Virchows Archiv A Pathol Anat (1989) 415:265–273

Virchows Archiv A
Pathological Anatomy and Histopathology

Heterogeneous malignant non Hodgkin's lymphomas as a causative disorder in lethal midline granuloma

R. Hubert Laeng, Heinz A. Gerber, Thomas Schaffner, and Kurt H. Bürki
Department of Pathology, University of Bern, Freiburgstrasse 30, CH-3010 Bern, Switzerland

Summary. The present report describes the results of a combined morphological, enzyme- and immunohistochemical analysis of nine cases of malignant non Hodgkin's lymphomas (NHL) clinically presenting as lethal midline granuloma. In a previous report written before antibodies directed against B and T lymphocytes were available, a histiocytic origin of such neoplasms had been suggested. A panel of antibodies reactive with most B cells (L26, MB1, KiB3) and a majority of T cells (MT1, UCHL1) was applied on paraffin sections of formalin fixed tissues as well as antibodies directed against leukocyte common antigen (LCA), myeloid/histiocyte antigen (MAC 387), lysozyme, alpha-1-antitrypsin, alpha-1-antichymotrypsin, S-100 protein, prekeratin and immunoglobulin light chains. Enzyme histochemistry included tests for non-specific acid esterase, acid phosphatase, beta-glucuronidase and chloroacetate esterase. As a result, five T, two B and two unclassified (malignant histiocytosis probable) NHL were identified, indicating distinct heterogeneity of NHL as causative disorders in lethal midline granuloma.

Key words: Midline granuloma – Histochemistry – B cell NHL – T cell NHL – Malignant histiocytosis

Introduction

Lethal midline granuloma is defined as a clinical entity characterized by rapidly progressing lesions leading to extensive destructions of midfacial structures (Friedman and Osborn 1982; Laeng et al. 1986). Its neoplastic nature – besides reactive proliferative disorders caused by infectious agents, foreign bodies, autoimmune response, vasculitis – is now generally accepted (for review see Schlegel and Kraft 1979; O'Connor and Robinson 1987).

Malignant non Hodgkin's lymphomas (NHL) are argued to represent the most frequent neoplasms in lethal midline granulomas (Aozasa et al. 1981; Eichel et al. 1966; Laeng et al. 1986). Malignant histiocytosis (histiocytic sarcoma, NHL true histiocytic) was suggested as an underlying disorder only a few years ago (Aozasa et al. 1981; Aozasa 1982; Aozasa and Inoue 1982; Laeng et al. 1986).

However, growing evidence has appeared that the criteria attributed to "histiocytic properties" of a given cell-line so far are also detectable in lymphoid cells (Isaacson et al. 1983; Isaacson et al. 1985; Isaacson and Spencer 1987). In addition, mucosa-associated malignant lymphomas, formerly termed histiocytic, were shown to express epitopes found on either B or T cells (Isaacson 1985). In recently presented series of lethal midline granuloma, mainly T cell lymphomas were identified in cases of NHL as a causative disorder (Chan et al. 1987; Chi-Sing et al. 1986; Chott et al. 1988; Ishii et al. 1982; Lippman et al. 1987; Ramsay et al. 1988). T cell NHL were also detected in most cases of lymphomatoid granulomatosis (Lipford et al. 1988). An angiocentric pattern of atypical infiltrates was suggested to be a morphological hallmark of lymphomas arising from the upper respiratory tract and paranasal sinuses (Chan et al. 1988). Therefore it appeared to be of interest to discuss the results of an extended immunohistochemical analysis on our own series, with particular emphasis on diagnostic difficulties concerning neoplasms formerly termed "histiocytic tumours".

Offprints requests to: R.H. Laeng

Table 1. Clinical data and histomorphologic classification

Case	Sex	Age at diagnosis (years)	Survival (years)	updated Kiel classification; site of first manifestation; distribution of lesions
1	male	41	5/12	T, low grade, small; epipharynx, maxilla; autopsy: generalized diasease
2	female	39	alive	T, low grade, small-medium; nasal area; limited disease patient in remission for 2 years
3	male	32	4	T, high grade, large, polymorphous; nasal septum and maxilla; autopsy: generalized disease
4	male	18	alive	T, high grade, medium-large, polymorphous; nasal area; limited disease patient in remission for 10 years
5	male	24	alive	T, high grade, large, polymorphous; nasal area; generalized disease diagnosis made recently
6	male	21	alive	B, high grade, centroblastic, polymorphous; maxilla and nasal area; limited disease patient in remission for 10 years
7	male	29	$1\ ^1/_2$	B, high grade, centroblastic; epipharynx; generalized disease confirmed by biopsies
8	male	71	3	malignant histiocytosis probable; nasal area; generalized disease (clinical diagnosis)
9	male	69	$1\ ^1/_4$	malignant histiocytosis probable; nasal area, epipharynx, maxilla; autopsy: generalized disease

Materials and methods

Nine cases of NHL initially diagnosed on biopsy specimens taken from the midfacial area (including the soft palate) were registered in our files over a period of 15 years. All cases fullfilled the criteria of so-called lethal midline granuloma. Infections, vasculitis, foreign body and autoimmune reactions could be excluded as underlying disorders by clinical data and histological analysis. An overview on the relevant clinical data and histomorphologic classification is given in Table 1.

Gentle treatment of generous biopsy material and often serial sections from the paraffin blocks were unconditional requirements in order to establish definite diagnosis of the underlying disorder. In every case, well preserved deeper areas of tumour tissue – being devoid of vasculitis – were used for microscopic evaluation. Portions of biopsy specimens were routinely fixed in neutral buffered formalin, embedded in paraffin, sectioned to 5 μm thickness and stained with haematoxylin and eosin, Giemsa's solution, silver (Gomori-Foot) and periodic acid-Schiff (PAS) reagent. In addition, biopsy material from most cases was embedded in methacrylate and sectioned to 2 μm thickness.

From all patients fresh unfixed biopsy material was collected for enzyme histochemical investigations as described in a previous report (Laeng et al. 1986). Reactions to detect chloroacetate esterase (Leder 1964) were performed on paraffin sections of formalin fixed tissue. Substrates and pH for each enzymatic reaction are indicated in Table 2.

For immunohistochemical studies, 5 to 7 μm thick paraffin sections were mounted on glass slides coated with polyvinyl acetate glue (Järvinen and Rinne 1983), deparaffinized, hydrated and, if necessary, treated with 0.1% trypsin for 10 min at 37° C. Sections were then washed and incubated at room temperature for 18 to 24 h with specific antibodies directed against human lysozyme (muramidase), human alpha-1-antitrypsin (AT), human alpha-1-antichymotrypsin (ACT), bovine brain S-100 protein (whole protein comprising alpha and beta chain), prekeratin (cases 1, 6, 8 and 9 only), leucocyte common antigen (LCA), myeloid/histiocyte antigen (MAC 387) as well as with antibodies detecting epitopes on B-lymphocytes (L26, KiB3, MB1) and T lymphocytes (UCHL1, MT1). Incubations without specific antibody served as negative controls. In case 5 acetone fixed frozen sections were incubated with antibody binding with antigens CD4 and CD8. The avidin-biotin-peroxidase complex (ABC) technique (Hsu et al. 1981), using either aminoethylcarbazole or diaminobenzidine (Sigma, St. Louis, USA) as a chromogen, was applied to visualize binding of specific antibodies, and the sections were counterstained with haematoxylin. The KiB3 antibody was gratefully donated by Dr. Feller, Kiel (FRG). The antibodies MB1 and MT1 were purchased from Bio Science Products, Emmenbrücke, Switzerland. All other antibodies and the ABC reagents were obtained from DAKO, Denmark.

For demonstration of intracytoplasmic kappa or lambda light chains of immunoglobulins, deparaffinized and hydrated paraffin sections were treated with trypsin and double-stained by direct immunofluorescence using rabbit antibodies, raised and labelled with fluoresceine or tetramethyl rhodamine in our laboratory.

Results

As shown in Table 1, the midfacial area was the site of the first manifestation of the disease corresponding to midline granuloma. Eight of nine patients were males and age ranged between 18 and 71 years at time of diagnosis. Local radiotherapy was applied in all cases, while polychemotherapy was administered in case 7 and has been initiated in case 5, which was recently diagnosed. Five patients died within five months to four years after diagnosis; autopsy carried out in three cases revealed generalized disease, whereas in two remain-

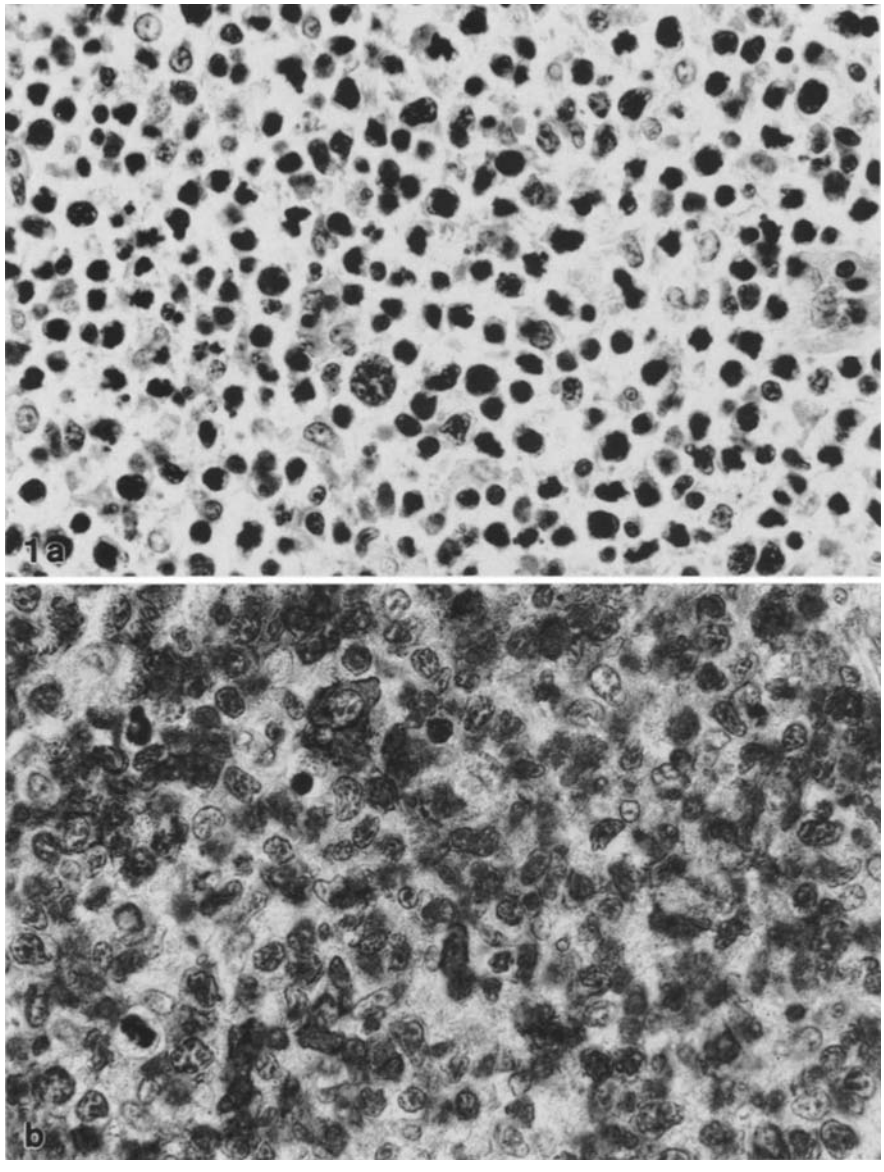

Fig. 1a. T cell NHL, high grade, large, polymorphous with hypereosinophilia (Giemsa, 550×, case 5). **b** Incubation with UCHL1 antibody resulted in an intense reaction with most tumour cells (550×)

ing cases generalisation of the neoplasms could either be registered on clinical parameters or verified on biopsy material taken from distant sites. Four younger patients are still alive and (for cases 2, 4 and 6) free of manifest disease at present times; relapse free intervals are ranging from four to ten years.

Extensive necrosis and dense inflammatory infiltrates comprising eosinophilic granulocytes were regular findings on ulcerating surfaces covered by fibrin and granulation tissue, whereas foam cells, haemosiderosis of macrophages and reactive giant cells were optional details. Presence of superficial bacterial and/or fungal colonies was a rule. In accordance with the Kiel classification (Stansfeld 1988; Stein et al. 1984), three different main groups of NHL could be distinguished:

(1) T cell NHL (immunohistochemical results see below) of small (case 1), small-to-medium (case 2) and pleomorphic medium-to-large or large cell type (cases 3, 4 and 5). In addition to the usual morphology of T cell types, giant cells were found in case 3, and hypereosinophilia was present in case 5 (Fig. 1a). Abundance of epithelioid venules was a prominent feature. Intestinal infiltrates of atypical cells in case 5 displayed an angiocenctric pattern.

(2) B cell NHL (cases 6 and 7) were of pleomorphic centroblastic type (Fig. 2a), assuming diffuse growth patterns.

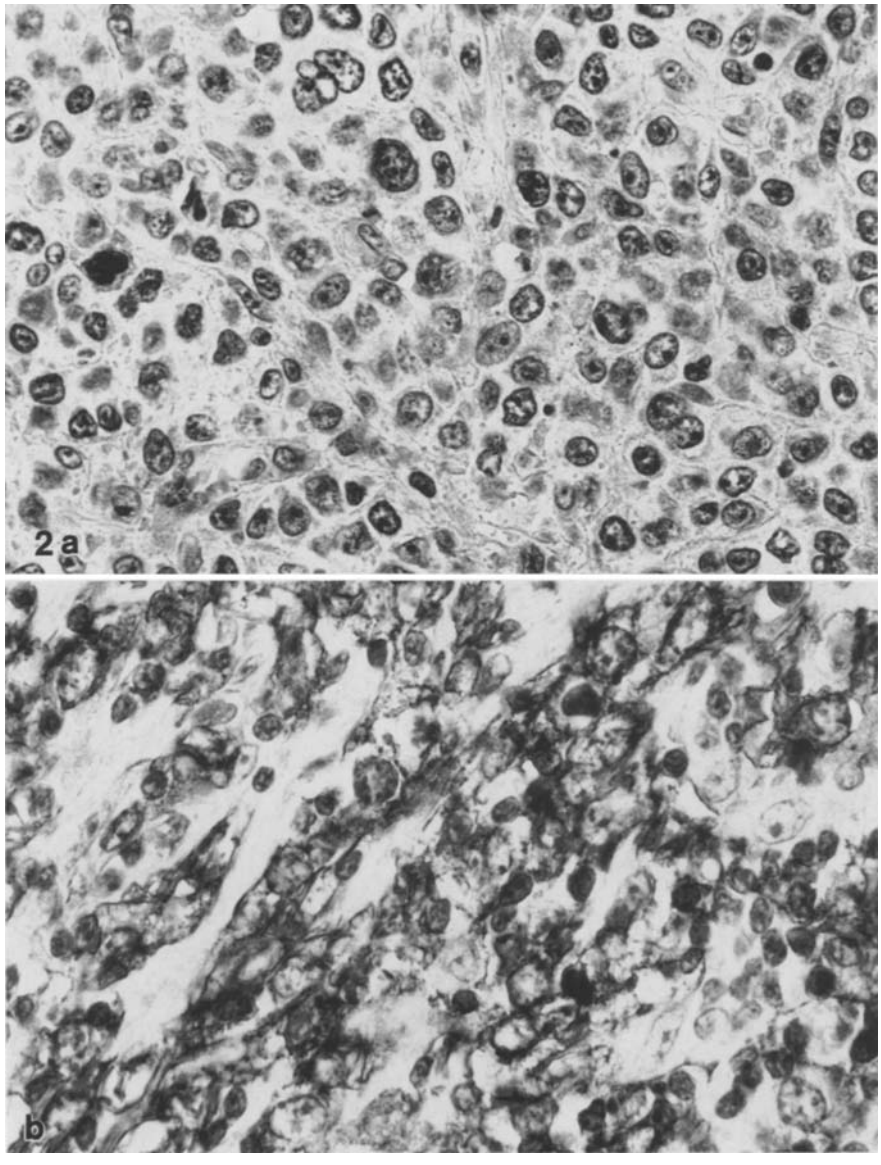

Fig. 2a. B cell NHL, high grade, centroblastic (methacrylate section, haematoxylin & eosin, 500×, case 7). **b** Strong membrane-associated staining reaction with a majority of tumour cells upon incubation with L26 antibody (500×)

(3) Unclassified NHL (cases 8 and 9) represented the most interesting neoplasias (Fig. 3 and 4), distribution of lesions found at autopsy (case 9) being in accordance with generalized NHL. The uniform cell population was of large cell type, embedded in a dense network of reticulin fibres. Giant tumour cells and so-called emperipolesis were frequent. Presence of erythrophagocytosis by neoplastic cells was seen occasionally, and haematogeneous pigment was abundant in focally infiltrating macrophages but was also displayed by some tumour cells. The morphological findings in these two tumours were consistent with neoplasms termed histiocytic reticulosarcoma or malignant histiocytosis (Lennert 1981).

In all cases strongly positive reactions for non-specific acid esterase were at least partly inhibited in the presence of sodium fluoride (see Table 2). In the majority of cases diffuse cytoplasmic activities for acid phosphatase and beta-glucuronidase were detected. A smaller fraction of cells found within dense inflammatory infiltrates displayed strong reactions for the above mentioned acid hydrolases, particularly for non-specific acid esterase in the presence of sodium fluoride. This observation reflects infiltration of the tissues by non-neoplastic, reactive histiocytes/macrophages. In none of the cases was chloroacetate esterase detected in tumour cells, while infiltrating granulocytes and mast cells were strongly reactive. With the excep-

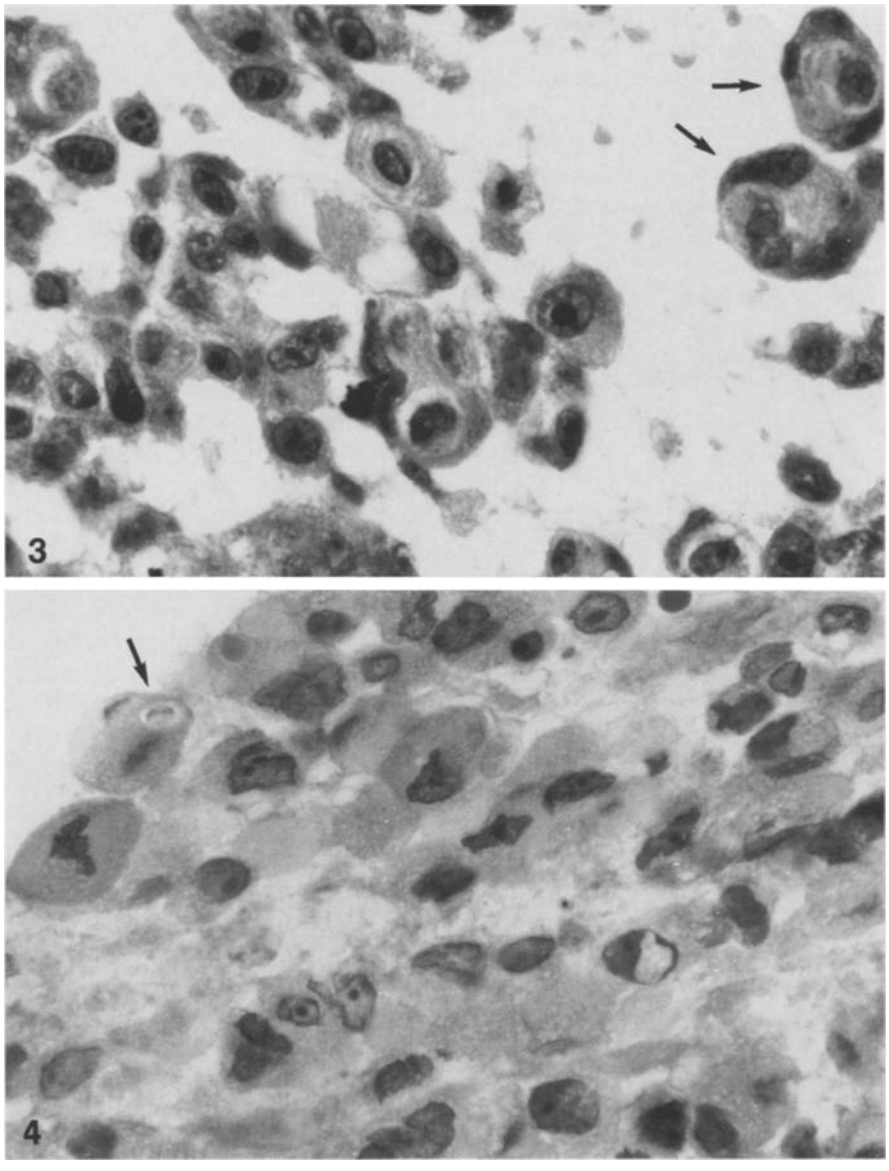

Fig. 3. Unclassified NHL, large, polymorphous with giant cells and so-called emperipolesis (arrows, haematoxylin & eosin, 780×, case 8)

Fig. 4. Unclassified NHL, large, polymorphous with erythrophagocytosis (arrow, methacrylate section, haematoxylin & eosin, 780×, case 9)

tion of case 5 the results of enzyme histochemistry were published and illustrated in a previous report (Laeng et al. 1986).

By immunohistochemistry LCA was detectable in atypical cells of all cases but weakly expressed in the tumours of cases 2, 5, 7, 8 and 9; it was diffusely distributed in the cytoplasm of the latter two cases. In all T cell NHL (cases 1–5), epitopes reactive with MT1 and UCHL1 (Fig. 1b) antibodies were present. A few neoplastic cells in case 1 were also stained with KiB3 antibody. In addition, the neoplastic T cell population of case 5 was identified as a CD8 positive subset. The two B cell lymphomas (cases 6 and 7) in our series reacted with the antibodies L26 (Fig. 2b, case 7) and KiB3, while in case 7 the tumour stained also with MB1 and partly with MT1 antibodies.

Alpha-1-antitrypsin and alpha-1-antichymotrypsin were recognized in a variable portion of atypical cells in all T cell lmyphomas, while a small amount of lysozyme was demonstrable in a minor fraction of tumour cells in case 1 only. One of the B cell NHL (case 7) expressed lysozyme, alpha-1-antitrypsin and alpha-1-antichymotrypsin in a variable proportion of neoplastic cells. In both, B and T cell lymphomas, interspersed histiocytes/macrophages, often present in abundance, were clearly detected by antibody MAC 387 in accordance with the demonstration of lysozyme containing cells in reactive cellular infiltrates.

A diffuse, granular cytoplasmic reaction was observed in two unclassified neoplasms (cases 8 and 9) with antibodies directed against LCA, B-cells, macrophages, alpha-1-antitrypsin, alpha-1-antichymotrypsin and S-100 protein. Further immunohistochemical investigations carried out with what little material remained of these two tumours revealed also diffuse, rather weak cytoplasmic staining with antibody to prekeratin, clearly differing from the strong staining displayed by overlying squamous epithelia. In contrast, prekeratin was not detected in the B and T cell NHL tested for.

Discussion

In a previous report (Laeng et al. 1986) comprising cases 1–4 and 6–9, a histiocytic origin of the neoplastic cell fraction had been argued based on morphological characteristics, the results of enzyme histochemical investigations and the presence of lysozyme, alpha-1-antitrypsin and alpha-1-antichymotrypsin in tumour cells. These arguments, at that time, were generally accepted for the putative histiocytic origin of a given cell (Isaacson et al. 1983).

However, enzyme histochemistry dose not allow distinction between B and T cells and histiocytes, respectively as illustrated by our results (Tables 2, 3). Lymphocytic neoplasms may share expression of acid hydrolases with histiocytes; this pertains to beta-glucuronidase and N-acetyl-beta-glucosaminidase (Crockard 1984), acid phosphatase and/or fluoride-sensitive non-specific esterase (Isaacson et al. 1985; Stansfeld 1985), whereas the presence of these hydrolases in interdigitating and dendritic reticulum cells is controversal (van Heerde et al. 1983; Stansfeld 1985). Moreover, there is evidence that in NHL particularly of T cell nature tumour cells may contain alpha-1-antitrypsin (Isaacson et al. 1985) and alpha-1-antichymotrypsin (Isaacson, personal communcation), being frequently correlated with phagocytic activity (Roholl et al. 1985). Necrosis, attracting reactive leukocytes, is possibly a consequence of the angiocentricity as observed in certain NHL; ischaemic colitis, a complication in case 5, may reflect this pathogenesis. Finally, neoplastic cells of lymphoid origin are likely to take up, at least in part, proteins produced by infiltrating reactive cells and mucosal epithelia (Isaacson et al. 1985), thus achieving puzzling antigenic patterns.

In our cases described, dense infiltration of tumour tissue by granulocytes (especially eosinophils), reactive macrophages (sometimes laden with lipids or haemosiderin) and mast cells was a regular finding. MAC 387, an antibody raised to detect epitopes expressed by most monocytes/macrophages, remains unreactive e.g. with dendritic reticulum cells and a fraction of histiocytes such as some types of epithelioid giant cells (Dakopatts specification sheet 1987). With the single exception of some atypical cells in case 3, in none of the other B and T cell NHL described here, neoplastic cells were reactive with antibody MAC 387. However, in cases 8 and 9 most of the neoplastic cells were found to bear determinants for the antibody MAC 387. Reactive histiocytes/macrophages infiltrating the tumourous tissues could clearly be demonstrated with this antibody.

In our series, two different antibodies, MT1 and UCHL1, directed against T lymphocytes were applied. Neither MT1 nor UCHL1 are able to detect T cells exclusively: MT1 is known to be reactive also with monocytes/macrophages, myeloid cells, erythrocyte precursors and some neoplastic B cells (Poppema 1987); UCHL1 antigen is found on some cells of myeloid lineage but very rarely on B cells (Linder et al. 1987; Smith et al. 1986).

Of the three antibodies used to detect B lymphocytes, L26 antibody has recently been shown to be the most reliable reagent (Cartun et al. 1987; Norton and Isaacson 1987a). The MB1 determinant is also present on an important fraction of mature T cells (Norton and Isaacson 1987b; Poppema et al. 1987); KiB3 antigen is displayed by some activated T cells and partly by monocytes of the peripheral blood (A.C. Feller, personal communication; Norton and Isaacson 1987b). On paraffin sections of these two tumours, immunoglobulin light chains were not detectable. The small number of cases precludes conclusions indicative for differences in the biological behaviour of B and T cell lymphomas arising from mucosa-associated lymphoid tissue.

Neoplastic cells in cases 8 and 9 reacted weakly with many antibodies. Based on the sum of the morphological findings, differential diagnostic alternatives such as poorly differentiated carcinoma, malignant melanoma and neuroblastoma were rejected.

Considering the histopathologic findings amplified by the results obtained with a panel of antibodies presently available, we would propose the following conclusions: The lesions presenting as lethal midline granuloma may be heterogeneous types of malignant NHL. To our knowledge only one B cell NHL has been identified so far as an underlying disorder (Yamanaka et al. 1985), while T cell NHL in have been documented previously by others. The detection of NHL with B cell prop-

Table 2. Results of enzyme histochemical reactions in neoplastic cell fractions

	Case number:								
	1	2	3	4	5	6	7	8	9
non-specific acid esterase, pH 5.8 (alpha-naphthyl acetate)	+	+	+	+	+ (few)	+	+	+	+
non-specific acid esterase, pH 5.8 (alpha-naphthyl acetate) in presence of NaF	−	−	−	−	(+)	−	−	−	−
acid phosphatase, pH 5.2 (naphthol-AS-Bi-phosphate)	n.d.	+	+	+	+	+	+	+	+
beta-glucuronidase, pH 5.2 (naphthol-AS-Bi-beta-glucuronidase)	n.d.	+	+	+	n.d.	+	−	+	+
chloroacetate esterase, pH 7.0 (naphthol-AS-D-chloroacetate)	−	−	−	−	−	−	−	−	−

+ = positive; (+) = very weak; − = negative

Table 3. Results of immunohistochemical reactions in neoplastic cell fractions

	Case number:								
	1	2	3	4	5	6	7	8	9
Disturbed ratio of kappa: light chains of immunoglobulins	no	no	no	no	no	no	no	no	no
LCA	+	(+)	+	+	(+)	+	(+)	(+)	(+)
L26	−	−	−	−	−	+	+	(+)	(+)
MB1	−	−	−	−	−	−	+	(+)	(+)
KiB3	+ (few)	−	−	−	−	+	+	(+)	−
MT1	+	+	+	+	+	−	+ (few)	−	−
UCHL1	+	(+)	+	+	+	−	−	−	−
MAC387	−	−	+ (some)	−	−	−	−	(+)	(+)
lysozyme (muramidase)	(+) (few)	−	−	−	−	−	+ (few)	−	−
alpha-1-antitrypsin	+	+ (some)	+ (some)	(+)	(+)	−	+ (some)	(+)	(+)
alpha-1-antichymotrypsin	+ (some)	+ (some)	+ (few)	+	(+)	−	+	(+)	+
S-100 protein	−	−	−	−	−	−	−	+	(+)
prekeratin	−	n.d.	n.d.	n.d.	n.d.	−	n.d.	(+)	(+)

+ = positive; (+) = very weak; − = negative

erties leading to lesions in accordance with lethal midline granuloma is not an unexpected finding. It is well known that B cell lymphomas may arise from mucosa-associated lymphoid tissue, in particular that of Waldeyer's ring (G. Kelenyi, personal communication; Yamanaka et al. 1985). In our series the epipharyngeal region, frequently harbouring tonsillar tissue, is clinically documented as the first site of the lesions in case 6 – representing a B cell tumour – and in case 1, a T cell neoplasm. However, the neoplastic B cell population (cases 6 and 7) differs from the centrocyte-like morpholo-

gy recognized as being typical for NHL of mucosa-associated lymphoid tissue. In the present series the nasal area is more often the primary site of a T than a B cell tumour, while a reversal of the proportion for tumours of the epipharynx is not evident but may be possible. In addition, this report indicates that malignant neoplasms, the classification of which is difficult, may cause lethal midline granuloma as well. The biological behaviour of tumours 8 and 9 does not differ from that of NHL of high grade malignancy although the morphologic findings and immunohistochemical results are different from B and/or T cell NHL and favour a diagnosis of malignant histiocytosis. Sufficient material, required for confirmatory investigation is not available at present.

Acknowledgements. We thank Mrs E. Schnegg and the laboratory staff of the Division for Histopathology for technical assistance.

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Received February 11, 1989 / Accepted April 12, 1989