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Histology and Histopathology

Primary B-cell gastric lymphomas of mucosa-associated lymphoid tissue. Histological and immunohistochemical study of ten cases on surgical specimens

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Summary. Ten cases of gastric mucosa-associated lymphoid-tissue B-cell lymphoma were studied on surgical specimens by histology and immunohistochemistry, with monoclonal and polyclonal antibodies for B- and T-cells. For the first time, percentage of centroblast-like cells was appreciated, using their LN1 positivity, by opposition to the negativity of centrocyte-like cells (LN2 immunoreactivity alone).

Lymphomas were divided into four main groups: A) centrocyte-like cells; B) centrocyte-like cells and immunocytoma; C) centrocyte-like cells admixed to centroblast-like cells; and D) centrocyte-like cells, immunocytoma and at least 30% of centroblast-like cells. Group C was divided into 3 subgroups: C1 (rare centroblast-like cells); C2 (30-50% of centroblast-like cells); and C3 (predominant centroblast-like cells).

Therefore low grade (A, B, C1) and high grade malignancy groups (C2, C3, D) were identified: this preliminary subdivision could be extended in larger series and applied to mucosa-associated lymphoid-tissue lymphoma from other sites.

Furthermore, the possible prognostic significance of this subdivision could be evaluated by correlation with long term follow up.

Key words: Gastric malignant lymphoma, MALT lymphoma, Immunohistochemistry, Low-grade lymphoma, High-grade lymphoma

Introduction

Lymphomas of the gastrointestinal tract, salivary glands, lung and thyroid gland are considered together as tumours arising in mucosa-associated lymphoid tissue (MALT) (Isaacson and Spencer, 1987; Isaacson and Wright, 1987; Myhre and Isaacson, 1987; Addis et al., 1988; Hyjek and Isaacson, 1988; Hyjek et al., 1988). The vast majority of MALT lymphomas are of B-cell origin and in Western countries B-cell gastric lymphomas of MALT (BGL-MALT) are the commonest (Isaacson and Spencer, 1987; Myhre and Isaacson, 1987).

The BGL-MALT tend to remain localized for long periods of time, respond well to locally directed therapy and when compared to lymphomas arising in lymph nodes, they have a considerably better prognosis (Ravaioli et al., 1986; Isaacson et al., 1987; Myhre et al., 1987). Because of their indolent biological behaviour, BGL-MALT had been previously designated as «pseudo-lymphomas», but with the advent of immunohistochemistry it has been shown that these tumours are true lymphomas by demonstration of monotypic cytoplasmic and/or surface immunoglobulin (Isaacson and Spencer, 1987; and Isaacson, 1987).

We report here the results of histological and immunohistochemical studies on gastrectomy specimens of 10 cases of BGL-MALT. On the basis of these results, we present preliminary data of subdivision of BGL-MALT in two morphologically distinct groups of low and high grade malignancy according to the relative percentage of small and large cell tumour components (Galian et al., 1989). This subdivision of BGL-MALT might have prognostic significance and could be used for MALT lymphomas arising in other sites (thyroid gland, lung, salivary glands).

Finally, we report results of immunotopographic assessment of non-neoplastic T-cells in BGL-MALT.

Materials and methods

Nine cases of BGL-MALT for which gastrectomy specimens and one case (case 1) for which surgical biopsy were available were selected for study.

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Locoregional lymph nodes were available in all but one case. Hepatic and bone marrow biopsies were performed for initial staging. Follow up information provided by clinical, biological and histological (biopsy) examinations was studied in all cases. Fresh tumour samples from six cases were snap-frozen at - 170° C in isopentane with liquid nitrogen and 6-micron cryostat sections were performed. The sections were tested with a panel of monoclonal antibodies including anti-immunoglobulin light and heavy chains, anti-CD2, CD3, CD5, CD7, CD4 and CD8 (Becton-Dickinson Mountain View Ca, USA). Paraffin sections from all gastrectomy specimens fixed in Bouin's fluid were tested with monoclonal antibodies including LN1, LN2 (ICN Immunobiologicals, Illinois, USA), MB2 (Eurodiagnostics, Holland), UCHL1 (Dakopatts Corporation, Denmark) and polyclonal antibodies including anti-immunoglobulins heavy and light chains (Dako). For polyclonal and monoclonal antibodies, peroxidase-anti-peroxidase (PAP) and avidin-biotin-complex methods (Vectastain ABC kit, Vector California, USA) were used. Appropriate dilutions and negative and positive controls were performed.

Results

In all cases, the four principal components which contributed to the histology of gastric lymphomas were centrocyte-like cells (CCLC), centroblast-like cells (CBLC), plasma cells and follicles (Table 1).

The CCLC displayed two main cytological types including standard CCLC and clear cell variant of CCLC. The standard variant which closely resembled follicle centre centrocytes was comprised of small- to intermediate-sized cells with irregularly-shaped, heterochromatic nuclei and a moderate amount of cytoplasm. The clear variant was comprised of medium-sized rounded cells with well-defined borders and clear cytoplasm.

The distinctive histological features of all 10 cases, which allowed histological diagnosis of malignant lymphoma of MALT to be made, was the presence of lympho-epithelial lesions (LE). These lesions were formed by infiltration and partial destruction of mucosa epithelium by clusters of CCLC (Fig. 1).

In cases 5-10, groups of CBLC were found to be components of the tumour population. Some of them were indistinguishable from typical centroblasts (Fig. 2) whereas others showed cleaved, angulated or polymorphic nuclei. When CBLC were the predominant feature of the tumour, LE lesions could be recognized only in areas where CCLC were the main tumour component. Admixed with CBLC, rare typical immunoblasts and immunoblast-like cells were also identified. These latter cells exhibited more irregular nuclear outlines than typical immunoblasts.

Plasma cells were distributed in the superficial area of lamina propria. They were non-invasive, showed no pleomorphism, lacked mitotic figures and were not observed in LE lesions. In two cases, intranuclear PAS-positive inclusions were found in plasma cells and subsequent immunohistochemical studies disclosed the neoplastic feature of these cells by demonstration of light chain restriction (Table 2).

Varying numbers of follicles were identified in all cases. They tended to be situated in the mucosa, near the *muscularis mucosae* and in superficial submucosa, but in more bulky tumours they were distributed throughout. It is of interest that in tumours where the CBLC was the main tumour component (cases 8, 9) the follicles were less prominent. In cases 1, 4 and 5 the majority of follicles were uninvolved tumour and were reactive in appearance, but in the remaining cases the follicles were frequently distorted and overgrown by the neoplastic infiltrate.

Lymphoma cells invaded submucosa (cases 1, 2, 4, 5, 7, 10) (Fig. 3), *muscularis propria* (case 3) and serosa (cases 6, 8 and 9) (Table 1). Histological examination of the limits of the gastrectomy specimens showed absence of tumour involvement in the nine studied cases. In four cases the gastric lymph nodes were invaded by CCLC with or without CBLC. The CCLC surrounded the reactive follicles of the lymph nodes

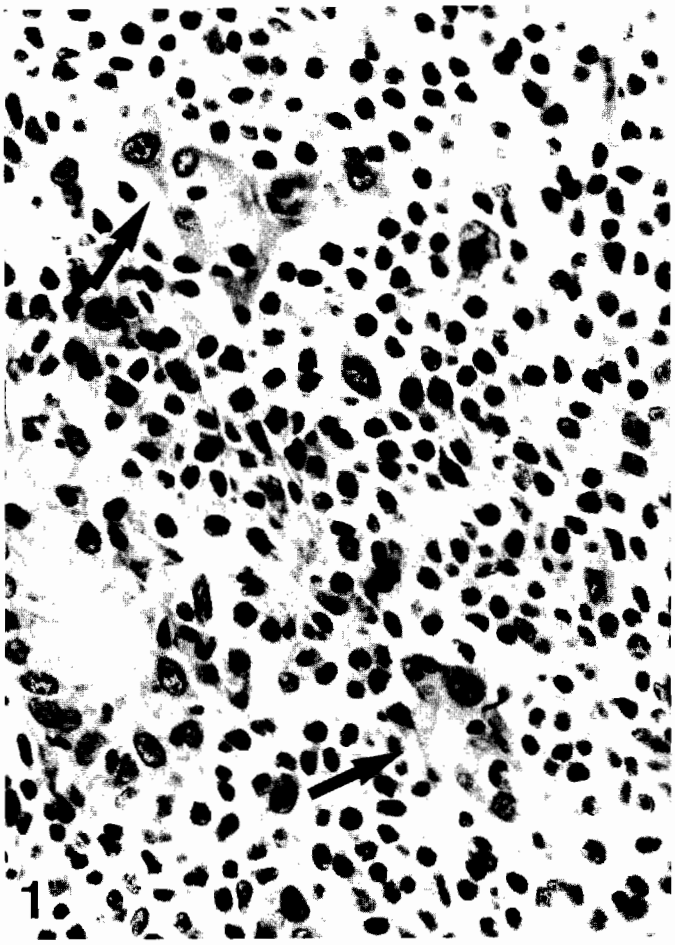

Fig. 1. Lympho-epithelial lesion showing partial destruction of epithelial cells by centrocyte-like cells (arrows). Hematoxylin-eosin. × 520

and involved the interfollicular areas (Table 1). Some lymph nodes were totally occupied by lymphoma cells.

Results of immunohistochemical studies are summarized in Table 2.

Frozen sections immunohistochemistry disclosed expression of monotypic surface immunoglobulin (SIg) by CCLC and CBLC if present, in all tested cases. In contrast, follicles displaying polytypic SIg staining were subsequently considered as reactive components. By paraffin-section immunohistochemistry CCLC and CBLC showed no production of cytoplasmic immunoglobulin (CIg) in seven cases, while in three cases a polytypic CIg staining, probably due to passive absorption of extracellular immunoglobulins, was found.

CCLC were positive for MB2 and LN2 antibodies (Fig. 4) but negative for LN1 antibody except for case 6, in which the clear cell variant of CCLC showed dot-like paranuclear staining with this latter antibody. CBLC were reactive for MB2 and LN2 antibodies and exhibited constant dot-like paranuclear staining, with or without membrane staining for LN1 antibody. The different staining pattern of CCLC and CBLC by LN1 antibody permitted semi-quantitative evaluation of the percentage of CBLC in the total number of lymphoma cells (Figs. 5, 6). In order to avoid confusion between CCLC and small non-neoplastic T-cells when evaluating the percentage of CBLC in the total of lymphoma population, we used UCHL1 antibody which stained the T-cells while CCLC remained unreactive with this antibody.

In cases 4 and 10, neoplastic plasma cell population was revealed by demonstration of monotypic cytoplasmic IgM/Kappa. In the remaining eight cases polytypic plasma cells were evidenced by anti-CIg polyclonal antibodies.

Using LN1 antibody the reactive germinal centres stained strongly with membrane and dot-like cytoplasmic positivity whereas the CCLC and normal mantle zone cells were LN1 negative (except for case 6). This different staining pattern by LN1 permitted in some areas identification of reactive germinal centres invaded by neoplastic CCLC.

Combined histological and immunohistochemical assessment of our series allowed us to divide the BGL-MALT into four major groups: 1) group A

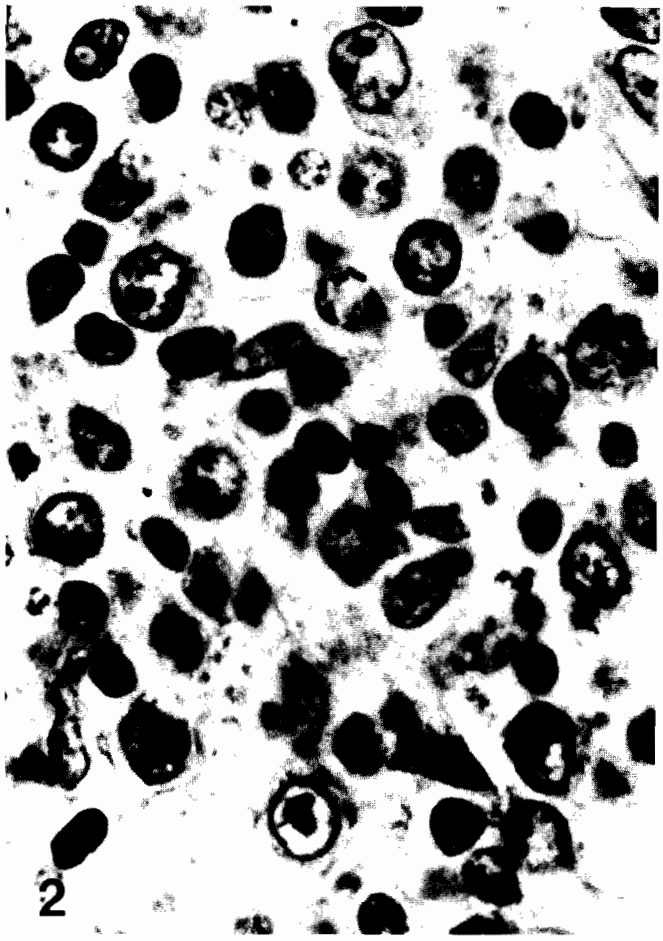

Fig. 2. Gastric lymphoma including a population of centroblast-like cells closely resembling typical centroblasts. May-Grunwald-Giemsa staining, original magnification × 1,300

Fig. 3. Gastric lymphoma: the lymphoid infiltrate invades the submucosa (arrows). Hematoxylin-eosin, original magnification × 30

(cases 1-3) comprised lymphomas almost exclusively composed of CCLC; 2) group B (case 4) comprised a CCLC lymphoma associated with immunocytoma; 3) group C comprised lymphomas composed of CCLC and CBLC. This group was divided into three subgroups; C1 : CCLC and less than 30% CBLC (cases 5 and 6); C2 : CCLC and 30% to 50% CBLC (case 7); and C3: CCLC and more than 50% CBLC (cases 8 and 9); 4) group D (case 10) comprised a lymphoma composed of CCLC and 30% to 50% CBLC, in association with immunocytoma.

Histologically, low grade malignancy BGL-MALT could include A, B and C1 groups while C2, C3 and D groups could be assigned to the morphologically high grade malignancy lymphomas associated with low grade BGL-MALT component.

The number and distribution of T-cells were studied in six cases by frozen section immunohistochemistry. Immunotopographic assessment by the Pan T-cell markers CD2, CD3, CD5 and CD7 evidenced numerous T-cells inside low grade BGL-MALT whereas these cells were rare in the high grade group. T-cells tended to be more frequently situated in the superficial lamina propria and in the interfollicular zones, while they were rare in the follicles centre and the mantle zone of reactive follicles. Some non-neoplastic T-cells were scattered among B-cells, but much more often they clustered around blood vessels. Interestingly, the number of CD7+ cells was inferior to that of CD2+, CD3+ and CD5+ cells in all cases. CD4+ cells predominated in all tested cases and were more frequently found in *lamina propria* whereas CD8+ cells resided preferentially in the mucosal epithelium. In all 10 cases, by using UCHL1 antibody on paraffin sections, small non-neoplastic T-cells were evidenced throughout the lymphoma infiltration and in some cases they underlay the tumour.

Hepatic and bone marrow biopsies were normal. Follow-up by clinical, radiological, haematological and histological (biopsy) examinations showed that the patients included in the group of low-grade BGL-MALT were free of disease from one to seven years after surgery. In the group of high-grade BGL-MALT the disease-free survival ranged from one to seven years (Table 1). However, the limited number of cases

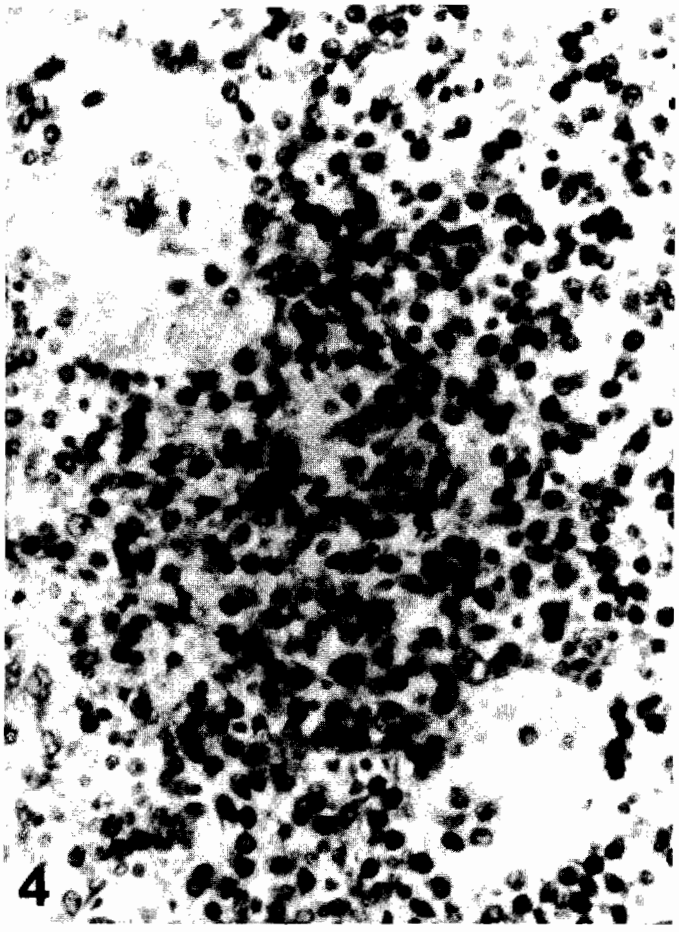

Fig. 4. Centrocyte-like cells show LN2 positivity. Immunoperoxidase method, original magnification × 300

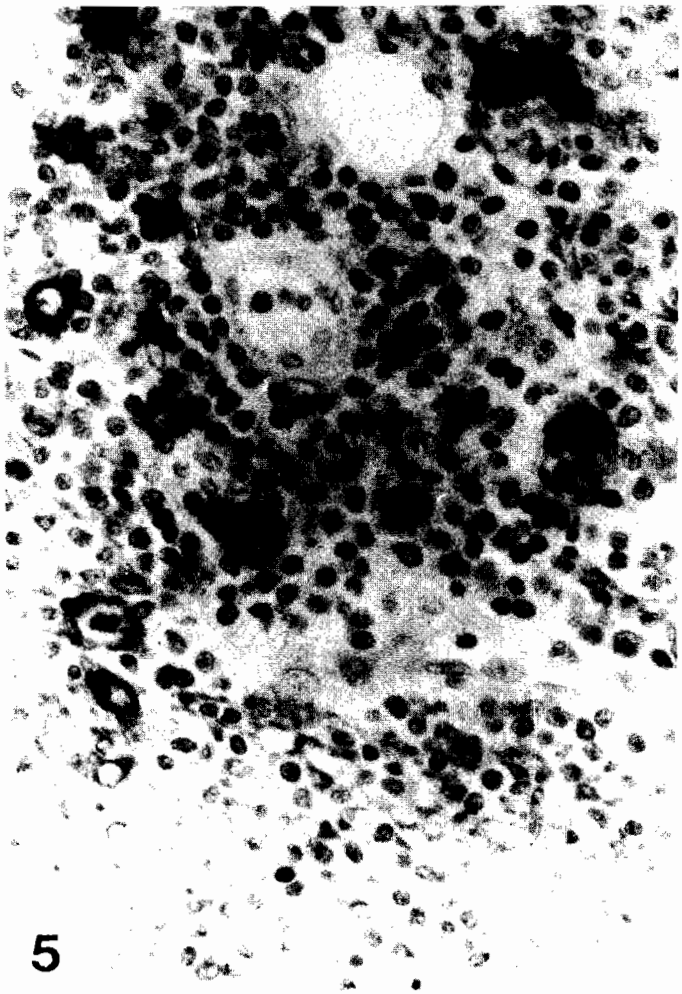

Fig. 5. Rare centroblast-like cells revealed by membrane and paranuclear dot positivity with LN1 antibody. Centrocyte-like cells are negative (case 6). Immunoperoxidase method, original magnification × 520

Table 1. Histological findings and evolution

GROUPS	CENTROCYTE-LIKE CELLS	CENTROBLAST-LIKE CELLS	IMMUNOCYTOMA	PARIETAL EXTENSION	LYMPH NODE	EVOLUTION (free of disease) Y: years M: months
A: 3 cases	+					
Case 1	clear			SM +	reactive	7 Y
Case 2	standard			SM +	involved	4 Y
Case 3	standard			M +	ND	4 Y
B: one case	+		+			
Case 4	standard			SM +	reactive	8 M
C: 5 cases	+	+				
C1	+	30%				
Case 5	standard			SM +	reactive	5 Y
Case 6	clear			S +	involved	1 Y
C2	+	30 - 50%				
Case 7	standard			SM +	reactive	5 Y
C3	+	50%				
Case 8	standard			S +	involved	1 Y
Case 9	standard			S +	reactive	4 Y
D: one case	+	30 - 50%	+			
Case 10	standard			SM +	reactive	3 Y

SM = submucosa, M = muscularis propria, S = serosa, ND = not documented.

Table 2. Immunohistochemical findings

CASES	CENTROCYTE-LIKE CELLS	CENTROBLAST-LIKE CELLS	PLASMA CELLS
1	Sig ND/LN1– LN2+ MB2+	not identified	polytypic
2	Sig Mu.Kappa/LN1– LN2+ MB2+	not identified	polytypic
3	Sig ND/LN1– LN2+ MB2+	not identified	polytypic
4	Sig Mu.Kappa/LN1– LN2+ MB2+	not identified	monotypic IgMu/Kappa
5	Sig Mu.Lambda/LN1– LN2+ MB2+	LN1+ LN2+ MB2+	polytypic
6	Sig Mu.Kappa/LN1+ LN2+ MB2+	LN1+ LN2+ MB2+	polytypic
7	Sig Mu.Kappa/LN1– LN2+ MB2+	LN1+ LN2+ MB2+	polytypic
8	Sig Kappa/LN1– LN2+ MB2+	LN1+ LN2+ MB2+	polytypic
9	Sig Mu.Lambda/LN1– LN2+ MB2+	LN1+ LN2+ MB2+	polytypic
10	Sig ND/LN1– LN2+ MB2+	LN1+ LN2+ MB2+	monotypic IgMu/Kappa

In all cases, no cytoplasmic monotypic immunoglobulin was identified in centrocyte like cells nor centroblast like cells. In cases 5 - 9, surface immunoglobulin was the same for centrocyte like cells and centroblast like cells. No heavy chain of immunoglobulin could be shown on lymphoma cells for case 8. ND = not documented ; Sig = Surface monotypic immunoglobulin.

studied in our series prevented conclusions based on the above follow-up data.

Discussion

The combined histological and immunohistochemical assessment of our cases disclosed four major groups of BGL-MALT composed of: A) CCLC lymphoma; B) CCLC and immunocytoma; C) CCLC and CBLC proliferation in a variable association, divided into three subgroups (C1: less than 30% CBLC; C2: 30% to 50% CBLC; C3: more than 50% CBLC); and D) CCLC with more than 30% CBLC and immunocytoma. Groups A, B, C1 could be assigned to the morphologically low grade malignancy BGL-MALT while groups C2, C3, and D were composed of morphologically high grade malignancy BGL-MALT associated with a low grade component. Recently, Chan et al. (1990) suggested that a BGL-MALT could be considered as a high grade

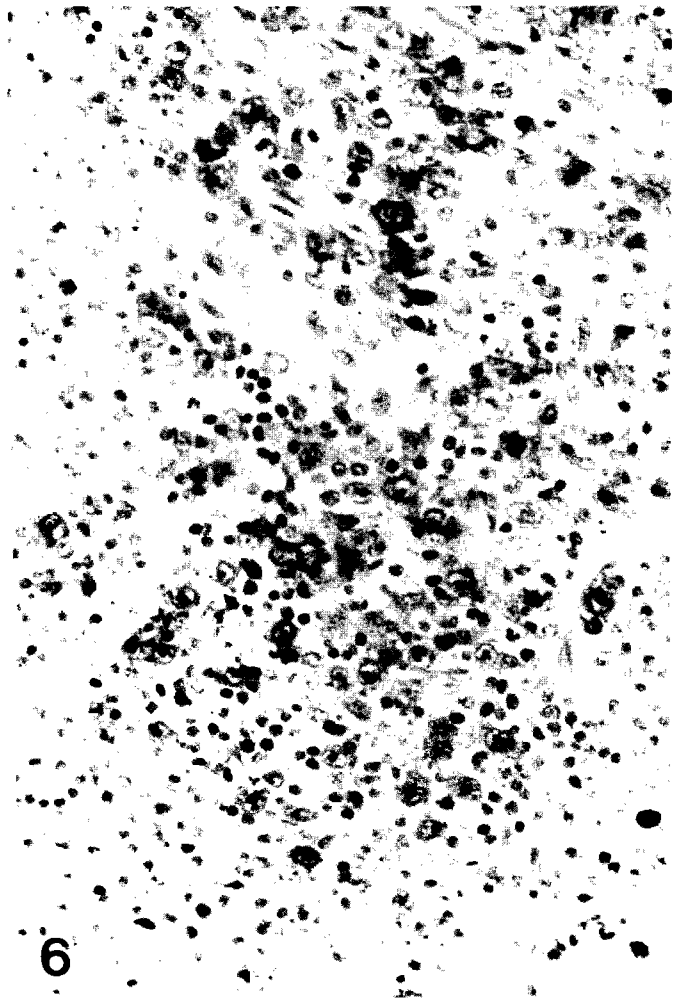

Fig. 6. Numerous centroblast-like cells (30 to 50 per cent) revealed by LN1 positivity (case 7). Immunoperoxidase method, original magnification × 300

lymphoma if blasts organized in clusters and/or sheets predominated among lymphoma cells as well as lymph nodes. However, in this report the count of the large cells is impracticable because of the variability of their percentage from one area to another. The significance of histological classification as a prognostic factor in gastric lymphomas has been extensively discussed in previous literature (Lim et al., 1977; Lewin et al., 1978; Dworkin et al., 1982; Brooks and Enterline, 1983; Shimm et al., 1983; Dragosics et al., 1985; Parlier et al., 1986; Ravaioli et al., 1986). The results generally provided evidence that histological classification was not a prognostically significant factor (Lim et al., 1977; Brooks et al., 1983; Dragosics et al., 1985; Ravaioli et al., 1986) and, in gastric lymphomas as a whole, the stage rather than histological grade was reported to be the most important determining factor of prognosis (Lewin et al., 1978; Shimm et al., 1983). However, other studies (Dworkin et al., 1982; Parlier et al., 1986; Aozasa et al., 1988; Van Krieken et al., 1989) reported that histological classification provides important information for the prognosis of GI lymphomas.

Taken together these data indicate than in GI lymphomas, the contribution of the histological type and grade to prognosis remains controversial and requires further studies with precise histological classification and long term follow up of large series. With regard to this, our preliminary subdivision of BGL-MALT into two distinct groups of histologically high and low grade malignancy, although based on only 10 cases, could be extended to larger series and its possible prognostic significance could be evaluated by correlation with clinical evolution.

Immunohistochemical evaluation of our series revealed that standard and clear cell variant of CCLC were MB2+, LN2+, LN1-, except for one case which was MB2+, LN2+, LN1+. CBLC were found to be LN2+, MB2+ and exhibited constant paranuclear dot-like staining with or without membrane staining with LN1 antibody. These findings are in keeping with those of Isaacson and Spencer (1987) and Myhre and Isaacson (1987), but our study emphasizes the usefulness of LN1 antibody to identify the precise number of CBLC.

Expression of monotypic SIg by tumour cells was found in all tested cases in this study. In contrast, monotypic CIg could be detected only in plasma cells in two cases. CCLC and CBLC were either CIg-negative or showed polytypic staining probably due to passive absorption of extracellular Ig. On the contrary, Myhre and Isaacion et al. (1987) were able to demonstrate monotypic cytoplasmic light chain restriction in CCLC in all cases tested in their study. It is of interest that in cases 4 and 10 the neoplastic plasma cells expressed monotypic CIg/Mu-Kappa in keeping with the expression of monotypic SIg/Mu-Kappa by CCLC. This finding, in agreement with Hyjek et al. (1988) suggest that, in MALT lymphomas, neoplastic plasma cells might be derived from maturation of neoplastic CCLC.

As far as the histogenesis of BGL-MALT is concerned, Myhre and Isaacson (1987) have proposed that these tumours are not derived from follicle centre cells but from CCLC. According to Isaacson and Spencer (1987) the benign equivalent of the neoplastic CCLC forms a broad parafollicular zone in human Peyer's patches, infiltrates the dome epithelium over each lymphoid follicles and displays the phenotype SIgM+ or SIgA+, SIgD–, CD22+, CD23–, CD5–, CD35+ and CD21+.

Recent developments in molecular biology have provided new insights into the histogenesis of B-cell lymphomas arising in the GI tract. By using Southern blot analysis, Pan et al. (1989) and Whaterspoon et al. (1990) found no rearrangements of the bcl-2 gene in low grade B-cell MALT lymphomas. Such rearrangements result from a translocation between chromosomes 14 and 18 and have been detected in 75%-90% of B-cell follicular lymphoma cases (Weiss et al., 1987; Pan et al., 1989). In view

of these data Pan et al. (1989) and Whaterspoon et al (1990) suggested that low grade B-cell GI lymphomas of MALT comprised a distinct entity and are not of follicle centre-cell lineage.

Non-neoplastic T-cells were identified inside tumour population in all cases of our study whatever the histological type of lymphoma. These cells, in keeping with previous studies (Al Saati et al., 1984; Berger et al., 1987) were numerous in low-grade B-cell lymphomas and scarce in high-grade subtypes. Immunotopographic evaluation of our series by pan T-cell markers revealed, in agreement with other reports (Berger et al., 1987; Jarry et al., 1987), a preferential perivascular and interfollicular localisation of the non-neoplastic T-cells. These cells might represent residual elements, but although such elements probably exist, this hypothesis does not satisfactorily explain their abundance in low-grade BGL-MALT and their rarity, in the high-grade subtypes.

Alternatively, as suggested by Jarry et al. (1987), it appears more likely that the non-neoplastic T-cells, in B-cell gastric lymphomas, in view of their preferential perivascular distribution, could be considered as reactive migrated T-cells and may represent a host reaction against the lymphomatous process. This hypothesis has been further supported in the study of Jarry et al. (1987) by the fact that most T-cells located inside lymphoma, in contrast to normal intestinal T-cells, were activated since they expressed CD25 antigen.

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