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Malignant lymphomas of the nasal cavity and paranasal sinuses

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Summary. The incidence of malignant lymphomas in the nasal cavity and paranasal sinuses was found to be 0.17% of all malignant lymphomas and 0.44% of all extranodal malignant lymphomas registered in the Kiel Lymph Node Registry from 1972 to 1987. Fifty-nine cases of malignant lymphoma presenting in the nasal cavity and paranasal sinuses were investigated with morphological and immunological methods. The median age of the patients was 64.5 years, with a female predominance (m:f = 0.87:1). In the 59 cases a marked preponderance of B-cell lymphomas was found (centroblastic $n=15$, immunoblastic $n=8$, Burkitt's lymphoma $n=6$, Immunocytoma $n=3$, centrocytic $n=1$, centroblastic/centrocytic $n=1$, plasmacytic $n=11$); only a small number ($n=5$) was of T-cell lineage (pleomorphic types). Nine further cases could not be assigned with certainty to either the T or B cell system. Angiocentricity with infiltration and destruction of vessel walls by tumour cells was demonstrated only in the T-cell lymphomas; the B-cell lymphomas, in contrast, often surrounded and compressed blood vessels with intact endothelium. No similarity to malignant lymphomas of mucosa associated lymphoid tissue, such as those in the gastrointestinal tract, was detected.

Key words: Malignant lymphoma – Nasal cavity – Paranasal sinuses

Introduction

Malignant lymphomas of the nasal cavity and paranasal sinuses are rare (Gall and Mallory 1942). Nasal lymphomas comprise 2.2% of extranodal lymphomas and 1.5% of all malignant lymphomas (Freeman et al. 1972). Among malignant tumours of the paranasal sinuses, 5.8% (Frierson et al. 1972) to 8% (Sofferman and Cummings 1975) are reported to be malignant lymphomas and constitute 9.3% of the extranodal lymphomas of the head and neck (Wong et al. 1975). Reports on malignant lymphomas of the nasal cavity and paranasal sinuses have usually comprised small series of up to 38 patients (Robbins et al. 1985). Lymphomas in these regions have been classified as reticulum cell sarcoma (Eichel et al. 1966) or as histiocytic lymphoma (Wong et al. 1975; Michaels and Gregory 1975; Reddy et al. 1980) in earlier lymphoma classifications. More recent studies have also demonstrated that these are predominantly high grade malignant lymphomas (Wilder et al. 1983; Robbins et al. 1985); however, in these studies the T or B-cell nature of these lymphomas was not verified immunohistologically. Frierson et al. (1984) reported on 11 cases of immunoblastic lymphoma in which no expression of monotypic immunoglobulin could be detected.

Immunohistochemically corroborated studies dealing with patient cohorts from the Far East indicate that the overwhelming majority of lymphomas of the nasal cavity and paranasal sinuses are of T cell origin (Ishii et al. 1982; Yamanaka et al. 1985; Ng et al. 1986; Chan et al. 1987). The question arises as to the distribution of malignant lymphomas in these sites in a western population (according to an updated classification) and including immunohistochemical findings regarding their T or B-cell nature.

This study aimed first, to determine the B or T-cell nature of malignant lymphomas initially presenting in the nasal cavity and paranasal sinuses in a western population and second, to evaluate whether these tumours have the same features as nodal malignant lymphomas (Stansfeld et al.

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Table 1. Types and number of malignant lymphomas of the nose and paranasal sinuses

	Nose ($n=50$)	Paranasal sinuses ($n=9$)
B-cell type		
Centroblastic	12	3
Immunoblastic	6	2
Burkitt's lymphoma	5	1
Immunocytoma	3	–
Centrocytic	1	–
Centroblastic/centrocytic	1	–
Plasmacytoma	9	2
T-cell type		
Medium-sized pleomorphic	4	–
Small cell pleomorphic	1	–
Lymphoblastic, convoluted-cell type	1	–
Large cell anaplastic	1	1
High grade unclassifiable	6	–

1988), or rather resemble mucosa-associated lymphomas as described in the gastrointestinal tract, salivary gland, and lung (Isaacson and Spencer 1987; Addis et al. 1988; Hyjek et al. 1988; Li et al. 1988).

Materials and methods

From a total of 33,402 malignant lymphomas registered in the Kiel Lymph Node Registry from 1972 to 1987, 13,453 were listed as extranodal. According to the clinical data, 59 of these extranodal malignant lymphomas were classified as malignant lymphomas with initial presentation in the nasal cavity ($n=50$) or in the paranasal sinuses ($n=9$; Table 1). Cases with extranasal or extrasinusoidal tumour at the time of biopsy were excluded from this study.

Tissue specimens were fixed in formalin (10%; pH 7.4) and embedded in paraplast. Sections were stained with H&E, Giemsa, periodic-acid Schiff (PAS), and silver impregnation (Gomori) was performed.

The lymphoma infiltrates were classified by cytological features according to the updated Kiel classification (Suchi et al. 1987; Hui et al. 1988; Stansfeld et al. 1988).

Paraplast blocks for retrospective immunohistochemical analysis were available in 54 cases. Immunohistochemistry on deparaffinized sections was performed according to the modified immunoperoxidase method described by Stein et al. (1982). The following primary monoclonal antibodies (mAb) were used: Ki-B3 (1:8000; Institute of Pathology, Kiel, FRG; Hansmann et al. 1986; Feller et al. 1987), L-26 (1:100, Dakopatts, Denmark), MT1 (1:200; Laboserv Diagnostica, FRG) and UCHL1 (1:100; Dakopatts, Denmark). As secondary antibody rabbit anti-mouse peroxidase-conjugated antisera (1:15; Dakopatts, Denmark) and as tertiary antibody goat anti-rabbit peroxidase-conjugated antisera (1:100, Ortho Diagnostic Systems, FRG) were used.

For detection of immunoglobulins (IgA, IgG, IgM, kappa and lambda chains) unconjugated monoclonal antisera were purchased from Dakopatts (Denmark) and diluted to 1:200–1:300. As secondary antibody biotinylated swine-anti mouse (1:300) was used for avidin-biotin-peroxidase method (Hsu et al. 1981) with the strept ABComplex-HRP-kit from Dakopatts, Denmark.

As negative controls for the immunohistochemical method we used phosphate-buffered saline, supernatant fluids of unfused myeloma cells, and sera of untreated mice in the first incubation step instead of the primary mAbs.

Results

The incidence of malignant lymphomas with sole clinical presentation in the nasal cavity and/or paranasal sinuses on file in the Kiel Lymph Node Registry from 1972 to 1987 was 0.17% (59/33,402) of all malignant lymphomas and 0.43% (59/13,453) of extranodal malignant lymphomas. Median age of the patients was 64.5 years. Females predominated (m:f=0.87:1). In the nasal region the most frequent clinically indicated site of infiltration was the cavum nasi ($n=35$), followed by the conchae nasales ($n=10$), septum nasi ($n=3$), and meatus nasi ($n=2$). In the paranasal sinuses, malignant lymphoma developed in nine cases (sinus maxillaris $n=8$, sinus ethmoidalis $n=1$) (see table 1).

Centroblastic lymphoma (cb) was the most frequent type in both the nasal and the sinusoidal regions ($n=15$). Cb consisted in nine cases of sheets of tumour cells resembling centroblasts with large, round or oval nuclei and several small to medium-sized nucleoli often located at the nuclear membrane. These were interspersed with blasts similar to immunoblasts which showed large, round nuclei with centrally located, solitary prominent nucleoli and abundant, usually deeply basophilic cytoplasm in Giemsa stain. The lymphomas in this group were subclassified as of polymorphous type. Seven cases with infiltrates composed purely of centroblasts (occasionally with a few blasts possessing multilobated nuclei; Fig. 1a), were subclassified as monomorphous type. The growth pattern was diffuse or mixed follicular and diffuse. In one case a portion of the tumour showed evidence of low grade non-Hodgkin's lymphoma (centroblastic/centrocytic type) and hence could be designated as "secondary" cb. In some areas of cb, tumour cells surrounded and compressed blood vessels (Fig. 1b) with an intact endothelial layer; complete destruction of blood vessel walls by infiltrating tumour cells was not found in this or any other group of B-cell lymphomas. In 12 cases, formalin fixed, paraplast embedded material was available for immunohistochemistry: Monotypic immunoglobulin was detectable in four cases, five cases showed outer cell membrane accentuated positivity with mAb Ki-B3, and nine

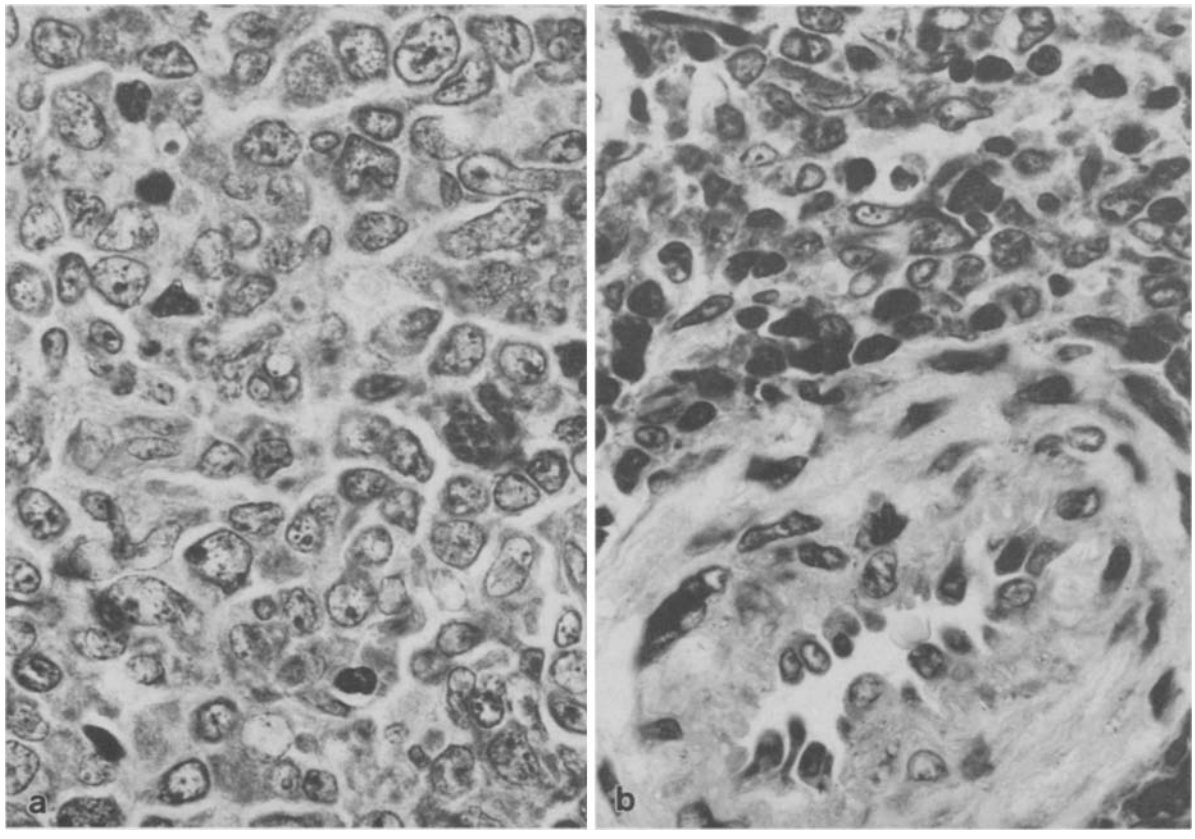

Fig. 1. (**a**) Malignant lymphoma, centroblastic type composed of blasts with medium-sized to large, occasionally multilobated nuclei and nucleoli often located at the nuclear membrane. Giemsa ×882. **b** Malignant lymphoma, centroblastic type (same case as in Fig. 1a): tumor cells surrounding blood vessel without destructive infiltration of the vessel wall; note intact endothelial layer. Giemsa ×882

cases were positive with mAb L26. The tumour cells in 3 of these cases reacted with mAb MT1.

Six cases showed the histological characteristics of Burkitt's lymphoma (medium-sized, cohesive cells with a basophilic cytoplasm, variable cell size and morphology, and interspersed with histiocytes) and one case of lymphoblastic "convoluted-cell type": B or T-cell lineage could not be strictly determined on histological grounds. Three cases each of Burkitt's lymphoma reacted with mAb Ki-B3 and mAb L26; in one case weak expression of light chain lambda was detected. Four cases showed positive reaction with mAb MT1.

Immunoblastic lymphoma ($n=8$) showed a diffuse proliferation of large, pale cells with mostly round or oval nuclei possessing often large, central nucleoli and abundant basophilic cytoplasm. Four cases showed plasmacytic differentiation with coarse chromatin and excentrically located nuclei in abundant, basophilic cytoplasm. Six cases were monotypic for IgM lambda and three cases showed membrane accentuated positivity with mAb Ki-B3 and mAb L26. In two cases (with monotypic immunoglobulin expression) a weak reaction with mAb UCHL1 was visible.

In the cases of immunocytoma ($n=3$), lymphoplasmacytoid type, only rare PAS-positive intranuclear inclusions of the lymphoplasmacytoid cells could be found. In two cases paraplast blocks were availabe: One case was monotypic for cytoplasmic IgM kappa, the other case for light chain lambda.

The centroblastic/centrocytic lymphoma ($n=1$) had a follicular growth pattern with a moderate degree of sclerosis; the neoplastic follicles consisted of a mixture of centrocytes and centroblasts without sharp borders to the follicular structures. Most of the tumour cells reacted with mAb L26.

The case of centrocytic type possessed large centrocytes with cleaved nuclei and was subclassified as large-cell (anaplastic) subtype. The cleaved tumour cells expressed variable degrees of membrane accentuated positivity with mAb L26.

Plasmacytoma (malignant lymphoma, plasmacytic) was found in 11 cases. At the time of biopsy no clinical indication of medullary involvement

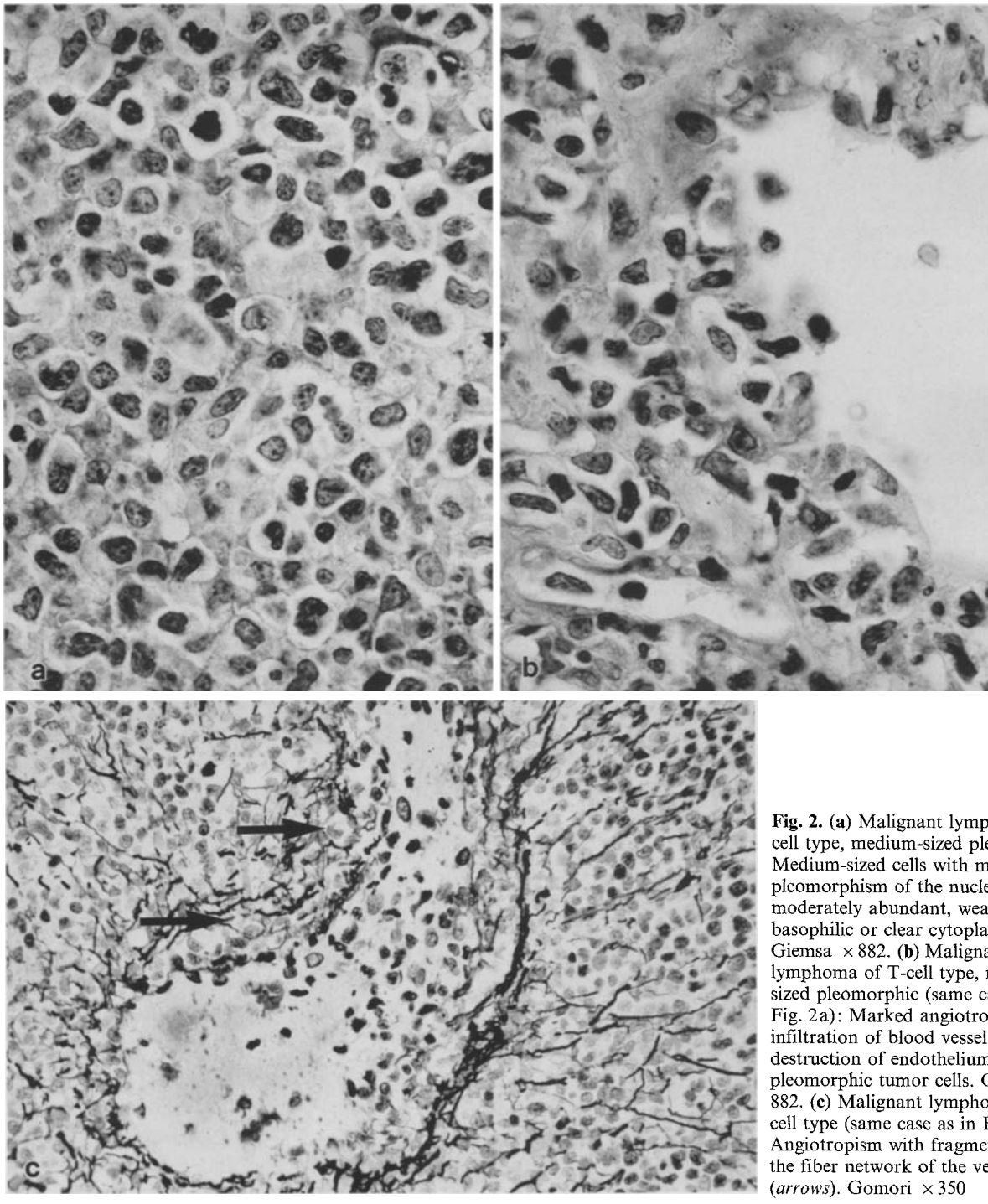

Fig. 2. (**a**) Malignant lymphoma of T-cell type, medium-sized pleomorphic: Medium-sized cells with marked pleomorphism of the nuclei and moderately abundant, weakly basophilic or clear cytoplasm. Giemsa ×882. (**b**) Malignant lymphoma of T-cell type, medium-sized pleomorphic (same case as in Fig. 2a): Marked angiotropism with infiltration of blood vessel wall and destruction of endothelium by pleomorphic tumor cells. Giemsa × 882. (**c**) Malignant lymphoma of T cell type (same case as in Fig. 2a): Angiotropism with fragmentation of the fiber network of the vessel wall (*arrows*). Gomori ×350

(myeloma) was evident. Most of the tumors consisted of well to moderately differentiated plasma cells at the same stage of maturity with abundant, basophilic cytoplasm and medium-sized to large, often excentrically located nuclei. In three cases, the tumour cells exhibited marked pleomorphism and centrally located, basophilic nucleoli within round or oval shaped nuclei. In all biopsies, the tumour cells were identifiable as plasma cells. The degree of necrosis was less than in the other tumour types. In 10 cases, the cytoplasmic immunoglobulin was monotypic kappa ($n=6$) or lambda ($n=4$) with heavy chains of alpha ($n=6$), gamma ($n=1$), or mu ($n=1$) type or without expression of heavy chain; two of these cases showed positivity with mAb MT1. In one further case, no un-

Table 2. Immunohistochemical results on malignant lymphomas of the nose and paranasal sinuses, B-cell type

	n	Monotypic Ig	Ki-B3	L26	MT1	UCHL1
Centroblastic	12	4	5	9	3	–
Immunoblastic	8	6	3	3	–	2
Burkitt's lymphoma	6	1	3	3	4	–
Immunocytoma	2	2	–	–	–	–
Centrocytic	1	–	–	1	–	–
Centroblastic/centrocytic	1	–	–	1	–	–
Plasmacytoma	11	10	–	–	2	–

Table 3. Immunohistochemical results on malignant lymphomas of the nose and paranasal sinuses, other than B-cell type

	n	Monotypic Ig	Ki-B3	L26	MT1	UCHL1
Medium-sized pleomorphic	4	–	–	–	4	4
Small cell pleomorphic	1	–	–	–	1	1
Lymphoblastic, (convoluted-cell type)	1	–	–	–	–	1
Large cell anaplastic	2	1	–	1	2	2
High grade malignant (unclassifiable)	5	–	–	–	–	–

equivocal immunoglobulin expression was detectable.

The two cases classified as large cell anaplastic type consisted of sheets of blasts with irregular, medium-sized to large nuclei and greyish cytoplasm in Giemsa stain. The tumour cells sometimes resembled Hodgkin and Sternberg-Reed cells. B or T-cell lineage was not determinable on formalin-fixed material.

Five cases showed the morphology of classical T-cell lymphomas as described recently by Suchi et al. (1987). Four of these cases were classified as medium-sized pleomorphic type (Figs. 2a, b) and one case as small cell pleomorphic type. These were the only cases exhibiting detectable angiotropism of tumour cells with infiltration and destruction of blood vessel wall (Figs. 2b, c). Tumour cells in all cases showed membrane-accentuated positivity for mAbs MT1 and UCHL1.

Six blastic malignant lymphomas were not further classifiable by morphology or immunohistochemistry; in one of these cases basophilia of the cytoplasm and round-shaped nuclei at least suggested a B-cell lineage of the tumour.

A variable degree of necrosis was present in all specimens; the surface epithelium was often destroyed by infiltration per continuitatem. Angiotropism with infiltration of blood vessel walls and destruction of the endothelium by tumour cells was found only in the cases of pleomorphic T-cell lymphoma. In the other cases, including the high grade B-cell lymphomas (representing the majority of cases), tumour sheets surrounded and constricted blood vessels with an intact endothelial layer. Intact submucosa often contained infiltrates of plasma cells and a few mast cells. Due to necrosis and the small size of the biopsy, no intact mucosa was seen in 20% of the cases. Necrotizing and/or granulomatous vasculitis was not found.

Discussion

Malignant lymphomas with initial presentation solely in the nasal cavity or paranasal sinuses were studied. The median age of patients in previous studied varied from 52 years to 61 years (Wilder et al. 1983; Robbins et al. 1985; Chan et al. 1987). Frierson et al. (1984) found the median age to be 76 years for females and 45 years for males. A predominance of males was found by Frierson et al. (1984); Robbins et al. (1985); and Chan et al. (1987); a predominance of females was reported by Wilder et al. (1983). The median age of our patients correlated well with the data in the literature; the sex distribution was m:f=0.87:1.

As to the nature of lymphomas in nasal cavity and in paranasal sinuses, some reports indicate a preponderance of T-cell lymphomas (Ishii et al. 1982; Yamanaka et al. 1985; Ng et al. 1986; Chan et al. 1987). However, these reports deal with patient cohorts from the Far East. These findings contrast with our results: we found a striking predominance of B-cell neoplasms and only a few T-cell lymphomas (Table 1). This was confirmed immunohistochemically by B and T-cell markers and/or by monotypic immunoglobulin expression in a majority of our cases (Tables 2 and 3). This result is compatible with other studies not based on Asian populations which classified most of their cases as "reticulum-cell sarcoma" (Eichel et al. 1966), "histiocytic lymphoma" (Wong et al. 1975; Michaels and Gregory 1977) and "diffuse – large cell lymphoma" (Wilder et al. 1983; Robbins et al. 1985). These types largely correspond to immun-

oblastic and polymorphous centroblastic lymphoma in the Kiel classification (although the rarely encountered T-cell type of immunoblastic lymphoma was not strictly excluded in all of these studies). From the difference in the nature of lymphomas of the nasal cavity and paranasal sinuses in a far eastern versus a western population one can speculate on an endemic cause for the predominance of T-cell lymphomas in the former.

The occurrence of plasmacytoma in our cases correlates well with data from Fu and Perzin (1978) and Kapadia et al. (1982), according to which the majority of extramedullary plasmacytomas were located in the upper respiratory tract, most frequently in the nasal and paranasal region (for literature see Kapadia et al. 1982). Nevertheless, due to the small size of the biopsy, histological evaluation could not absolutely rule out tumour spread from adjacent cranial bones. At the time of biopsy, clinical evidence of medullary involvement was not found.

In discussion of malignant lymphomas of the nasal cavity and paranasal sinuses, "midline granuloma" has to be considered: This term designates a clinical syndrome with many synonyms (for lit. see Editorial 1977), and describes the clinical expression of a wide spectrum of diseases (Crissman 1979; Crissman et al. 1982). Wegener's granulomatosis is certainly included in this clinical term. It could be excluded in all our cases by the lack of characteristic histological changes such as necrotizing, granulomatous vasculitis and the lack of lung or kidney involvement (Wegener 1939). But at least one subtype of so-called "midline granuloma", namely "polymorphic reticulosis" (Eichel et al. 1966) is now recognized as a malignant lymphoma (for literature see Editorial 1977 and Chan et al. 1987). In our view, the descriptions in the literature (pleomorphism of the neoplastic cells, angiocentricity; Michaels and Gregory 1977; Fu and Perzin 1979; Frierson et al. 1984), show at least most of these lesions to represent a T-cell lymphoma – as suggested by Ishii et al. (1982); Chan et al. (1987); Lippman et al. (1987); and Chott et al. (1988). In our cases of confirmed T-cell lymphoma an angiocentric growth pattern was found, as described by Jaffe (1984). This pattern correlates with the frequent clinical finding of prominent necrosis.

Reactions with mAb MT1 (a T-cell marker, West et al. 1986) must be interpreted very cautiously since this antibody also recognizes malignant lymphomas of B type (Mason and Gatter 1987; Poppema et al. 1987). In our study, a good number of B-cell lymphomas (see Table 2) showed additional positivity with this antibody. Most of these cases were Burkitt's lymphomas which had previously been classified as a subtype of lymphoblastic lymphoma and are now defined as a discrete entity (Hui et al. 1988). Similar limitations may exist in the interpretation of mAb UCHL1 (Norton et al. 1986): We found two immunoblastic lymphomas of proven B-cell type (by monotypic immunoglobulin expression) with weak, membrane accentuated positivity of tumour cells.

The topographical relation to mucosal tissue raises the question whether some special subtype or behavior in this location correlates to malignant lymphomas of mucosa associated lymphoid tissue (MALT) in the gastrointestinal tract as described by Isaacson and Spencer ("centrocyte-like" lymphoma; 1987). We detected no morphological resemblance to MALT lymphomas. Our cases lacked the so-called "lymphoepithelial lesions" (Isaacson and Spencer 1987) composed of centrocyte-like cells destroying mucosal epithelial structures, a hallmark of MALT lymphomas. A further argument against a correlation to lymphomas of MALT is the fact that most malignant lymphomas in MALT are of low grade malignancy ("centrocyte-like lymphoma"); this is also true of malignant lymphomas of bronchus-associated lymphoid tissue (Addis et al. 1988; Li et al. 1988). In contrast, the overwhelming majority of our cases were of high-grade malignant type without evidence of low-grade lymphoma.

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