frequently with signs of epidermotropism. In contrast to this, in China skin involvement is not usual in cases of peripheral T-cell NHL (Liang et al. 1986). The same is true of baboon T-cell lymphomas.

Comparing the NHL of peripheral T type in baboons with peripheral T-cell lymphomas in man, classified according to the updated Kiel classification (Stansfeld et al. 1988; Lennert and Feller 1992), we can see many parallels and a few differences. T-cell lymphomas in both baboons and man can be differentiated into low- and high-grade types. The high-grade types may be primary, but appear to be more frequently secondary to a low-grade T-cell lymphoma. Such transformed cases may be more frequent than in man, but this assumption is based on the small number of cases presented here. It is also based on autopsy material, whereas most of the statistics in man are made on the basis of biopsy specimens.

The lymphocytic, immunoblastic and large cell anaplastic types are found in baboons and man, but the prolymphocytic-lymphocytic type has no equivalent in man. Immunoblastic and large cell anaplastic lymphomas of baboon and man are isomorphic. The lymphocytic type in baboons corresponds to chronic lymphocytic leukaemia of T type and to T-zone lymphoma in man. Indeed there was one case of lymphocytic lymphoma (no. 3) that showed strong lymphocytosis in the peripheral blood (in addition to another case of prolymphocytic-lymphocytic type, no. 12), indicating clear-cut leukaemia. However, half of the cases of lymphocytic and prolymphocytic-lymphocytic lymphoma also had a relatively high absolute number of lymphocytes in the peripheral blood, probably indicating that the lymphoma was in a subleukaemic state.

The prolymphocytic-lymphocytic type is character-

ized by the formation of large nodules, which may be interpreted as very large proliferation centres, analogous to the proliferation centres in chronic lymphocytic leukaemia of B-cell type in man. Such proliferation centres are not found in chronic lymphocytic or prolymphocytic leukaemia of T type in man (Lennert and Feller 1992).

Whereas all the cases of immunoblastic lymphoma described in this paper were secondary, three of four cases of large cell anaplastic lymphoma appeared to be primary. We cannot exclude the possibility that one or another of these cases may actually have been secondary after having overgrown and destroyed a putative pre-existing low-grade lymphoma.

In the lymphocytic type we included two cases that were morphologically similar to lymphoepithelioid ("Lennert's") lymphoma (LeL) in the updated Kiel classification (Stansfeld et al. 1988). Indeed, the cases in which epithelioid cell clusters had formed showed tumour cells with helper phenotype, tonsil involvement and absence of fibrosis and necrosis. The detection of single large perivascular granulomas and the lack of focal PAS positivity in the cytoplasm of epithelioid-like cells, however, testify in favour of infectious granulomatosis and against real LeL.

Simian large cell anaplastic lymphomas have a specific cytological and histological structure similar to that of human lymphoma (Stein et al. 1985; Suchi et al. 1987; Lennert and Feller 1992). They are characterized by highly anaplastic tumour cells, considerable fibrosis of the capsule and node parenchyma, partial preservation of the normal B-cell tissue of nodes and intrasinusoidal tumour growth.

Immunological typing of baboon NHL showed that these tumours, like the corresponding human lymphomas, had a mainly helper phenotype (Schwartz et al. 1984; Van der Valk et al. 1986; Voevodin et al. 1987). Tumours of suppressor phenotype were rare. In some cases loss or co-expression of T-helper and T-suppressor antigens was observed, which has also been described in human peripheral T-cell lymphomas (Picker et al. 1987; Ramsay et al. 1987). Most baboon NHL originated from activated T-cells, as they express a high frequency of Ia-like antigens and IL-2R. In their expression of IL-2R, baboon lymphomas lie somewhere between European human peripheral T-cell NHL with 30% IL-2R-positive cells (Krayewski et al. 1988) and Japanese human NHL of adults with a high level of IL-2R-positive cells that can reach 100% in human populations associated with a high occurrence of HTLV-1 (Doi et al. 1989).

In conclusion, T-cell type malignant lymphomas of *P. hamadryas* very closely resemble human peripheral T-cell malignant lymphomas, especially those tumours that are not HTLV-1 induced. These monkey lymphomas are a good model of non-HTLV-1-induced human lymphomas, although they also have a few morphological peculiarities. Since the antibody level against T-lymphotropic virus is usually elevated in monkeys with T-cell lymphomas, it appears useful to investigate the presence of DNA provirus in the genome of lymphoma cells, preferably in situ in histological sections.

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