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Diagnosis of primary cerebral lymphoma with particular reference to CT-guided stereotactic biopsy

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Summary. In establishing the histological diagnosis of primary cerebral lymphoma, stereotactic brain tumour biopsy is the method of choice as the mainstay of therapy is radiation and chemotherapy. This study describes the histopathology and diagnostic immunohistochemistry of 54 primary brain lymphomas in a mainly non-AIDS population. The stereotactic biopsies were performed using the Leksell CT stereotactic frame and a spiral needle which procured about 10-mm-long tissue cylinders. Usually, three successive biopsy cylinders were taken along the target trajectory. Histological examination revealed the prevalence of high-grade non-Hodgkin's lymphoma of the polymorphous centroblastic type. The series did not include any low-grade lymphomas or T-cell lymphomas. L-26 immunohistochemistry resulted in a positive staining of the blasts, thus confirming the B-cell origin of primary brain lymphomas. Small reactive T-lymphocytes and monohistiocytic cells were also found within and at the periphery of the lymphomas and in areas of degeneration. In the biopsies of nine patients, who had shown significant reduction of the lesions on the CT scans, after corticosteroid medication, regressive tissue changes were predominant and consisted of T-lymphocytes, macrophages, and occasionally bizarre reactive astrocytes.

Key words: Non-Hodgkin's lymphoma – Brain neoplasm – Stereotactic brain biopsy – Histological diagnosis – Immunohistochemistry

Introduction

Primary malignant lymphomas of the central nervous system are a well-defined clinicopathologic entity although the origin of the neoplastic cells and the pathogenesis of brain lymphoma are still obscure (Hochberg and Miller 1988; Rubinstein 1989). Primary cerebral lymphomas have represented about 1% of brain tumours (Jellinger 1983), but in recent years an apparent increase in frequency has been found, an increase independent of the increase of patients with acquired immunodeficiencies, either drug-induced (Penn 1983) or associated with HIV infection (So et al. 1986; Formenti et al. 1989; Hochberg and Miller 1988).

Currently, the mainstay of therapy for primary brain lymphomas is radiation (Berry and Simpson 1981; Letendre et al. 1982; Mendenhall et al. 1983; Bogdahn et al. 1986; Murray et al. 1986; Richter 1988) and, additionally, chemotherapy (Neuwelt et al. 1986; Hochberg and Miller 1988). Surgery, other than for diagnostic biopsy, is usually not beneficial. Moreover, these infiltrative neoplasms are often multifocal and deep-seated, including the basal ganglia, the thalamus and the periventricular areas. For these reasons, stereotactic brain tumour biopsy (Bosch 1980; Ostertag et al. 1980; Edner 1981; Kelly et al. 1985; Apuzzo et al. 1987; Davis et al. 1987; Lunsford 1988) seems to be the method of choice to establish the histological diagnosis as the basis for therapy and its evaluation. Clinically, the differential diagnosis of primary cerebral lymphomas includes glioma, meningioma, metastases, and focal inflammatory lesions like toxoplasmosis, especially in the immunodeficient (Jiddane et al. 1986; Jack et al. 1988; Kazner et al. 1988).

We report on the histopathology and diagnostic immunohistochemistry of 20 surgical and 34 out of 311 consecutive stereotactic brain biopsies (Feiden et al. 1989) with a diagnosis of non-Hodgkin's lymphoma (NHL) involving the brain. We also focused our attention on regressive changes in the tumour tissue which may predominate in the histological picture and make the morphological diagnosis more difficult, especially on stereotactic biopsy specimens.

Materials and methods

The study was performed on 20 surgical specimens obtained by open craniotomy and on stereotactic biopsies of 34 patients. The tissue specimens were collected between 1984 and July 1989. Eight cases with tumour resection or open biopsy were from other institutions and referred to us. Complete autopsy was performed on 3 patients who had died of cardiovascular and pulmonary diseases

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10 weeks, 1 year, and 2.5 years after the diagnosis of brain lymphoma had been established; these patients had received radiation therapy of the head, and the 2 with longer survival had additionally received systemic chemotherapy.

The group consisted of 29 men and 25 women aged 20–85 years (median 55 years). Most patients (57%) were in the age group between 45 and 65. The presenting cerebral symptoms, either increased intracranial pressure or local tumour effects, had been of short duration, generally 1–3 months. CT scans of the head revealed homogeneous contrast-enhancing mass lesions in the majority of the cases. In 14 patients (26% of the group) multiple tumours were visible. In order of decreasing frequency, the localization of the lesions was: the frontal region including the corpus callosum in about one-third of the cases; the basal ganglia, thalamus and periventricular areas; the occipital and the parietotemporal regions. Three surgically removed tumours were located in the cerebellar hemispheres. Stereotactic biopsy specimens were taken exclusively from supratentorial lesions.

At the time of admission and tumour diagnosis, only 1 of the patients had a history of neoplasia elsewhere in the body. This patient was a 65-year-old woman with an extranodal NHL of the breast and the skin 7 years before cerebral disease. Two homosexual male patients of the stereotactic series were HIV-seropositive and suffered from AIDS (Feiden and Backmund 1990). In the other patients, no findings indicative of immunodeficiency were known. Eight months, 1, and 2 years, respectively, after the diagnosis of primary brain lymphoma, 3 patients developed subcutaneous lesions of their NHL.

Generally, the indications for stereotactic biopsy were either (1) deep-seated single or multiple intracerebral lesions well imaged on CT scans in patients mainly without a previous tumour history or (2) intracerebral tumour-like lesions of a type poorly defined on imaging studies. The biopsies were performed through a burr hole and using the Leksell CT stereotactic frame (Leksell and Jernberg 1980; Lunsford and Leksell 1988). A special aspect of the technique consists of the use of a spiral needle (U.S.) which is a further development of the instrument quoted by Backlund (1971). This 12-mm-long spiral needle is guided through a CT-stereotactically placed cannula and turned into the tissue like a corkscrew. By pushing the cannula, the bevelled tip of which is sharpened, over the spiral, vermiform tissue cylinders 10–12 mm in length and 1–1.5 mm in diameter are obtained (Fig. 3). Usually, three to four successive biopsy cylinders were taken along the target trajectory, one before reaching, one to two in, and one behind the CT image of the lesion.

Tissue samples and brain from autopsy were fixed in 4% neutral buffered formaldehyde solution and processed routinely for paraffin sections. Intraoperatively, one Giemsa-stained smear preparation was made from a small piece of each stereotactic specimen to control the target trajectory. Deparaffinized sections were stained conventionally by haematoxylin and eosin (H&E) and the Giemsa stain, and immunohistochemically with the monoclonal antibodies listed in Table 1. For immunolabelling with the MAC387, tissue sections were digested in a 0.01% solution of type VII protease (Sigma, Deisenhofen, FRG) for 15 min. The detection system (all reagents from Dako, Hamburg, FRG) generally used consisted of biotinylated anti-mouse immunoglobulins and peroxidase-conjugated avidin. Part of the samples was complementarily stained with a streptavidin-biotin-alkaline phosphatase complex, which was also used for some double immunolabellings. The chromogenes were made visible by the H_2O_2-diamonobenzidine and the fast red reaction, respectively. Generally, the immunolabelled sections were counterstained with haematoxylin.

Table 1. Antibody panel used to characterize primary cerebral lymphomas

Monoclonal antibody[a]	Predominant expression	Reference
LC	Lymphocytes, granulocytes, monocytes	Warnke et al. (1983)
UCHL1	*T*-lymphocytes	Smith et al. (1986) Norton et al. (1986)
L26	*B*-lymphocytes	Ishii et al. (1984) Norton and Isaacson (1987)
MAC387	Monohistiocytes	Flavell et al. (1987)
GFAP	Astrocytes	Debus et al. (1983)

[a] Dako (Hamburg, FRG)

Results

Histologically, the characteristic growth patterns of cerebral lymphomas, consisting of angiocentric arrangements around blood vessels and a diffuse, partly dense tumour-forming invasion of blasts into the brain parenchyma, were conspicuous to a varying extent (Figs. 1, 3). Fifteen of the 20 surgical specimens were mainly composed of centroblast-like cells with prominent nucleoli situated at the nuclear membrane and variable numbers of immunoblasts with centrally placed large singular nucleoli (Fig. 1a). According to the Kiel classification, these neoplasms were classified as malignant centroblastic lymphoma, polymorphous type (Table 2). Furthermore, there were 3 B-lymphoblastic lymphomas (non-Burkitt's type) and 1 immunoblastoma, each composed of nearly pure proliferations of atypical cells of lymphoblastic and immunoblastic differentiation, respectively. One high-grade lymphoma situated in the cerebellar hemisphere was not classifiable due to freeze artefact.

Immunohistochemistry, using the monoclonal antibody L26, revealed strong cytoplasmic membrane positivity of the blasts in the majority of the surgical specimens (Fig. 1b), with the exception of the lymphoma tissue destroyed by freeze artefact. Between the blasts which generally showed a high mitotic activity, varying numbers of small lymphocytes and monohistiocytic cells reactive to UCHL1 and MAC387, respectively, were present (Fig. 1c, d). Extensive areas of regressive changes were conspicuous within and at the periphery of the lymphomas, composed of small UCHL1-positive lymphocytes, partly foamy macrophages and monohistiocytes, and reactive astrocytes with large, GFAP-positive cell bodies and vesicular nuclei (Figs. 1d, 2). In the regions of previous tumour manifestation of the

Fig. 1a–d. Surgical specimens of primary cerebral lymphomas. **a** Histology: malignant centroblastic lymphoma, polymorphic. Giemsa, ×700. **b–d** Immunohistochemistry (peroxidase-labelled avidin-biotin method, DAB, counterstained with haematoxylin). **b** Positive staining of the cell membranes of perivascularly arranged tumour cells with L26; small lymphocytes not reactive. ×700. **c** Numerous MAC387-positive monohistiocytes between angiocentrically arranged large lymphoid blasts. ×340. **d** Small nodule of L26-positive blasts with a wide rim composed of small reactive T-lymphocytes; some macrophages within the nodule; regressive tissue changes without the presence of tumour cells in the periphery. ×140

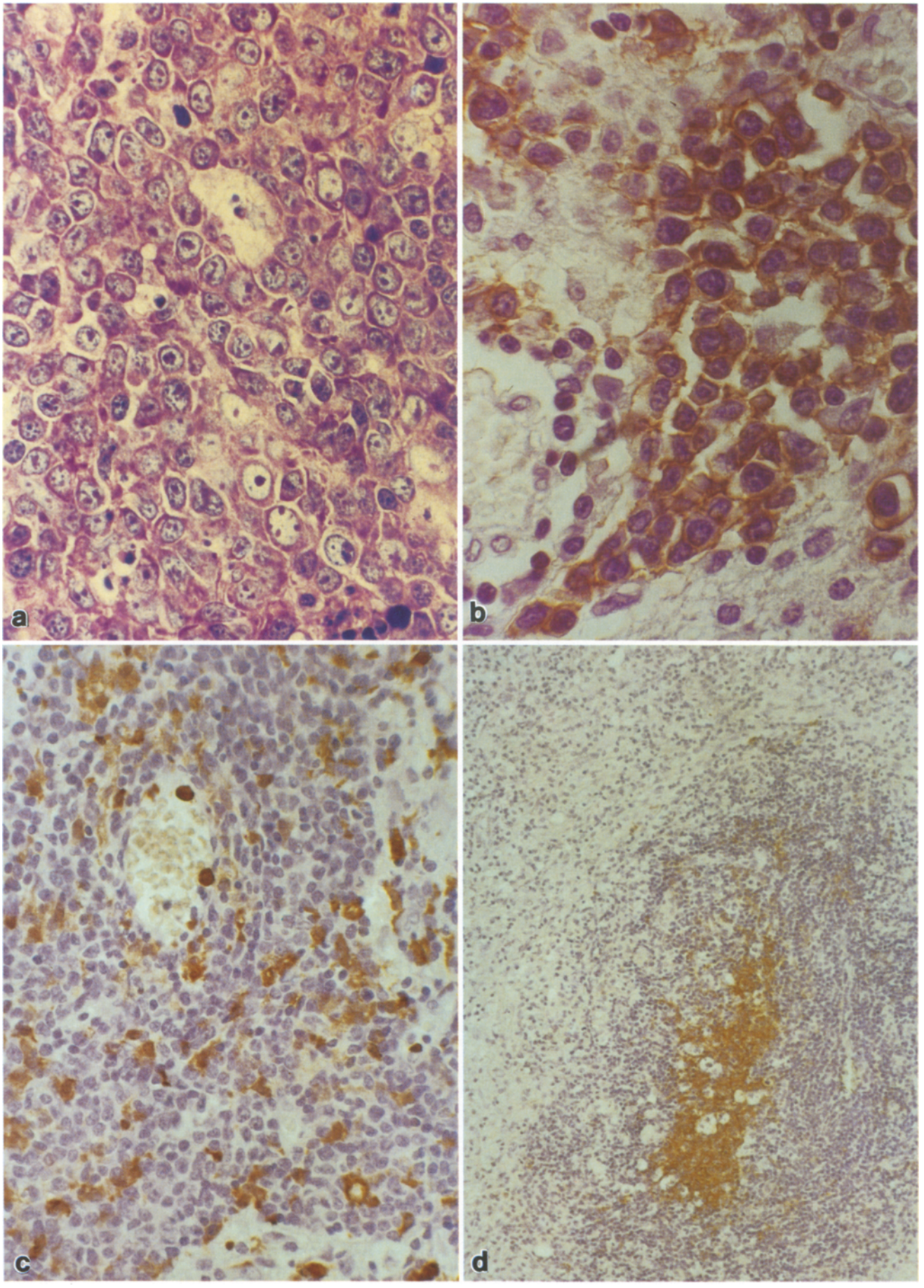
a
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Table 2. Histological classification of primary cerebral lymphomas (Kiel classification)

	Surgical specimens	Stereotactic biopsies	Total
Centroblastic, polymorphous (large non-cleaved FCC)	15	10	25
Immunoblastic (immunoblastic sarcoma-*B*)	1	6	7
B-lymphoblastic (small non-cleaved FCC, non-Burkitt's)	3	5	8
Mainly large cell-*B*, not classified further	0	3	3
Not classifiable	1[a]	1[b]	2
Brain lymphoma, highly suspected	0	9[c]	9
Total	20	34	54

(Lukes-Collins classification in parentheses)

[a] Freeze artefacts,
[b] Preponderant tumour necrosis
[c] Regressive changes

3 autopsy cases, similar regressive changes but no neoplastic proliferations were found.

On stereotactic biopsy, 25 of the 34 patients had a clear-cut histological diagnosis of malignant NHL of the brain. Histologically, the typical brain lymphoma patterns were reflected in the small tissue cylinders of the stereotactic biopsies (Figs. 3, 4). In 2 cases, only some vessels with scanty cuffs of small lymphocytes and a few blasts mimicking an encephalitic pattern were seen. With some reservation because of the relatively small sample size and a less than optimal tissue preservation, the classification of the stereotactically biopsied lymphoma tissue specimens was: 10 centroblastic polymorphic, 6 immunoblastic, and 5 B-lymphoblastic lymphomas (Table 2). The tumour tissue of 3 cases, mainly composed of large polymorphous, blast-like cells, was not classified further. The stereotactic biopsy specimen of the 1 AIDS-patient was not classifiable because of the preponderance of tumour necrosis.

Immunohistochemistry gave results comparable to those from the larger surgical specimens. In 4 of the 25 cases, the L26 reaction was doubtful because of partial necrosis and intercellular staining artefacts. In 9 stereotactically biopsied patients, the histological diagnosis

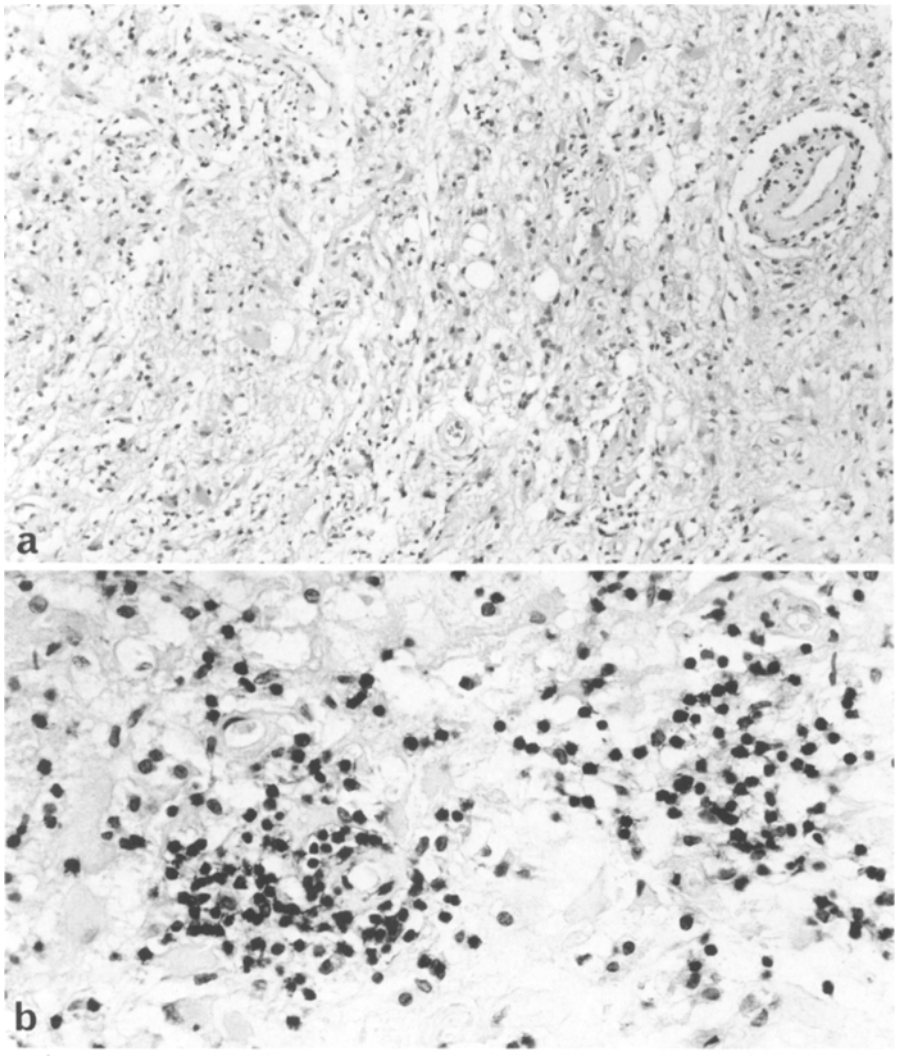

Fig. 2a, b. Regressive changes in brain lymphomas. **a** Small lymphocytes and monohistiocytic cells within a loose texture mainly composed of reactive astrocytes; blood vessel with thickened wall and remnants of a vascular cuff (*right*). Patient under dexamethasone medication at the time of biopsy. H&E, ×140. **b** UCHL1-reactive T-lymphocytes accumulated around small blood vessels; numerous reactive astrocytes with abundant homogeneous cytoplasm. Peroxidase-labelled avidin-biotin method, DAB, counterstained with haematoxylin. ×340

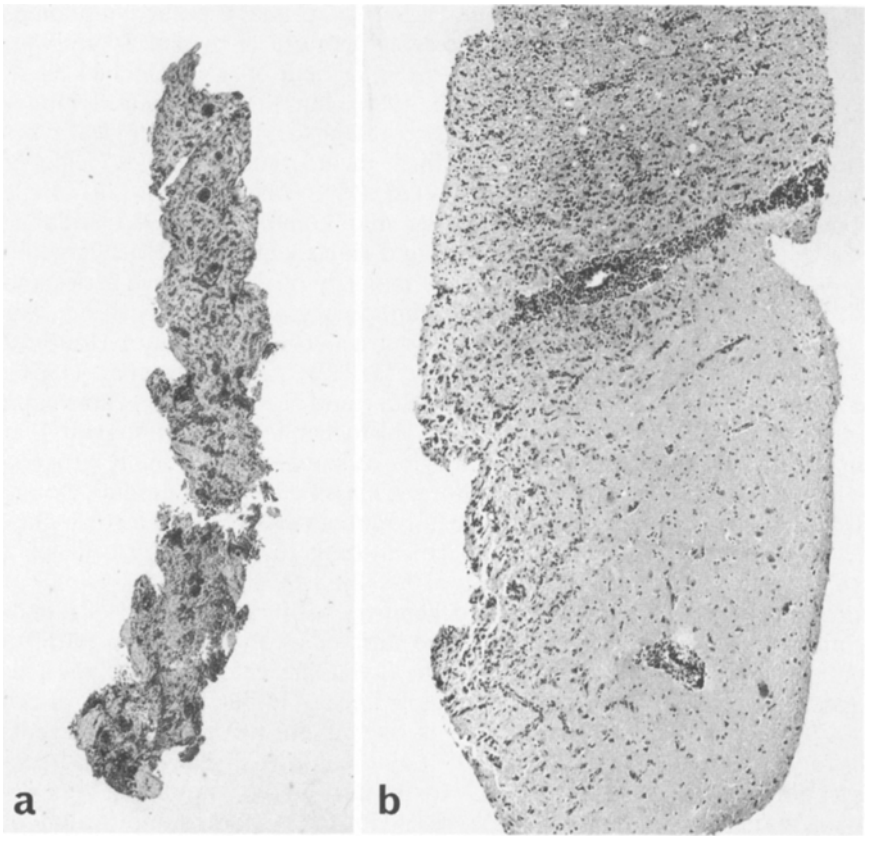

Fig. 3a, b. Stereotactic biopsies of primary brain lymphomas. **a** Third specimen of the trajectory from the central portion of the CT image; intracerebral mass lesion located in the basal ganglia. Typical angiocentric pattern of cerebral lymphoma. Giemsa, ×14. **b** Second specimen of the trajectory from the border zone of the CT image of an intracerebral mass lesion suspected of metastasis. Pseudoencephalitic pattern of a primary cerebral lymphoma. H&E, ×55

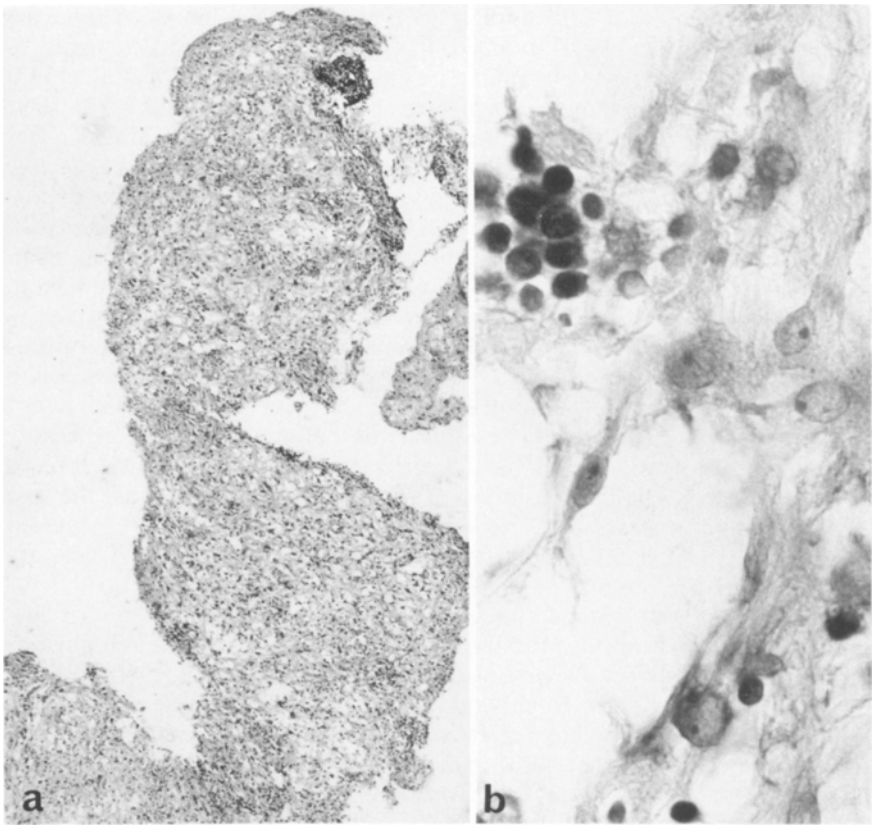

Fig. 4a, b. Stereotactic biopsies with the highly suspected diagnosis of brain lymphoma; patients with significant reduction of their intracerebral mass lesions in the CT image at the time of biopsy with prior dexamethasone medication. **a** Third biopsy cylinder of the target trajectory through a lesion in the deep occipital white matter near the posterior horn. Regressive changes similar to those seen in the surgical specimens (Figs. 1d, 2); dense perivascular cuff (*top*) mainly composed of small UCHL1-positive lymphocytes and a few in part L26-reactive blasts. Giemsa, ×55. **b** Small biopsy specimen from a lesion in the basal ganglia near the third ventricle. Reactive astrocytes characterized by vesicular nuclei with prominent nucleoli and fibrillary cytoplasm (*right*); small cluster of dark stained lymphoid blasts (*upper left*). Giemsa, ×800

of brain lymphoma was not clear-cut but highly suspected. In these specimens, regressive changes predominated. In 6 of the cases, serial sections revealed small clusters of partly L26-reactive, blast-like cells (Fig. 4b). All of the nine patients with this peculiar pattern had received dexamethasone for several days prior to biopsy, and at the time of stereotactic procedure, the CT image of the lesions was distinctly reduced in comparison to the first CT examination.

Discussion

In our material of 311 consecutive stereotactic brain biopsies obtained since 1984 (Feiden et al. 1989), brain lymphomas represent 15% of the 230 neoplasms diagnosed histologically. In the series of Bosch (1980), Edner (1981), Kelly et al. (1985), Davis et al. (1987), and Lunsford (1988), brain lymphomas constituted 2 of 60 (3%), 4 of 117 (3%), 3 of 36 (8%), 28 of 367 (8%), and 16 of 240 (7%) stereotactically diagnosed brain tumours, respectively. The large series of stereotactic brain tumour biopsies of the Freiburg group (Kleihues et al. 1984; Anagnostopoulos et al. 1987) included only a small number of cerebral lymphomas, ranging from 0.5% to 0.7% of all neoplastic lesions diagnosed. The reasons for the relatively high percentage of brain lymphomas in our material may be (1) the indications and selection of patients for stereotactic brain biopsy; (2) the increase on frequency of primary cerebral lymphomas in recent years (Hochberg and Miller 1988) and (3) the applied stereotactic biopsy technique and strategy, which is characterized by relatively large tissue cylinders and successive sampling along the target trajectory, thus providing a representative profile of the lesion and the adjacent infiltrated brain. This strategy is based on the observation that neoplastic lesions within the brain may be far more extensive than they appear on enhanced CT scans, and that in the case of highly malignant neoplasms with extensive regressive changes and tumour necrosis, very small specimens may be inadequate for morphological diagnosis. However, stereotactic brain lymphoma diagnosis has also been made on very small specimens procured by forceps instruments (1–2 mm^3) and the target point concept of sampling, including diagnostic smear preparations (Namiki et al. 1988) and frozen-section immunohistochemical methods (Pearl et al. 1985; O'Neill et al. 1987). In our view, H&E- and Giemsa-stained paraffin sections provide the basis for an accurate diagnosis and classification of brain lymphomas on stereotactic biopsy, provided that the tissue material is representative for the lesion (Bise et al. 1988).

The majority of the neoplasms of our series correspond to the polymorphous centroblastic type of NHL (Lennert 1978, 1981; Hui et al. 1988; Stansfeld et al. 1988). A similar prevalence of malignant centroblastic lymphoma was seen by Spaun et al. (1985), Grant et al. (1986), Schiffer et al. (1987), and Nakamine et al. (1989). Furthermore, diffuse large cell malignant lymphoma of the "Working Formulation" (The Non-Hodgkin's Lymphoma Pathologic Classification Project 1982) also constitutes the main group of primary brain lymphomas reported in the recent literature (Freeman et al. 1986; Kumanishi et al. 1986; O'Neill et al. 1987; Jack et al. 1988; Namiki et al. 1988). Immunoblastic and lymphoblastic lymphomas represent the main histological types in other reports which include autopsy series (Jellinger et al. 1975; Taylor et al. 1978; Hassoun et al. 1981; Helle et al. 1984; Casadei and Gambacorta 1985; Jiddane et al. 1986; Merkel and Hansmann 1986; Hochberg and Miller 1988). In the majority of these quoted series and in our own, lymphoplasmacytoid immunocytoma was rare or absent, in contrast to the reports of Houthoff et al. (1978), Jellinger (1983), Allegranza et al. (1984), Bogdahn et al. (1986), and Merkel and Hansmann (1986). Our immunohistochemical results suggest that the small lymphocytes of some of these highly progressive brain lymphomas, classified as LP-immunocytoma, might be reactive *T*-lymphocytes, the pleomorphic plasmacytoid blasts constituting the neoplastic cells of a high-grade NHL of *B*-cell type.

Immunohistochemistry with a small panel of monoclonal antileucocyte antibodies that react on paraffin sections confirms the B-cell lineage of our cerebral lymphomas. In assigning lineage in the high-grade B-cell lymphomas, L26 is one of the most reliable reagents (Cartun et al. 1987; Hall et al. 1988; Norton and Isaacson 1989a, b). No primary T-cell lymphoma was detected in our series. However, marked infiltration of small UCHL1-positive lymphocytes, obviously corresponding to reactive *T*-lymphocytes, was found around blood vessels and in the diffuse infiltration areas as well as in regressively changed parts of the *B*-cell neoplasms. The occasional presence of small lymphocytes reactive to *T*-cell markers in frozen sections has been reported by Pearl et al. (1985), Grant et al. (1986), Kumanishi et al. (1986), Garson et al. (1988) and Smith et al. (1988) in some cases of primary cerebral lymphomas. In their study of 37 primary lymphomas of the brain, Schiffer et al. (1987) observed varying numbers of small reactive *T*-lymphocytes ranging from 5% to 30%; they were positively stained by UCHL1 in paraffin sections. Our own investigations confirmed these findings (Feiden et al. 1988) and also the observation made by Grant et al. (1986) of many reactive monohistiocytic cells, partly resembling so-called microglia. The finding of an infiltration of some lymphocytes in biopsy tissue from a lesion which is suspected to be a cerebral lymphoma is not sufficient to establish the definite diagnosis, especially in the very small specimens from stereotactic forceps biopsies using the target point strategy. Thus, the two cases of O'Neill et al. (1987) stereotactically diagnosed as malignant lymphoma, small lymphocytic, T-cell, are suspect.

Some clinical case reports have documented remission of primary brain lymphomas after the administration of corticosteroids (Kikuchi et al. 1986; Todd et al. 1986). Hochberg and Miller (1988) have seen partial or complete regression of the clinical and CT-lesions in 37% of 48 of their patients treated with dexamethasone for 10 days, obviously representing glucocorticoid cytotoxicity for lymphoid cells of these neoplasms (Homo-

Delarch 1984). Furthermore, spontaneous regression of cerebral lymphomas might be considered to have been demonstrated in the surgically resected lymphomas of this series. The regressive tissue changes described above are not specific but commonly occur in brain lymphomas. For critical assessment of the histopathological diagnosis on stereotactic specimens, serial sections and immunohistochemical stainings using the above antisera may be helpful in detecting blasts of B-cell lineage. On morphological grounds alone both chronic encephalitic disease (multiple sclerosis) and astrocytoma are significant differential diagnostic considerations. In the 9 patients with the constellation of remission of the CT lesion under dexamethasone medication and predominance of regressive tissue changes, the tentative diagnosis of cerebral lymphoma was made on the histological and immunohistochemical findings in conjunction with a detailed knowledge of the clinical and neuroradiological findings; in all cases, radio-chemotherapy was given.

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