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Relationship Between High-grade Lymphoma and Low-grade B-cell Mucosa-associated Lymphoid Tissue Lymphoma (MALToma) of the Stomach

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The distinctive low-grade B-cell mucosa-associated lymphoid tissue lymphoma (MALToma) of the stomach has been well characterized in recent years, but its relationship with the more commonly occurring large B-cell gastric lymphoma has not been clarified. This study aimed to elucidate their relationship. Among 48 consecutive cases of primary malignant lymphoma found in gastrectomy specimens, there were 10 cases showing coexistence of these two elements, which were further studied in detail. The high-grade component predominated in six cases, the low-grade component predominated in two cases, and the two components were intermingled in two cases. In the low-grade component, the small neoplastic cells possessed irregular nuclei (centrocytelike), and glandular invasion was a prominent feature. In the high-grade component, the blasts occurred in clusters or sheets, and often possessed plasmacytoid cytoplasm; glandular invasion was a rare event. In both components, the neoplastic cells frequently showed formation of nodules suggestive of colonization of reactive lymphoid follicles. Immunohistochemical studies showed that the neoplastic cells in the low- and high-grade components expressed the same class of immunoglobulin light chain in eight of the nine cases studied; staining in one case was unsatisfactory. Their intimate relationship as well as identical light chain restriction suggests that the high-grade component arises through blastic transformation of the low-grade component. (Am J Pathol 1990, 136:1153–1164)

The gastrointestinal tract, particularly the stomach, is the commonest primary site of extranodal lymphomas.[1] As reported in the literature, most gastric lymphomas are large cell ("histiocytic") lymphomas of B-cell lineage.[2–11]

Isaacson and colleagues[12–15] have in recent years characterized the B-cell mucosa-associated lymphoid tissue lymphomas (MALTomas) of the stomach as indolent tumors that usually remain localized for a long time before dissemination occurs. Some cases of gastric lymphoma previously reported as lymphoplasmacytoid/lymphoplasmacytic, plasmacytic, or centroblastic-centrocytic (follicular center cell) lymphoma, and many cases of gastric "pseudolymphoma" may represent examples of this tumor[16,17]; the frequency of true follicular center cell and pure plasmacytic lymphomas of the stomach requires reevaluation.[17] The cytologic composition varies from case to case, but most cases are composed predominantly of small cells; such cases were designated "low-grade B-cell lymphoma of mucosa-associated lymphoid tissue" in the first meeting of the European Association for Hematopathology, 1988.[15] However, their relationship with the more commonly occurring high-grade B-cell lymphomas of the stomach has not been directly addressed.

Low-grade lymphomas are known to be able to transform into high-grade large-cell lymphomas, such as transformation of follicular lymphoma, small lymphocytic lymphoma (Richter's syndrome), or mycosis fungoides into large-cell lymphoma.[18,19] Immunohistochemical, karyotypic, and genotypic studies have provided convincing proof that the supervening large-cell lymphomas arise from the same clone as the low-grade lymphoma.[18,20–22] Therefore, it is conceivable that the same can occur in the stomach. However, longitudinal studies to trace the stages of evolution from low-grade to high-grade lymphoma are difficult if not impossible in the stomach because it is usually resected once a diagnosis of gastric

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Table 1. *Antibodies Used*

Antibody	Source	Major specificity
Anti-Kappa	Dakopatts	Kappa light chain
Anti-Lambda	Dakopatts	Lambda light chain
Anti-IgM	Dakopatts	μ heavy chain
Anti-IgG	Dakopatts	γ heavy chain
Anti-IgA	Dakopatts	α heavy chain
UCHL1	Dakopatts	T cells
MT1	Biotest	T cells
MB1	Biotest	B cells
MB2	Biotest	B cells
L26	Dakopatts	B cells
2G7 (CD21)	Dr. T. F. Schultz[28]	Dendritic reticulum cells

lymphoma is made. To elucidate the relationship between large-cell lymphoma and low-grade MALToma, we retrospectively studied the histologic sections of 48 gastrectomy specimens harboring primary malignant lymphoma. The 10 cases showing histologic features of both low-grade MALToma and large-cell lymphoma were further studied, forming the subject of this report.

Materials and Methods

In the surgical pathology file of Queen Elizabeth Hospital, Hong Kong, 48 cases of primary gastric lymphoma were identified in gastrectomy specimens over a 9-year period (1980 to 1988). These patients had no pre-existing lymphoma, were found at laparotomy to have disease confined to the stomach and/or regional lymphatic tissue, and had no new disease appearing in other sites within 6 months of surgery. Cases of gastric lymphoma diagnosed by endoscopic (three cases) or incisional (five cases) biopsy alone were excluded because there was insufficient histologic material for this study. Gastrectomy specimens were not available in these cases, either because the patient refused operation or because the tumor was found to be inoperable at laparotomy.

The specimens had been fixed in buffered formalin and processed routinely for paraffin embedding. All available histologic sections were examined, and the 10 cases showing features of both low-grade MALToma and high-grade lymphoma were chosen for further immunohistochemical studies (except case 1, in which paraffin blocks were not available). The histologic features of low-grade MALToma have been previously detailed,[13-15] and a high-grade component was considered to be present whenever compact clusters or sheets of large nucleolated cells were present. The latter criterion was adapted from Lennert's definition of high-grade lymphoma arising in follicular centroblastic-centrocytic lymphoma.[23,24] Immunohistochemical studies were carried out, both in Hong Kong and London, on 4 μ-thick paraffin sections using the avidin-biotin peroxidase complex technique. The antibodies used are listed in Table 1.[25-30] After deparaffinization, sections were hydrated and blocked for endogenous peroxidase using hydrogen peroxide. The primary antibody was applied for 1 hour at room temperature, followed by incubation with biotinylated rabbit anti-mouse (for monoclonal antibodies) or swine anti-rabbit (for polyclonal antibodies) for 30 minutes, and then avidin-biotin-peroxidase complex for 30 minutes. The sections were thoroughly washed with TRIS buffer saline between the steps. The color reaction was developed with diaminobenzidine. Hematoxylin was used for counterstaining. Appropriate positive and negative controls were included.

Results

Clinical Features

Among the 48 cases of gastric lymphoma, 12 were classified as low grade, 26 as high grade, and 10 as mixed low- and high-grade lymphoma (Table 2). The mean ages of these three groups of patients were 56.4, 62.1, and 47.4 years, respectively. All were Chinese. The ages as well as the histologic types were similar to those reported in the Western literature, suggesting that this was a representative sample of gastric lymphomas.[2-11] For the 10 patients with mixed low- and high-grade lymphoma, seven men and three women, the tumor was located in the pyloric

Table 2. *Classification of Gastric Lymphomas*

	No. of cases	Gender (M:F)	Age	No. of slides from stomach available
Low-grade lymphoma	12	9:3	24 to 80 years (mean, 56.4; median, 61.5)	2 to 19 (mean, 8.7; median, 7.5)
High-grade lymphoma	26	16:10	21 to 90 years (mean, 62.1: median, 65.5)	2 to 11 (mean, 5.2; median, 4)
Mixed low-grade MALToma and high-grade lymphoma	10	7:3	21 to 68 years (mean, 47.4; median, 49.5)	3 to 15 (mean, 8.5; median, 8.5)

Table 3. *Clinicopathologic Features of the 10 Patients with Mixed Low-grade and High-grade Gastric Lymphoma*

Case	Gender/age	Location of tumor	Size of tumor (cm)	No. of slides available*	Lymph nodes	Spleen
1	F/52	Antrum	NA	3	NA	NA
2	M/38	Antrum	10 × 4	10	−	−
3	M/21	Antrum	2 × 1.5	6	−	−
4	F/42	Antrum	4 × 4	9	−	NA
5	F/57	Antrum	6 × 4	4	−	NA
6	M/68	Antrum	8 × 3	11	−	NA
7	M/47	Antrum	4 × 4	7	+	+
8	M/57	Antrum	3 × 1	12	−	−
9	M/39	Antrum	7 × 7	8	+	NA
10	M/53	Cardia/fundus	6 × 4	15	+	−

NA, not available.
* Number of slides from stomach that were available for examination; + Lymphomatous involvement present; − No evidence of lymphomatous involvement.

antrum in nine, and in the cardia and fundus in one. The number of tissue blocks taken from the stomach ranged from three to 15, with a mean of 8.5. In the nine cases in which the regional lymph nodes were available for examination, three showed involvement by high-grade lymphoma (Table 3). Splenic involvement was seen in one of the five cases available for review; there was selective involvement of the germinal centers in the white pulp by large-cell lymphoma.

Pathologic Features

Among the ten cases showing features of both low- and high-grade lymphoma, five (cases 1, 2, 5, 9, and 10) were predominantly high grade, two (cases 3 and 6) were predominantly low grade, and three (cases 4, 7, and 8) showed the presence of the two components in about equal proportions. The low- and high-grade components were readily identified as being discrete (Figure 1), but they were more intermingled in two cases (Figure 2). Even in the latter two cases, the intermingling was in the form of islands of small cells alternating with islands of large cells, which was unlike the diffuse admixture in the conventional mixed-cell lymphomas (Figure 2B). The high-grade component usually infiltrated the wall of the stomach to the same or a deeper level compared with the low-grade component. In cases 1, 2, 4, and 6, a chronic peptic ulcer was present in the central portion of the lymphoma; lymphoma cells were absent in the floor of the ulcer.

Table 4. *Immunohistologic Features of Low- and High-grade Components*

Case	Estimated percentage of entire tumor area	Maximum depth of invasion	Relationship between the components	Lympho-epithelial lesion	Follicular colonization	Immunohistochemistry MB1	MB2	L26	Ig	Intensity of T-cell infiltrate
1-L	5	Mucosa	Discrete	+	−	NA	NA	NA	NA	NA
-H	95	Submucosa	Discrete	−	NA	NA	NA	NA	NA	NA
2-L	5	Mucosa	Discrete	−	−	−	+	+	IgM-λ (+PC)	++
-H	95	Muscularis	Discrete	−	+	−	+	+	IgM-λ	++
3-L	80	Submucosa	Discrete	+	+	−	+	+	IgM-λ	++
-H	20	Submucosa	Discrete	−	+	−	+	+	IgM-λ	+++
4-L	50	Submucosa	Mixed	+	+	+	+	+	IgM-λ (+PC)	++
-H	50	Submucosa	Mixed	±	+	+	+	+	IgM-λ	++
5-L	5	Mucosa	Discrete	+	−	−	−	+	IgM-λ	+
-H	95	Muscularis	Discrete	−	+	−	−	+	IgM-λ	+
6-L	60	Submucosa	Discrete	+	+	+	+	+	IgM-λ	+
-H	40	Submucosa	Discrete	−	+	+	+	+	IgM-λ	++
7-L	50	Mucosa	Discrete	+	+	+	+	+	IgG-λ	++
-H	50	Muscularis	Discrete	−	+	+	+	+	IgG-λ	+++
8-L	45	Submucosa	Mixed	+	+	+	+	+	IgM-λ (+PC)	+
-H	55	Submucosa	Mixed	±	+	+	+	+	IgM-λ	+
9-L	5	Mucosa	Discrete	+	+	−	+	+	?	+
-H	95	Muscularis	Discrete	−	+	−	+	+	κ	++
10-L	5	Submucosa	Discrete	+	−	+	−	+	IgM-λ (+PC)	+
-H	95	Muscularis	Discrete	−	+	+	−	+	λ	++

L, low-grade component; H, high-grade component; + present; − absent; NA, not available; ± rare lymphoma cells invade the gastric glands; ? = unsatisfactory staining; (+PC) = monotypic plasma cells expressing same immunoglobulin class. Intensity of T-cell infiltrate graded as follows: + = mild; ++ = moderate; +++ = heavy.

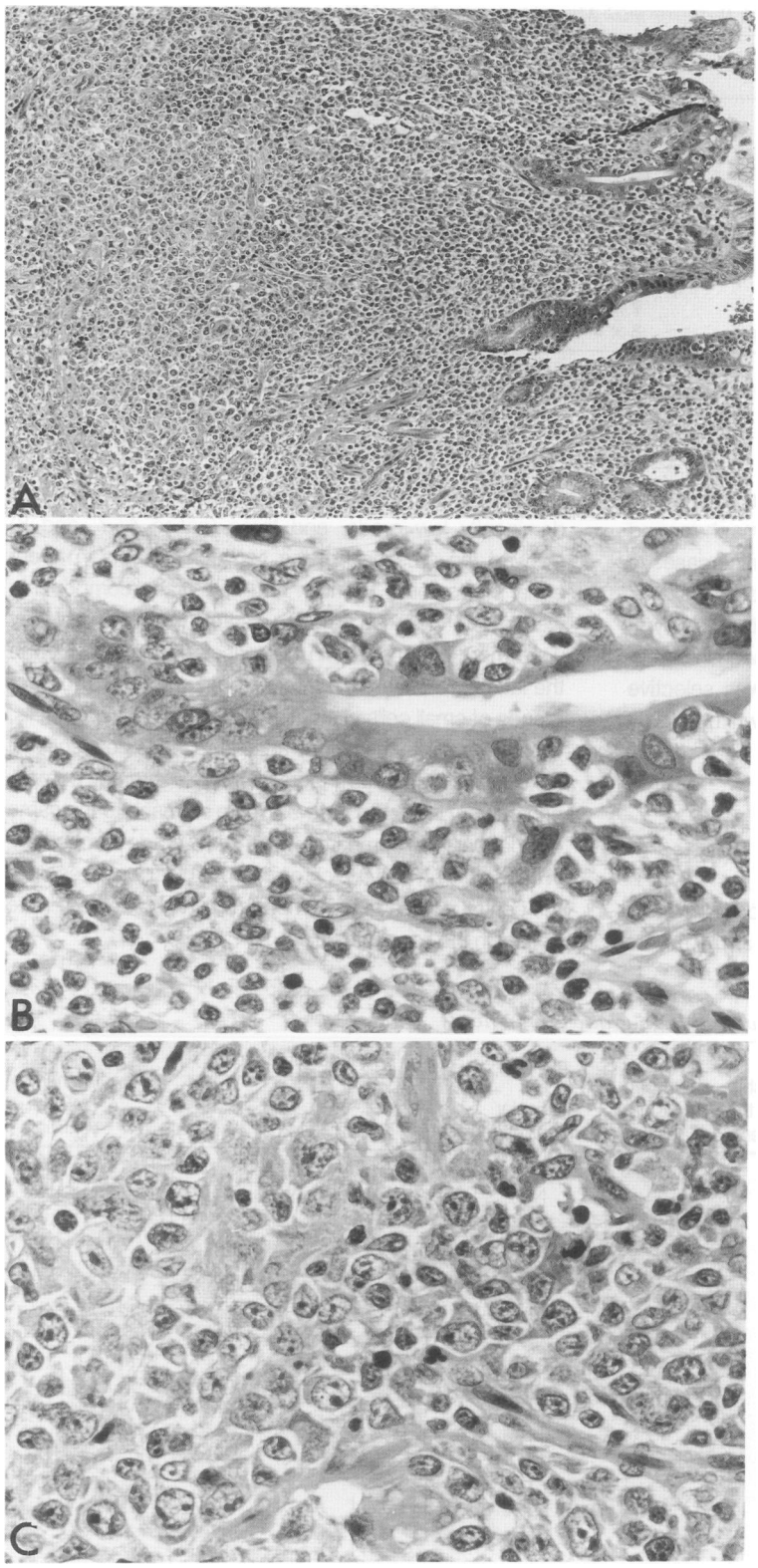

Figure 1. *Lymphoma with discrete low- and high-grade components.* **A:** *Low-power view. The portion immediately beneath the luminal surface represents low-grade lymphoma, while the deep portion represents high-grade lymphoma (H&E ×150).* **B:** *Higher magnification of low-grade component, which is composed of centrocytelike cells with formation of lymphoepithelial lesions (H&E ×480).* **C:** *High-grade component composed of centroblastlike cells (H&E ×480).*

In the low-grade component, the neoplastic cells were centrocytelike, and were 1.5 to 2 times the size of small lymphocytes. The nuclei were indented, irregularly folded, or elongated, with dense chromatin and indistinct nucleoli. Cytoplasm was scanty to moderate, and was pale or clear (Figures 1B, 2B). These centrocytelike cells

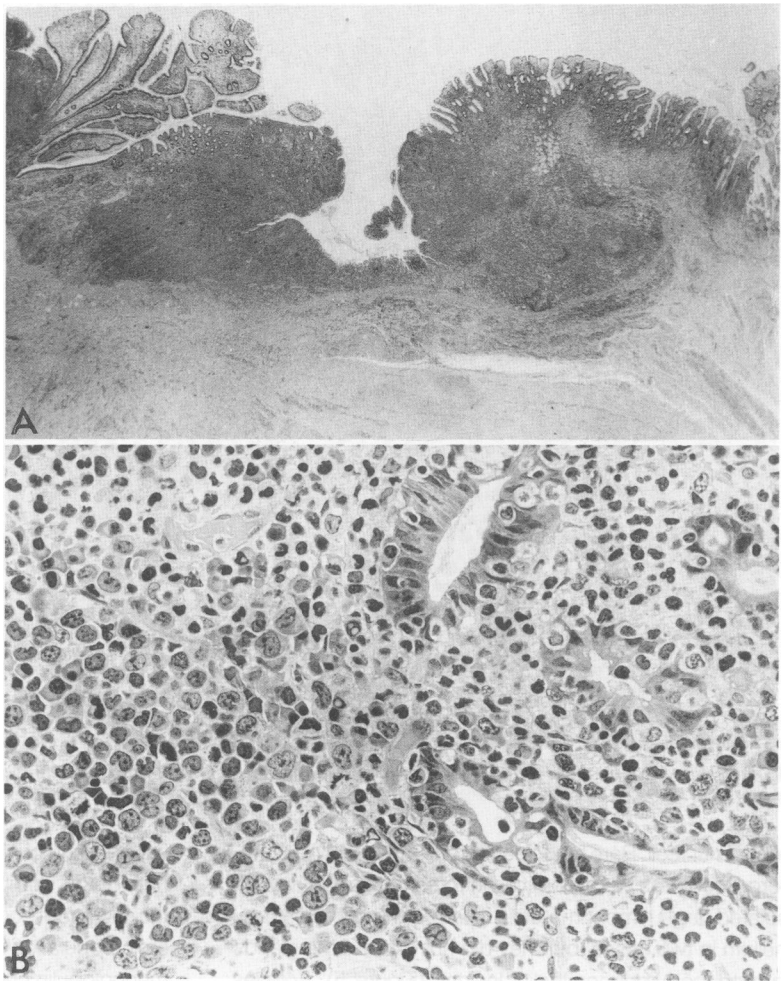

Figure 2. *Lymphoma with the low- and high-grade components intermingled.* **A:** *Lymphoma confined to mucosa and submucosa (H&E×10).* **B:** *Although intermingled, the two components are clearly identifiable to be occurring in alternating clusters. The right and upper fields are dominated by low-grade component; the lymphoma cells have irregularly folded nuclei and clear cytoplasm. The glands are infiltrated by the centrocytelike cells and plasma cells (which prove to be monotypic in this case). The left field is dominated by blasts with irregular nuclei and basophilic cytoplasm (H&E×400).*

proliferated in sheets between the gastric glands and around the hyperplastic lymphoid follicles, which abutted on the muscularis mucosae or were situated in the submucosa. In nine cases, there were appreciable numbers of centrocytelike cells invading and expanding the gastric glands to produce lymphoepithelial lesions (Figures 1B, 2B). More advanced glandular destruction resulted in isolated pink-staining epithelial cells in a background of lymphoma cells. In six cases, the centrocytelike cells infiltrated the mantles and germinal centers of the reactive lymphoid follicles, suggestive of "follicular colonization." In some follicles, the neoplastic centrocytelike cells were admixed with small islands of reactive germinal center cells (predominantly centroblasts mixed with tingible body macrophages). However, some follicles were formed entirely by a monotonous population of centrocytelike cells, and were devoid of tingible body macrophages and mantles. The centrocytelike cells that were found within the follicles often were slightly larger with less condensed chromatin compared with those outside the follicles (Figure 3), and some showed high-grade (blast) transformation. Mature-looking plasma cells invariably were present in variable numbers, being particularly numerous immediately beneath the surface epithelium. It could not be determined from their cytologic features whether they were part of the neoplastic population or reactive. Very rarely, plasma cells also invaded the glands (Figure 2B). The histologic features were consistent with those described as "low-grade B-cell lymphoma of mucosa-associated lymphoid tissue."[13,14]

In the high-grade component, the infiltrate of large cells was more destructive, causing marked loss of glands; reactive lymphoid follicles were fewer. The large cell occurred in diffuse sheets and clusters, and often were intermingled with some small round lymphocytes. They had variable appearances; most were centroblastlike. The nuclei were round, indented, or multilobated, and had vesicular chromatin. There were multiple distinct nucleoli that were apposed to the nuclear membrane or randomly disposed (Figures 1C, 2B, 4). Unlike classical centroblasts (large noncleaved cells), there was a fair amount of cytoplasm that was deeply basophilic to amphophilic; the perinuclear Golgi was well developed in some. Some were immunoblastlike, with large nuclei and solitary prominent

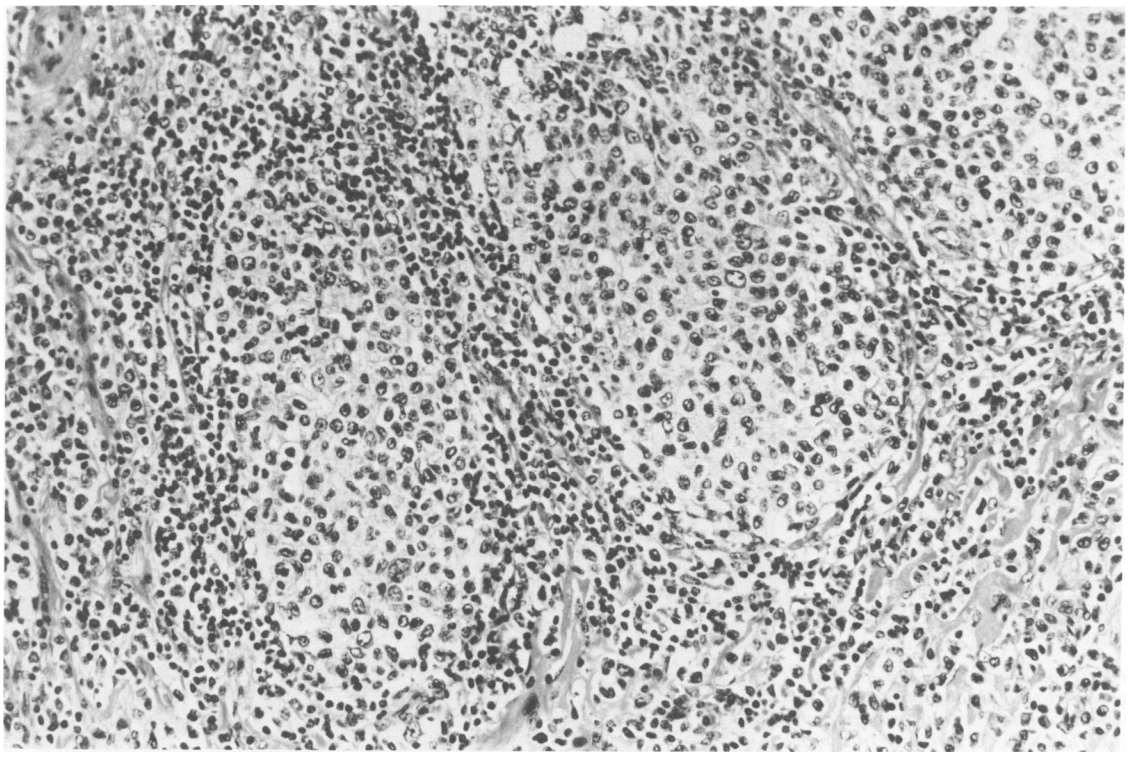

Figure 3. *Several lymphoid follicles formed by a monotonous population of medium-sized lymphoma cells. Their mantles are deficient (H&E×200).*

central nucleoli. Rare binucleated forms resembling Sternberg-Reed cells were identified in three cases (Figure 4d). Isolated large lymphoma cells invaded the glandular epithelium in two cases, but they did not expand the glands to produce lymphoepithelial lesions (Figure 5). Follicles containing large neoplastic cells were observed in all the nine cases in which this feature could be assessed.

Immunohistochemistry

The immunophenotype of the lymphoma cells in the high-grade component was identical to that of the low-grade component with respect to staining with the three B-cell antibodies MB1, MB2, and L26; staining with MT1 and UCHL1 was uniformly negative. In the four cases showing negative staining with MB1, even the reactive lymphoid cells were negative, suggesting that the epitope recognized by this antibody might have been destroyed by prolonged fixation rather than being truly absent on the neoplastic cells. Identical monotypic immunoglobulin (lambda light chain) could be demonstrated in both the low- and high-grade components in eight of the nine cases studied. The staining was intense and diffuse in the cytoplasm in the high-grade component, while the staining in the centrocytelike cells of the low-grade component was mainly in the perinuclear space (Figure 6). In case 9, kappa light chain restriction was demonstrated in the high-grade component, but immunoglobulin staining in the low-grade component was unsatisfactory. A monotypic population of plasma cells expressing the same immunoglobulin class as the low- or high-grade component was identified in four cases. Among the neoplastic B cells, there was a mild to heavy infiltrate of small T lymphocytes (MT1+, UCHL1+), the density of which was generally higher in the high-grade component. Staining for dendritic reticulum cells using 2G7 (CD21) showed a dense network within reactive follicle centers, but in those follicles showing colonization by neoplastic cells, the network was disrupted (Figure 7).

Discussion

The coexistence of low- and high-grade lymphomas in the stomach has been previously alluded to by Brooks and Enterline,[5] who reported that six out of 58 cases of gastric lymphoma showed features of both low-grade lymphoma (poorly differentiated lymphocytic or mixed cell type) and large-cell lymphoma. Although the authors suggested that the latter evolved from the former, there was no firm proof that the two components indeed belonged to the same clone. Similar composite lesions also have been reported in the gastrointestinal tract, salivary gland, thyroid, or lung,

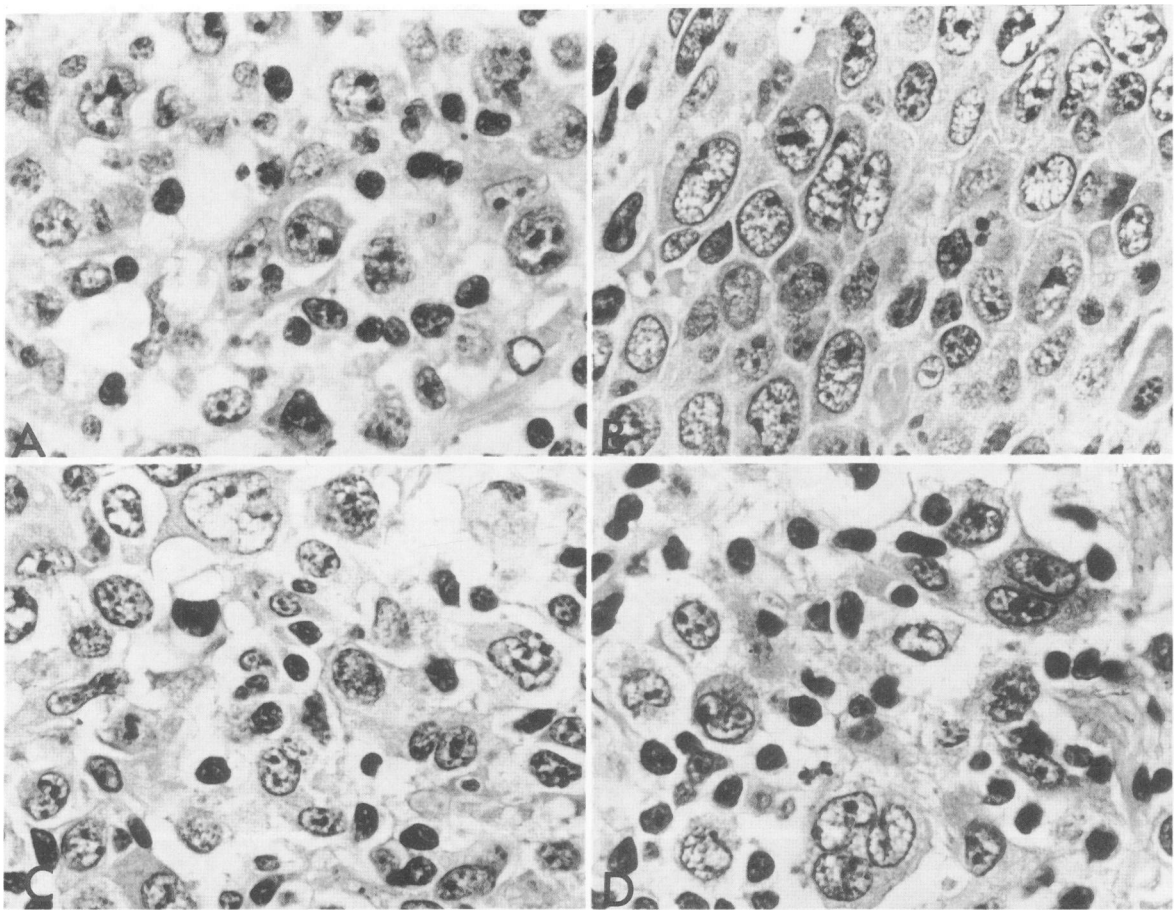

Figure 4. *Varied cytologic appearances of high grade lymphoma.* **A, B:** *Centroblastlike cells with basophilic, occasionally plasmacytoid cytoplasm.* **C:** *Some show more variation in size and nuclear shape.* **D:** *Cells with indented nuclei and multinucleated forms. (All H&E×750).*

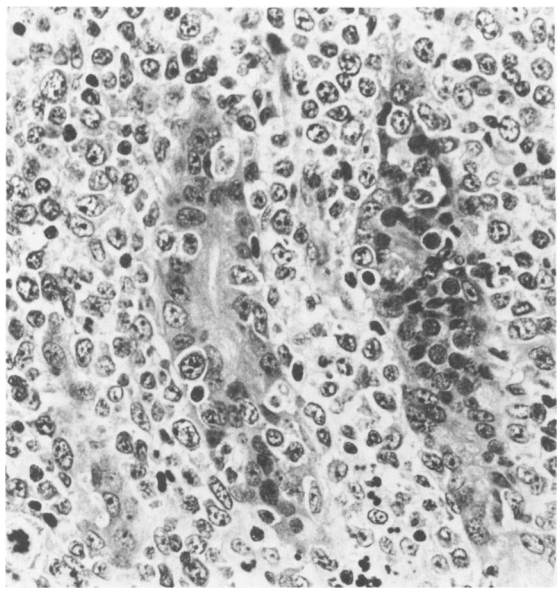

Figure 5. *Gastric glands invaded but not expanded by large lymphoma cells (H&E×300).*

but the relationship between the two components has not been fully addressed.[15,31-34]

Based on information derived from studying colorectal lymphomas, Hall et al[35,36] proposed the term 'polymorphic B-cell lymphoma' for MALTomas of the gastrointestinal tract. The high-grade category was distinguished from the low-grade category by the presence of over 20% blast cells. We consider the term 'polymorphic' not entirely accurate because some cases may be quite monomorphic.[15] We also prefer to specify the components present instead of using an arbitrary figure, as such a count is impracticable because of the variability of percentage of large cells from area to area and the rich infiltrate of reactive cells. Whenever large cells occur in readily identifiable compact clusters or sheets, we consider that a high-grade component has supervened.[23,24]

In low-grade B-cell MALToma of the stomach, the neoplastic centrocytelike cells tend to grow around reactive lymphoid follicles and to invade gastric glands to produce lymphoepithelial lesions.[12-14] Provided that a sensitive immunoperoxidase technique is used, cytoplasmic immu-

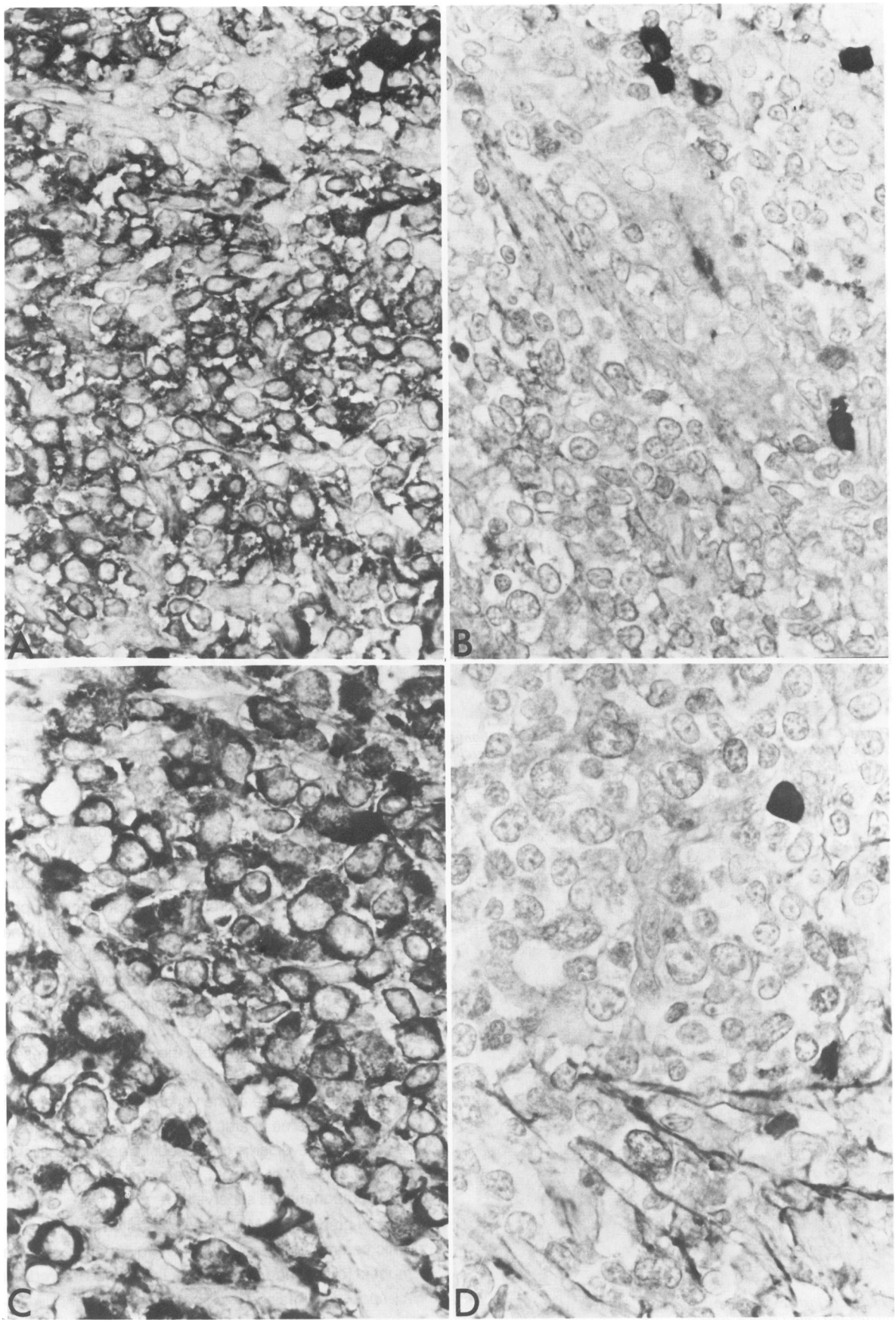

Figure 6. A, B: *Low-grade and* C, D: *high-grade components of the same case immunostained for lambda and kappa light chains, respectively. Lambda light chain restriction is demonstrated in both components. Note positive staining in the perinuclear space of the centrocytelike cells in* A *(Immunoperoxidase, ×600).*

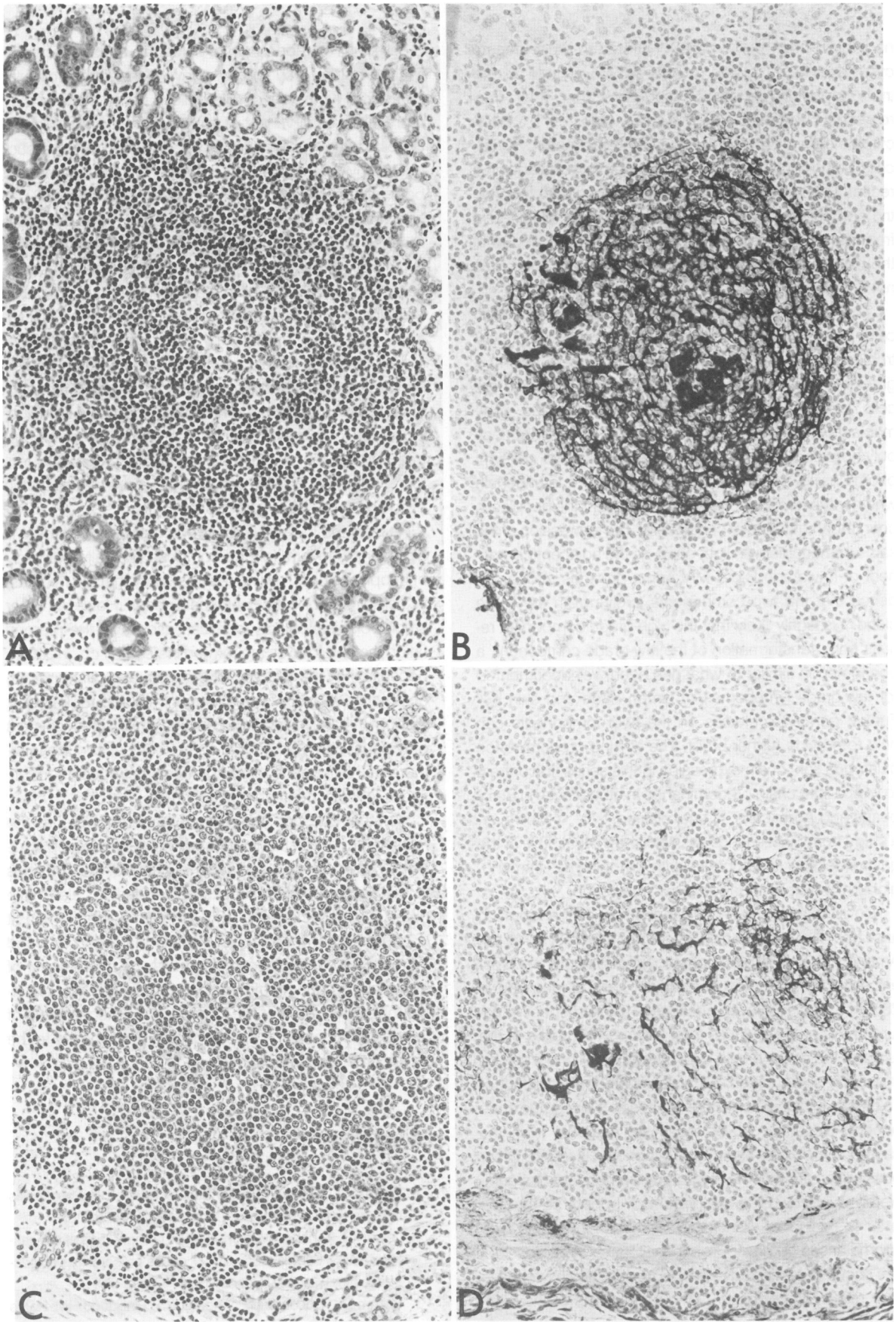

Figure 7. **A:** *A reactive follicle center in the mucosa.* **B:** *Same follicle stained with 2G7 (CD21) revealing a tight network of follicular dendritic cells.* **C:** *Follicles from same section showing replacement by centrocytelike cells that have undergone high-grade transformation within the follicle.* **D:** *Same follicle stained with 2G7, showing disruption of follicular dendritic cell network (H&E and immunoperoxidase, ×150).*

noglobulin often can be demonstrated in these centrocytelike cells.[13,14,37] The growth pattern as well as the immunophenotypic profile suggests that they may represent neoplastic marginal zone cells.[13,14,38] Centrocytelike cells are morphologically similar to monocytoid B-cells, with which they may share a common lineage. In a recent series of monocytoid B-cell lymphomas; the gastric and salivary gland lesions appear to be no different from those of low-grade B-cell MALTomas, except that the plasma cell component and relation to follicles was not emphasized.[39]

The high-grade component is composed of blastic cells, most of which possess nuclei resembling centroblasts (large noncleaved cells), but differ in having a greater amount of basophilic cytoplasm. There also are cells indistinguishable from immunoblasts and plasmablasts. Although these cases may be classified as polymorphic centroblastic or large noncleaved cell lymphoma using established classifications,[40] it is uncertain whether the neoplastic cells truly represent the neoplastic counterpart of follicular center cells. The expression of the same immunoglobulin light chain as the adjacent component of low-grade B-cell MALToma provides strong evidence that the two components evolve from the same clone. It is highly likely that the high-grade component results from transformation of the low-grade component, a phenomenon similar to what has been well documented for low-grade lymphomas of lymph node and skin.[18,19] Further genotypic studies on the two components can help to provide further proof. The striking predominance of lambda light chain expression in this series, in contrast to kappa light chain predominance in other series in Europeans and Americans, is unexplained.[10,12,41,42] However, a study from Switzerland[4] has also shown that 90% of the gastrointestinal lymphomas with cytoplasmic immunoglobulin exhibit lambda light chain restriction.

Do all high-grade B-cell lymphomas of the stomach arise from low-grade B-cell MALTomas? At least some do. Among the 36 high-grade gastric lymphomas in the present series, a low-grade component can be identified in 28% of cases. However, because of the retrospective nature of this study and less than thorough sampling of the tumor in the earlier cases, a low-grade component can be missed in some cases. As an example, only one out of 15 blocks of tissue from case 10 reveals a low-grade component. Generally, fewer slides are available from the cases in which only high-grade lymphoma is found. Other possibilities are that the high-grade component has completely overgrown the low-grade component so that the latter is no longer identifiable, and the high-grade lymphoma arises *de novo*. Probably all these three possibilities occur, but this study cannot provide the answer as to their relative importance. Do the large cells of the high-grade gastric lymphomas, either arising from low-grade B-cell MALToma or *de novo*, belong to a distinct cellular lineage or are they mostly conventional large follicular center cell lymphomas? We believe that a majority may represent blastic variant of marginal zone (parafollicular) B cells[43] rather than true follicular center cells, as suggested by the absence of *bcl-2* gene rearrangement in both gastric low-grade MALTomas and high-grade B-cell lymphomas in a small series of 17 cases,[17] and the failure of these tumors to express CD10 antigen (Isaacson PG, Wotherspoon AL, Diss TC, Pan L, unpublished observation). It is possible that both the low-grade and high-grade lymphomas of the stomach belong to the same cell lineage, which may explain why both do so well with locoregional therapy (5-year survival over 50% when treated by surgery and/or radiotherapy).[3,5,9,44] In gastric lymphomas, unlike nodal lymphomas, pathologic stage (including depth of invasion) rather than histologic grade appears to be the single most important prognostic factor,[2–5,9,45] although some other studies have demonstrated histologic type to be a prognostic factor.[6,41,46]

In both the low- and high-grade components, there is a propensity to form follicles composed partially or entirely of neoplastic cells, raising the possibility that the neoplastic cells are of follicular center cell lineage. However, other studies on histologically identical cases favor the interpretation that the follicles are formed instead by colonization; because they are always CD10-negative as different from *de novo* neoplastic follicles, immunostaining for immunoglobulin in paraffin sections can highlight discrete clusters of residual polytypic cells in some follicles, and these tumors lack *bcl-2* gene rearrangement, as frequently identified in follicular center cell lymphomas.[13,14,17,47]

Another question that remains to be answered is the relationship of gastric lymphoma with chronic peptic ulcer. Chronic peptic ulcer is found in four of the 10 cases in the present series; Brooks and Enterline[5] also have noted this association in 19% of gastric lymphomas. It is possible that the chronic gastritis that often is found surrounding chronic peptic ulcers may be a forerunner of malignant lymphoma of the stomach, but it is also possible that disturbance of the local defence mechanisms of the gastric mucosa by the lymphoma predisposes to the development of peptic ulcer.

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