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Sinonasal non-Hodgkin's lymphomas and Wegener's granulomatosis: a clinicopathological study

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Summary. Reports of sinonasal non-Hodgkin's lymphomas, analysed with monoclonal antibodies, are scarce, and differentiation of these lymphomas from Wegener's granulomatosis can be difficult. In this study, we investigated histopathologically and immunohistologically 20 cases of non-Hodgkin's lymphoma, primary in the sinonasal region, and sinonasal biopsies from 11 patients with Wegener's granulomatosis. All T-cell lymphomas ($n=7$) and plasmacytomas ($n=4$) were stage I at clinical presentation, while all B-cell lymphomas ($n=9$) presented at higher stages. T-cell lymphomas tended to be more frequent in the nasal cavity and paranasal sinuses; B-cell lymphomas more often presented in the nasopharynx. Remarkably, 1 B-cell lymphoma expressed MT1, and 1 T-cell lymphoma expressed L26 (CD 20). The follow-up of 2 patients with a clinical diagnosis of Wegener's granulomatosis was suggestive of non-Hodgkin's lymphoma. Retrospective immunohistochemical analysis revealed that the original histological diagnosis of non-specific inflammation had to be changed to T-cell lymphoma, pleomorphic small cell type. We conclude that a biopsy from the sinonasal region with a dense inflammatory infiltrate, consisting predominantly of T-lymphocytes, renders a diagnosis of Wegener's granulomatosis unlikely and is at least suspicious of T-cell lymphoma. Immunohistochemical analysis is warranted for this type of biopsy.

Key words: Non-Hodgkin's lymphoma – Wegener's granulomatosis – Immunohistochemistry – Nasal cavity – Paranasal sinuses

Introduction

In the nasal cavity and the paranasal sinuses, subtypes of malignant lymphoma and Wegener's granulomatosis (WG) can be hard to differentiate, both clinically and histopathologically (Batsakis 1982; Costa and Delcatraz 1986; Chan et al. 1987b; Chott et al. 1988). The diagnosis of non-Hodgkin's lymphoma (NHL) can be difficult because biopsies from this region are often small, necrosis can be extensive and admixed cells can obscure the histological picture. NHLs in this region are relatively poorly described, as is illustrated by the varying and contradictory frequencies which are reported for B-cell non-Hodgkin's lymphoma (B-NHL) and T-cell non-Hodgkin's lymphoma (T-NHL) (Chan et al. 1987b; Fellbaum et al. 1989; Yamanaka et al. 1985). Other publications have not discriminated between B-NHL and T-NHL at all (Frierson et al. 1984; Robbins et al. 1985; Shibuya et al. 1987).

WG is a disease which, like NHLs, can also give rise to the clinical picture of a necrotizing and nonhealing disorder, and is characterized by granulomas and vasculitis in classical cases. However, these features are often absent in biopsies from the sinonasal region (Fauci et al. 1983), which makes a definite diagnosis difficult. Distinction between WG and malignant lymphoma is clearly very important because of the differences in treatment and prognosis between these diseases. In this study we investigated cases of WG, B-NHL and T-NHL, comparing clinical data, histology and immunohistochemistry of these disorders, to establish criteria helpful in differentiating these diseases from each other.

Materials and methods

Biopsy material from 20 patients with primary sinonasal NHL, diagnosed between 1983 and 1989, was retrieved from the files of the Institute of Pathology of the Free University Hospital, Amsterdam. Cases were considered to have arisen in the sinonasal tract, if the presenting symptoms were of sinonasal origin and extensive involvement of this region was present. Because biopsy material from patients with WG often reveals a nonspecific histology, the biopsy material from those patients was retrieved by selecting patients who eventually received a clinical diagnosis of WG and were treated as such. The clinical diagnosis of WG was based on the clinical picture (mucosal crusting of the nasal cavity, without destruction of bony structures, involvement of other localizations

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in the upper respiratory tract, involvement of other organ systems, such as lungs, kidneys, joints or eyes, and negative results of cultures) and the results of biopsies (granulomatous or nonspecific inflammation, exclusion of malignancy). In this way, biopsy material was retrieved from 11 patients in whom a clinical diagnosis of WG was made. All cases were studied with help of routine histology and immunohistochemistry of paraffin-embedded tissue. Sections of paraffin-embedded tissue were stained with monoclonal antibodies MT1 (Poppema et al. 1987), directed against an antigen present on T-lymphocytes, and the neoplastic cells of some small cell B-cell lymphomas and UCHL1 (CD 45R0; Norton et al. 1986), directed against an antigen present on memory T-cells. In addition, staining was performed with MB2 (Poppema et al. 1987), directed against an epitope, predominantly present on B-lymphocytes, and L26 (Cartun et al. 1987), which detects the CD20 antigen (Mason et al. 1990). MT1 and MB2 were purchased from Organon Technica (Oss, The Netherlands), UCHL1 and L26 from Dakopatts (Copenhagen, Denmark). Plasmacytomas were also stained with immunoglobulin light chains kappa and lambda. Immunohistochemical staining was performed according to standard procedures, which have been described in more detail elsewhere (Mullink et al. 1985, 1986). Clinical data and follow-up were retrieved from the medical records. In all cases of NHL, the staging procedure included physical examination, routine laboratory investigation, an X-ray of the chest, a computed tomographic scan of the abdomen, and bilateral bone marrow biopsy of the iliac crest.

Results

The histological and clinical features, and the results of the immunohistochemical analysis from the cases of B-NHL, plasmacytoma and T-NHL are summarized in Table 1, from the cases of WG in Table 2. The diagnoses given in Tables 1 and 2 are the primary histopathological diagnoses, in the cases of NHL based on routine histology, and on marker studies that were available at that time. In the cases of WG the primary histopathological diagnoses were based on routine histology and clinical information.

Of the 9 B-NHLs (Fig. 1a), 4 were located in the nasopharynx, 2 in the nasal cavity, 2 in the paranasal sinuses, and 1 case showed localization in both the paranasal sinuses and the nasal cavity. All 8 cases of B-NHL for which clinical follow-up was available were stage II or higher at presentation. All patients with stage IV disease had microscopic involvement of the bone marrow, without bulky disease outside the sinonasal region. The mean age of the patients with B-NHL was 71.9 years, and the male to female ratio 5:4. The degree of atypia of the infiltrate was assessed in all biopsies. The infiltrate in the biopsies was considered clearly atypical if it contained many lymphoid blasts, or if the infiltrate was very dense and monotonous. All but 1 of the 9 cases of B-NHL showed a clearly atypical infiltrate. In this remaining case, the diagnosis of B-NHL could be made because the normal compartimentalization of lymphoid tissue was absent, the infiltrate contained almost exclusively B-lymphocytes, and staging showed involvement of the bone marrow, by cells identical to the cells

Table 1. Histological, immunohistochemical and clinical features of B-cell lymphomas ($n=9$), plasmacytomas ($n=4$), and T-cell lymphomas ($n=7$)

Case no.	Atypia[a]	CD20 (L26)	MB2	MT1	CD45RO (UCHL1)	Necrosis[b]	Diagnosis[c]	Localization[d]	Stage[e]	Age (years)	Sex	ANCA	Treatment[f]	Follow-up
1	+	+	+	−	−	−	CB	NC	IIE	69	M	NA	CH	DOD 2
2	+	+	+	−	−	−	CC large	NP	IV	64	M	NA	CH	ANED 46
3	+	+	−	−	−	−	CC large	NP	IIE	77	F	NA	RT+CH	ANED 62
4	+	−	+	+	−	F	CC large	NC	IIE	81	F	NA	CH	DOD 14
5	+	+	−	−	−	−	CB	NP	IV	74	F	NA	CH	DOD 4
6	−	+	+	−	−	F	CC small	NP	IV	77	M	NA	CH	DOD 6
7	+	+	+	−	−	−	CC small	Se	IV	64	M	NA	CH	AWD 48
8	+	+	+	−	−	F	CC large	Sm/NC	IIE	66	M	NA	RT+CH	DOD 39
9	+	+	+	−	−	−	CC small	Sm	NA	75	F	NA	RT	NA
10	+	−	−	−	−	F	Plasmac.	NC/Sm	IE	73	M	NA	RT	ANED 12
11	+	−	−	−	−	−	Plasmac.	NC	NA	54	M	NA	NA	NA
12	+	−	−	−	−	F	Plasmac.	NC	IE	73	F	NA	RT	ANED 30
13	+	−	−	−	−	−	Plasmac.	Ss/Np	IE	44	M	NA	RT+CH	DOD 34
14	+	−	−	+	+	E	T Pl m+1	NP/Sm	IE	30	M	−	RT+CH	ANED 21
15	+	−	−	+	−	E	T Pl m+1	NC	IE	43	M	−	RT	AWD 19
16	+	−	−	+	+	E	T Pl sm	NC/Sm	IE	53	M	NA	RT+CH	ANED 3
17	+	−	−	+	+	E	T Pl sm	NC	IE	74	M	NA	CH	DOD 4
18	+	+	−	+	+	F	T Pl m+1	Se	IE	78	F	NA	RT	ANED 8
19	+	−	−	+	+	E	T Pl m+1	NC	IE	64	M	NA	CH	ANED 36
20	−	−	−	−	+	E	T Pl sm	NC	IE	64	M	NA	CH	DOD 3

[a] An infiltrate was considered clearly atypical if it was very dense and highly monotonous, or contained many blasts
[b] F, Focal; E, extensive
[c] CB, Centroblastic; CC large, centrocytic large cell; CC small, centrocytic small cell; T pl sm, T-cell pleomorphic small cell; T pl m+1, T-cell pleomorphic medium and large cell; Plasma, plasmacytoma
[d] NC, Nasal cavity; NP, nasopharynx; Sm, maxillary sinus; Se, ethmoid sinus; Ss, sphenoid sinus
[e] Ann arbor; NA, not available
[f] CH, Polychemotherapy; RT, radiotherapy
[g] ANED, Alive no evidence of disease; AWD, alive with disease; DOD, died of disease (number of months)

Table 2. Histological, immunohistochemical and clinical features of cases of Wegeners granulomatosis (n=11)

Case no.	Atypia[a]	% lymphocytes[b]	T/B ratio[c]	Histiocytic giant cells	Necrosis[d]	Diagnosis[e]	Localization[f]	Stage[g]	Age	Sex	ANCA	Follow-up[h]
21	–	80%	10/1	–	–	Non-sp	NC	L	57	M	–	DOD 27
22	–	80%	10/1	–	E	Non-sp	NC	E	44	F	–	DOD 17
23	–	40%	3/1	–	F	Non-sp	NC	E	31	F	+	A 5
24	–	60%	3/1	–	–	Non-sp	NP	E	49	M	+	A 50
25	–	60%	3/1	+	F	Comp WG	Se	L	19	F	+	A 8
26	–	20%	3/1	+	F	Comp WG	NC	E	32	F	+	A 43
27	–	20%	3/1	+	F	Comp WG	NC	E	64	F	+	A 55
28	–	40%	3/1	+	F	Comp WG	NC	E	55	F	+	A 120
29	–	50%	4/1	+	F	Comp WG	NC/Sm	E	52	F	NA	A 61
30	–	30%	5/1	+	F	Comp WG	NC/Sm	E	24	M	NA	A 65
31	–	40%	3/1	+	F	Comp WG	Sm	L	56	M	+	A 4

[a] An infiltrate was considered clearly atypical if it was very dense and highly monotonous, or contained many blasts
[b] Percentage lymphocytes in inflammatory infiltrate
[c] T/B ratio as assessed with help of immunohistochemistry
[d] F, Focal; E, extensive
[e] Non-sp, non-specific inflammation; Comp WG, compatible with WG
[f] NC, Nasal cavity; NP, nasopharynx; Sm, maxillary sinus; Se, ethmoid sinus; Ss, sphenoid sinus
[g] L, Limited to the upper respiratory tract; E, extended to other organs
[h] A, Alive; DOD, died of disease (number of months)

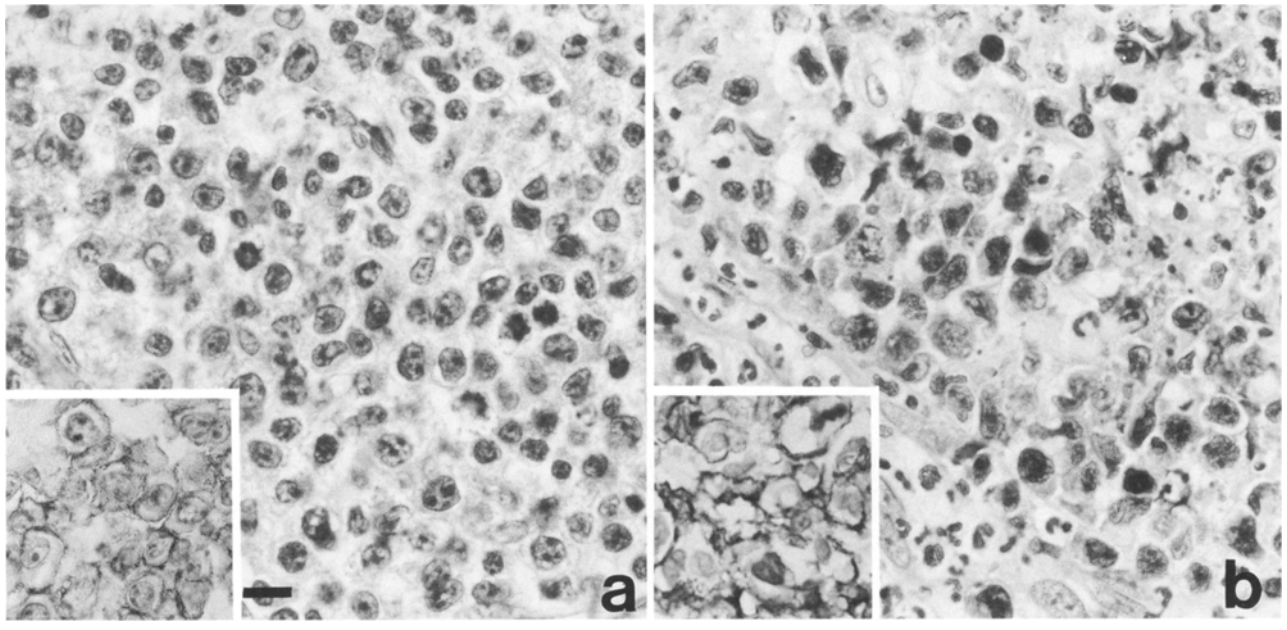

Fig. 1. a Large cell B-cell lymphoma, classified as centroblastic (case 5). Dense, atypical infiltrate with many blasts. *Inset*: staining with L26 (CD 20). **b** T-cell lymphoma, pleomorphic medium and large cell (case 19). Dense infiltrate with atypical, hyperchromatic lymphoid cells and extensive necrosis. *Inset*: Staining with MT1. Original magnification ×630; *bar*=11 μm

seen in the nasal biopsy. Focal necrosis was present in 3 cases. Extensive necrosis, vasculitis or angiocentric growth was not seen. In all cases, the infiltrate contained predominantly lymphocytes, while neutrophils, eosinophils, plasma cells and histiocytes were present only in limited numbers. Of the 9 B-NHLs, 6 expressed both B-cell markers and no T-cell markers, 2 expressed L26 (CD 20) and no T-cell markers, and 1 expressed MT1 and MB2 only (see Table 1). This tumour (case 4) was classified as a B-NHL on morphological grounds. None of the B-NHLs showed intracytoplasmatic immunoglobulin light chains as demonstrated by immunohistochemistry of paraffin-embedded tissue.

Two of the 4 plasmacytomas were located in the nasal cavity, 1 was located in the nasal cavity and the maxillary sinus, and 1 in the nasopharynx and the sphenoid sinus. The 3 cases for which clinical follow-up was available were all stage I at presentation, their mean age was 61 years and the male to female ratio 3:1. According to the definition given previously, an atypical

infiltrate was seen in all 4 cases of plasmacytoma, with focal necrosis in 2 cases. In all cases, the infiltrate consisted virtually exclusively of mature and/or immature plasma cells, without admixed reactive cells. All cases of plasmacytoma showed monotypic intracytoplasmatic kappa light chain expression.

Of the 7 T-NHLs (Fig. 1b), 4 were located in the nasal cavity, 1 was located in the ethmoid sinus, 1 in the nasal cavity and the maxillary sinus, and 1 in the nasopharynx and the maxillary sinus. All were stage I at clinical presentation. The mean age of the patients with T-NHL was 58 years and the male to female ratio 6:1. The infiltrate was atypical in 6 of the 7 cases of T-NHL. The 1 other case could be diagnosed as T-NHL because angiocentric growth was noted, the infiltrate consisted predominantly of T-lymphocytes, and extensive necrosis was present. Two other T-NHLs also showed angiocentric growth. All but 1 showed extensive necrosis. In all cases, the infiltrate contained predominantly lymphoid cells. Four cases of T-NHL expressed two T-cell markers and no B-cell markers, 2 cases expressed one T-cell marker and no B-cell markers, and 1 case expressed both T-cell markers and L26 (see Table 1).

The mean age of the 11 patients with a clinical diagnosis of WG was 43.9 years, the male to female ratio 4:7. Eight patients showed clinically extended WG (involvement of organ systems other than the upper respiratory tract), the 3 other cases showed limited disease (disease confined to the upper respiratory tract). The anti-neutrophil cytoplasmic antibody test (ACPA/ANCA test) was negative in 2 patients, positive in 7, and not performed in the other 2 patients. Of the 11 cases of clinical WG (Fig. 2a), none showed an atypical infiltrate, 8 cases showed focal necrosis, and 1 case extensive necrosis. Conclusive granulomas were present in only 1 case. Classical vasculitis was not seen. In only 2 cases did the infiltrate contain about 80% lymphocytes; in the other cases, the infiltrate contained 60% lymphocytes or less. The other cells in the infiltrate were neutrophils, eosinophils, plasma cells and histiocytes in varying amounts. Immunohistochemical analysis of the biopsies showed that 9 cases had a T to B ratio ranging from 3:1 to 5:1, and that both cases with an infiltrate containing a relatively high number of lymphocytes showed a T to B ratio of about 10:1.

Follow-up of the patients with B-NHLs showed that 5 patients died with a mean survival of 13 months and 3 patients were alive after a mean follow-up of 52 months. There was no relation between tumour subtype and survival. One patient with a plasmacytoma died after 34 months, and 2 were alive after 12 and 30 months respectively. Of the patients with T-NHL, 2 died after a mean survival of 3.5 months, and 5 were alive after a mean follow-up of 17.4 months. The patients with NHLs or plasmacytoma were treated with chemotherapy, radiotherapy or a combination of both (see Table 1).

All patients with a clinical diagnosis of WG were treated with prednisone and cyclophosphamide. Follow-up of the patients with WG showed that 2 patients died after a mean survival of 22 months; the other 9 patients were alive after a mean follow-up of 45.7 months. The course of the disease of the 2 patients with a clinical diagnosis of WG who died was atypical for WG. Both patients had a negative ANCA test, showed a poor response to cyclophosphamide therapy and died of disease after 17 and 27 months, respectively. No autopsies were performed, but a bone marrow biopsy from patient 21,

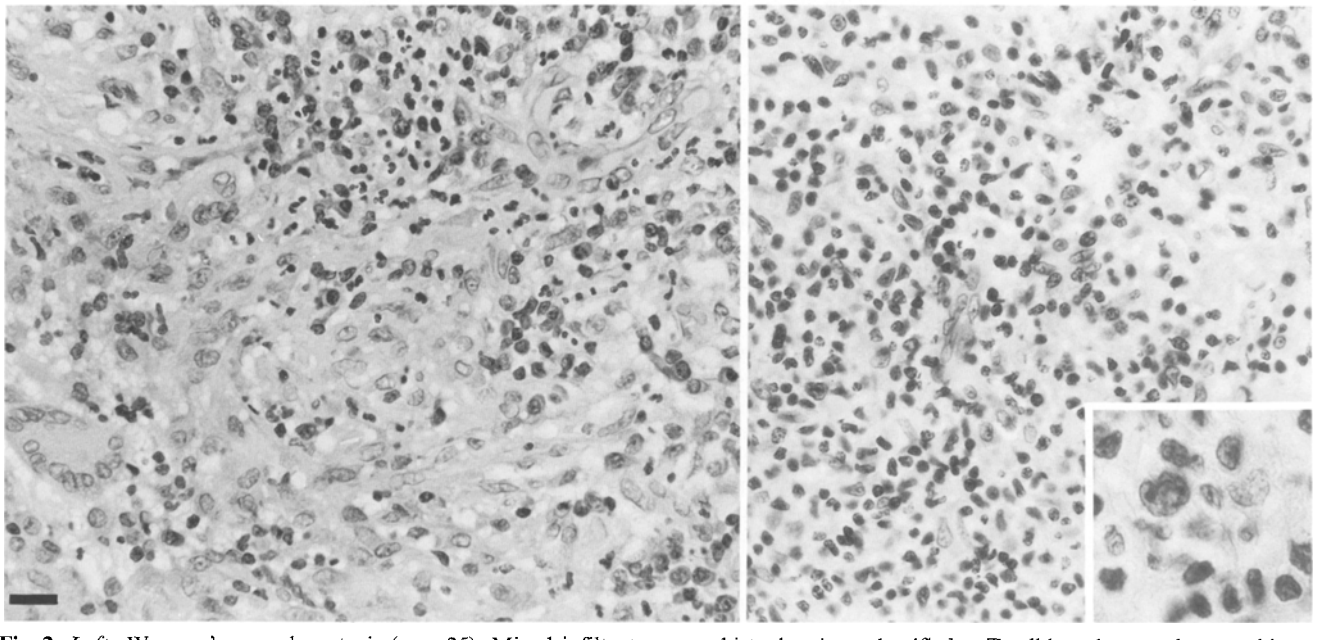

Fig. 2. *Left:* Wegener's granulomatosis (case 25). Mixed infiltrate with lymphocytes, granulocytes, histiocytes, plasma cells and multinucleate giant cells. *Right*: Case 21, originally diagnosed as non-specific inflammation. After follow-up, re-examination and immunohistochemistry classified as T-cell lymphoma, pleomorphic small cell type. Moderately dense infiltrate. Original magnification ×250; *bar* = 30 μm. *Inset*: Single atypical large lymphoid cell. ×630; *bar* = 11 μm

performed at another institution shortly before death, showed diffuse infiltration by NHL, probably T-NHL. Unfortunately, no material was left for immunohistochemical analysis. Patient 22 died from extended lung disease. Biopsy material from the lung showed a non-specific necrotizing inflammation, without granulomata and vasculitis, which are almost invariably seen in WG in this localization. The slides from the original biopsies of these 2 patients were re-examined. In both cases, the infiltrate was unusually compact if compared with the other cases of WG, contained a high percentage of lymphocytes, and a few large, atypical lymphocytes were present (Fig. 2b). Therefore, in retrospect, the clinical diagnosis of WG must be seriously doubted, and we feel that both cases represented examples of T-NHL, of the pleomorphic small cell type.

Discussion

The literature on extranodal NHLs in the nose, paranasal cavities and nasopharynx which includes NHLs from the ring of Waldeyer outside the nasopharynx in some instances (Chan et al. 1987a; Shibuya et al. 1987; Yamanaka et al. 1985) presents an unclear picture at present. Chan et al. (1987b) reported that most nasal/nasopharyngeal lymphomas are T-NHLs, while Fellbaum et al. (1989), found a strong predominance of B-NHL of the nasal cavity and paranasal sinuses. Yamanaka et al. (1985) reported a predominance of B-NHL in the nasopharynx, and a predominance of T-NHL in the nasal cavity. In our series, we found a predominance of B-NHLs compared to T-NHLs in the sinonasal region. These differences illustrate that the clinicopathological picture of sinonasal NHL is far from clear at this time. Our results lend support to the view that extranodal NHLs in the sinonasal region more often show a T-cell phenotype if compared to nodal lymphomas, especially when located in the nasal cavity. In general, primary non-cutaneous T-NHLs have a poor prognosis when compared with B-NHLs (Brown et al. 1989; Noorduyn et al. 1990). Thus, determining the T- or B-cell lineage of a NHL is important. However, because biopsies from the sinonasal region are often suboptimal, interpretation of monoclonal antibody staining on frozen sections is often difficult. Although monoclonal antibodies reactive on formalin-fixed, paraffin-embedded material are not completely specific (Norton and Isaacson 1989) we were able to assign nearly all NHLs to the B-cell or T-cell lineage.

Interestingly, all T-NHLs and plasmacytomas presented at stage I, while all other B-NHLs were stage II or higher. Extramedullary plasmacytomas usually present in stage I in other localizations also (Kotner and Wang 1972). Although several other authors have found T-NHLs to present at higher stages more often (Chott et al. 1988; Yamanaka et al. 1985), Chan et al. (1987b) also found a tendency for T-NHLs to present at lower stages.

The extensive necrosis in T-NHLs is assumed to be caused by the angiocentric growth shown by these tumours. In our series, however, 6 of 7 cases showed extensive necrosis, whereas angiocentric growth was observed in only 3 cases.

In this study, it appeared that B-NHL in the sinonasal region has a poorer prognosis than T-NHL. This may be due to the fact that the T-NHLs presented as stage I tumours, which has been shown to be a major prognostically favourable sign (Noorduyn et al. 1990). Despite the fact that the group studied is small, this difference is striking.

Compared with patients with NHLs, patients with WG were younger (especially when compared with patients with B-NHLs), more likely to be female, and to show focal necrosis histologically. This study also shows that the classical histological features of WG (granulomas and vasculitis) are rarely present in patients who eventually receive a clinical diagnosis of WG. A completely diagnostic histological picture was more often seen by other investigators (Fauci et al. 1983) but they also noted that granulomas and vasculitis are frequently absent and that the combination of these features is rarely seen. Another reason for the low prevalence of granulomas and vasculitis may be the fact that we selected patients on basis of the clinical diagnosis they eventually received. In 9 of the 11 patients in whom a diagnosis of WG was made, clinical follow-up and histology gave no grounds to doubt the diagnosis of WG. These patients had a positive ANCA test, which is reported to be very specific for WG (Ludemann and Gross 1987; Parlevliet et al. 1988), granulomatous inflammation with multinucleate giant cells, a clinical follow-up with classic involvement of other organ systems, or a combination of these items. The 2 other patients, however, showed an atypical course of their disease and died from it. The original diagnosis on the biopsies of these 2 patients was non-specific inflammation. Retrospectively, a few atypical lymphocytes were present. The infiltrate consisted predominantly of lymphocytes with a T-cell phenotype, while the other 9 patients showed an infiltrate containing not more than 60% lymphocytes, with a T to B ratio not higher than 5:1. These findings suggest that if the infiltrate in a biopsy from the sinonasal region is dense and consists predominantly of T-lymphocytes, WG is unlikely and T-NHL must be suspected, even if the infiltrate contains only a few morphologically atypical cells. Therefore, we think that in the differential diagnosis of WG and T-NHL routine immunohistochemical staining of biopsies from the sinonasal region is a useful tool.

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