Low grade B cell mucosa associated lymphoid tissue lymphoma of the stomach: clinical and endoscopic features, treatment, and outcome

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Abstract

A retrospective study of the clinical and endoscopic features of low grade gastric lymphomas of mucosa associated lymphoid tissue (MALT) in 16 patients together with treatment and outcome was undertaken. Immunohistochemical studies of fresh tissue easily distinguished MALT lymphoma from benign reactive lymphoid hyperplasia (pseudolymphoma) and showed that tumour cells had the characteristic phenotype indicative of their origin from MALT. Persistant epigastric pain was the main presenting complaint, and was often associated with acute bleeding, anaemia, or weight loss. Eight patients had a past history of recurrent peptic ulcers or gastritis. The endoscopic appearance suggested malignancy in only half the cases and was compatible with gastritis or a benign peptic ulcer in the remainder. There was extragastric involvement of other mucosal sites in eight patients (mainly the lung, but also the parotid gland and small bowel), but rarely was bone marrow and never the spleen or peripheral lymph nodes affected. Conservative treatment with long term cyclophosphamide was effective in both stage I and stage IV disease, and all the patients are alive after a median follow up of 4·5 years. These findings confirm that low grade gastric MALT lymphomas are usually indolent tumours with non-specific endoscopic aspects and show that dissemination to other mucosal sites was more frequent than previously reported. Monochemotherapy could be an effective alternative treatment to surgery.

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The gastrointestinal tract, particularly the stomach, is the most common primary site of extranodal lymphomas.[1] Most gastric lymphomas are large cell lymphomas of B cell lineage.[2 3] Primary small cell gastric lymphomas are less frequent and are usually localised, solitary lesions that can be completely excised. Because of their favourable prognosis, they were long known as pseudolymphomas.[4–7] However, immunohistochemical methods have now shown that most of these tumours are monoclonal B cell proliferations.[8–11] A number of recent pathological studies have emphasised the specificity of these B cells, suggesting that they originate from mucosa associated lymphoid tissue (MALT).[12–14] Indeed, they have the same cytological and immunophenotypic characteristics as the B cells that are normally found around the mantle zone of Peyer's patches. These properties are now commonly used by pathologists in the diagnosis of MALT lymphomas. A large clinicopathological study based on the review of surgical specimens has recently confirmed results from previous shorter series.[13 15 16] by showing the good prognosis of small cell gastric lymphomas from MALT origin.[17]

Details of symptoms and endoscopic aspects of the stomach in this type of lymphoma, however, remain scarce in the published reports, and the best treatment has not yet been established. This prompted us to report 16 consecutive cases of low grade gastric MALT lymphomas diagnosed in our institution. In this series, the histological diagnosis was based on biopsy specimens, staging procedures systematically included abdominal and chest computed tomography and bone marrow biopsy, and most patients were not operated on but were successfully treated with monochemotherapy.

Patients and methods

PATIENTS

Sixteen patients with low grade gastric MALT lymphoma diagnosed in our institution between 1980 and 1990 were reviewed. The patients, nine men and seven women, ranged in age from 25 to 70 years, with a mean of 54 years.

DIAGNOSTIC PROCEDURES

Fifteen patients were referred to our endoscopic unit for the investigation of epigastric pain, sometimes associated with acute bleeding or anaemia. Several biopsy specimens (>6) were taken, with forceps in every case. One patient with an established diagnosis was referred for additional treatment after partial gastrectomy. The diagnosis of lymphoma was based on histological and immunophenotypic criteria.[18]

Tissue specimen preparation

Tissue specimens were processed for routine

TABLE I *Antibody panel*

Antigen	*Antibody*	*Pattern of reactivity*
CD 3	Anti-Leu 4	T lymphocyte
CD 4	Anti-Leu 3a	T helper lymphocyte
CD 5	Anti-Leu 1	T lymphocyte, subset of B-cells
CD 8	Anti-Leu 2	Cytotoxic/suppressor T lymphocyte
CD 19	B 4	B lymphocyte
CD 22		B lymphocyte
—	Anti-K, λ, γ, μ, δ	Light and heavy chains

The Leu series was obtained from Becton Dickinson & Co, Mountain View, CA, USA. B4 antibody and Ig chain antibodies were obtained from Coulter Immunology, Hialeah, FL, USA. CD 22 antigen was obtained from Dakopatts AIS, Glostrup, Denmark.

histology and immunohistology. In each case, several tissue specimens were fixed with aqueous Bouin's solution. Paraffin embedded sections were stained for conventional study with haematoxylin-eosin-safran (HES) and periodic acid Schiff (PAS). In 12 of the 16 cases, fresh tissue specimens were snap frozen in liquid nitrogen after 30 minutes' incubation in gum sucrose for immunohistological studies.

Immunophenotypic studies

Deparaffinised and cryostat sections of the gastric biopsy specimens were evaluated for the presence of various antigens using the immuno-alkaline phosphatase method (APAAP).[19] The monoclonal antibodies used, their specific immunoreactivities and commercial sources are shown in Table I. Rabbit antimouse immunoglobulins and alkaline phosphatase-antiphosphatase complexes were purchased from DAKO (Dakopatts A/S, Glostrup, Denmark). Alkaline phosphatase activity was determined after incubation in fast-red TR (1 mg/ml, Sigma Chemical Company, St Louis, MO, USA) and naphthol AS-TR phosphate (0·2 mg/ml, Sigma) solution, which contained levamisole (0·24 g/ml) to block endogenous alkaline phosphatase activity.

STAGING PROCEDURES

Staging systematically included a bone marrow biopsy, chest and abdominal computed tomography, oropharyngolarynx examination, and liver function tests. A small bowel barium meal and colonoscopy were performed in eight cases and gastric endosonography was performed in one patient. The patients were staged using the Ann Arbor system.[20]

TREATMENT

In 14 of the 16 patients, initial treatment was an alkylating agent alone (cyclophosphamide 100 mg/day). This monochemotherapy was continued until complete remission was obtained (normal appearance of the gastric mucosa, negative biopsy specimens, and absence of extragastric localisation). One patient with a severe form of the disease (large tumour, poor general condition, and a rapid course) was treated with an anthracin-containing regimen (cyclophosphamide, adriamycin, vincristine, prednisone) combined with radiotherapy (25 Grays). Another had been operated on (partial gastrectomy) before referral to our institution and received additional radiation therapy (30 Grays).

FOLLOW UP

Endoscopy with biopsies was repeated every three months in every case. Chest and abdominal computed tomography was performed every six months when lymph node or lung involvement was present at the initial staging. Patients who achieved complete remission underwent endoscopy with biopsies every six months.

Complete remission was defined as resolution of clinical evidence of disease and of endoscopic lesions, with negative biopsy specimens and absence of extragastric localisation. Partial remission was defined as improvement of clinical symptoms and endoscopic lesions with a decrease in tumoral infiltration.

Analysis was performed in November 1991

TABLE II *Clinical features*

Case no	Age (yr)	Sex	Presenting symptoms (duration)	Past history	Extent of disease (stage)	Endoscopic findings	Treatment (duration)	Follow up
1	52	F	Epigastric pain, weight loss 10 kg	Gastric ulcer, gastric bleeding	I	Thickening of folds and erosions of angulus	Cyclophosphamide (1 year)	18 months*
2	58	M	Epigastric pain (6 months), bleeding	Gastric ulcer, gastric bleeding	I	Suspect† ulcer of the gastric body	Cyclophosphamide (9 months)	18 months*
3	62	F	Epigastric pain (5 years), weight loss 7 kg	Gastritis, pseudolymphoma (3 years)	I	Thickening of gastric folds, erosions	Cyclophosphamide	Lost to follow-up
4	72	M	Epigastric pain (1 year)	—	I	Suspect ulcer of the antrum+small nodules, thickening of folds	Surgery, radiotherapy	7 years*
5	50	F	Epigastric pain (1 year), weight loss 2 kg	—	I	Small nodules of the antrum	Cyclophosphamide	Lost to follow-up
6	65	M	Epigastric pain (5 years)	Gastritis	I	Thickening of gastric folds in body	Cyclophosphamide (1 year)	3 years*
7	25	F	Epigastric pain (1 year), anemia	—	I	Ulcerative mass of angulus and body, thickening of folds in antrum	Polychemotherapy (CHOP), radiotherapy	4 years*
8	56	M	Gastric bleeding	—	I	Suspect ulcer of the body	Cyclophosphamide (1 year)	1 year*
9	55	M	Epigastric pain, weight loss 10 kg	Pseudolymphoma (10 years)	IV (regional lymph nodes lung)	Thickening of gastric folds in body and antrum‡	Cyclophosphamide (1 year)	1 year partial remission
10	67	M	Epigastric pain (2 months), weight loss 5 kg	Bleeding ulcer requiring surgery (7 years)	IV (lung)	Small nodules in gastric stump	Cyclophosphamide (6 months)	1 year*
11	53	M	Epigastric pain (1 year)	—	IV (bone marrow)	Suspect ulcer of the body	Cyclophosphamide (1 year)	5 years*
12	70	F	Gastric bleeding	Pseudolymphoma of lung and parotid glands	IV (lung)	Suspect ulcer of angulus	Cyclophosphamide (2 years)	Relapse at 6 years, partial remission 7 years
13	57	F	Epigastric pain (3 years)	Gastric ulcer, gastritis, lung lymphoma	IV (lung, bone marrow)	Thickening of antrum	Cyclophosphamide (1 year)	Relapse at 6 years, small bowel, stomach, and lung
14	50	M	Epigastric pain, anaemia	—	IV (lung mediastinal lymph nodes)	Suspect ulcer of body	Cyclophosphamide (1 year)	6 years*
15	54	F	Epigastric pain	Recurrent gastric ulcer, gastric bleeding	IV (lung)	Ulcer of body	Cyclophosphamide (1 year)	18 months*
16	42	M	Epigastric pain (6 months)	Lung lymphoma	IV (lung)	Diffuse small nodules, erosions	Cyclophosphamide (2 years)	Relapse at 7 years, partial remission 7·5 years

*=free from disease; †=suspected of malignancy; ‡=gastric endosonography disclosed massive infiltration of the gastric wall with perigastric lymph node enlargement.

providing minimum and median follow up of 1 and 4·5 years respectively.

Results

CLINICAL FEATURES

The main characteristics of the patients are given in Table II.

Persistent epigastric pain lasting from 6 months to 5 years was the predominant complaint, associated with acute gastric bleeding in three patients, anaemia in two (haemoglobin <10 g/dl), and weight loss (>5 kg) in five at the time of diagnosis. Eight patients had a past history of recurrent gastric ulcer (n=5), endoscopic gastritis (n=3), or gastrointestinal bleeding (n=4) from 2 to 10 years before diagnosis. One patient had been operated on (partial gastrectomy) for a bleeding ulcer seven years previously. Two patients had a past history of small cell lung lymphoma treated surgically (n=1) or with chemotherapy (n=1). One of the latter patients had previously presented with a parotid gland localisation.

ENDOSCOPIC ASPECTS

Endoscopic lesions affected the body of the stomach in seven cases, the antrum in five, and both the body and the antrum in four. In eight cases, the lesion consisted of an irregular and large ulcer with raised edges and was highly suggestive of malignancy. In the other eight cases endoscopy showed only lesions of a benign nature (erythematous gastritis, erosions, small nodules, localised or diffuse thickening of gastric folds).

PATHOLOGICAL STUDY

Biopsy specimens

In 15 of 16 patients the diagnosis was based on multiple endoscopic biopsies (>6) showing invasion of the gastric mucosa by lymphoid tissue. The infiltrate consisted of small lymphoid cells mixed with medium and occasionally large cells. Small cells were lymphocytes with either a small round nucleus or an irregular nucleus giving a centrocyte like appearance. Large cells with a centroblastic aspect were rare. Superficial plasma cells infiltrated underlying lymphoid cells. Residual crypts were rare or absent. Characteristic lymphoepithelial lesions (lymphoid cells invading gastric glands) were found in every case. In half the specimens studied these lesions were found only after careful examination of numerous sections and staining with an anti-cytokeratin antibody. A lymphoid follicle was seen in two cases. Erosions and ulcerations were generally present.

TABLE III *Histological and immunohistochemical findings*

Case no	Lymphoepithelial lesions	Centrocyte like cells	Follicular centres	Immuno-phenotype		
				Ig	CD 5	IgD
1	+	+	−	IgM Kappa	−	−
2	+	++	−	ND	ND	ND
3	+	+	−	IgM Kappa	−	−
4	+	+	+	ND	ND	ND
5	+	+	+	IgM Kappa	−	−
6	+	+	+	ND	ND	ND
7	++	++	−	IgM Lambda	−	−
8	+	+	−	IgM Lambda	−	−
9	++	++	−	IgM Lambda	−	−
10	+	+	++	IgM Kappa	−	−
11	+	+	−	IgM Kappa	−	−
12	+	++	−	IgM Kappa	−	−
13	+	++	−	IgM Lambda	−	−
14	+	+	−	IgM Lambda	ND	ND
15	+	++	−	ND	ND	ND
16	+	++	−	IgM Kappa	−	−

ND=Not done.

Surgical specimens

Two surgical specimens were examined. In patient 4, who had been operated on before being referred to our institution, neoplastic cells including centrocyte like appearance infiltrated the mucosa, submucosa, and stomach muscles, with sparse extensions into the perigastric conjunctive tissue. Characteristic lymphoepithelial lesions and rare lymphoid follicles were present. In patient 10, who had been operated on for a bleeding ulcer seven years previously, a gastric lymphoma was diagnosed on the basis of biopsy specimens. A review of the surgical specimen showed that the gastric mucosa contained very numerous lymphoid follicles with follicular centres suggestive of benign lymphoid infiltration. The follicles were surrounded by a population of small round lymphocytes, intermingled with a few small cleaved cells and centrocyte like appearance. A small number of gastric glands exhibited characteristic lympho-epithelial lesions. Proliferation was limited to the mucosa and submucosa. These features led to the retrospective diagnosis of low grade MALT lymphoma.

Immunohistochemical findings

Immunohistochemical findings are given in Table III. Lymphoepithelial lesions were shown on deparaffinised sections using anticytokeratin and antiepithelial membrane antibodies.

In the 12 cases in which cryostat sections were studied, tumour cells expressed CD 19 and CD 22 B cell antigens, indicating a B cell origin. Kappa light chain restriction was present in eight cases and lambda light chain restriction in four cases. Tumour cells exhibited the IgM +ve, IgD−ve, CD 5−ve phenotype. These histopathological results were consistent with the diagnosis of MALT lymphoma.

STAGING

The lymphoma was localised within the gastric wall with no evidence of regional lymph node involvement (stage I) in eight patients. Eight patients had stage IV disease, because of bone marrow involvement in two patients and/or lung involvement in seven. Lung involvement was suspected on the basis of *x* ray abnormalities and was confirmed histologically in a surgical biopsy specimen in three cases and in a transbronchial biopsy specimen in one. No biopsy was performed in the other cases but the lung opacity on the chest *x* ray or computed tomogram had the same macroscopic aspect as in the cases of proved

TABLE IV *Macroscopic aspect of lung involvement in seven patients*

Case no	*Chest radiograph and computed tomogram*	*Histological proof*
9	Round opacity of 4 cm in right lung	−
10	Round opacity of 2 cm in left lung	−
12	Bilateral opacities and diffuse shadowing	+
13	Round opacity in right lung (1977) Round opacity in left lung (1983)	+
14	2 round opacities of 2 and 5 cm in left lung	+
15	Round opacity of 5 cm in left lung	−
16	Bilateral opacities with diffuse shadowing	+

lung lymphoma and responded to chemotherapy as well as the gastric lesion. The macroscopic aspect of the lung involvement is described in Table IV. Gastric endosonography, performed in patient 9, who had thickening of gastric folds in the body and the antrum at endoscopy (Table II), showed massive infiltration of the gastric wall together with perigastric lymph node enlargement.

TREATMENT AND OUTCOME

Fourteen patients were initially treated with cyclophosphamide, one with polychemotherapy, and one with surgery and irradiation. Treatment efficacy could be evaluated in 14 of the 16 patients. Two patients (nos 3 and 5) were lost to follow up. The mean duration of follow up in the 14 remaining patients was 4·5 years (range: 1–7·5 years).

Four of the six evaluable stage I patients were treated with cyclophosphamide. Patient 4 who had been operated on before referral received additional radiation therapy. Another patient (no 7), who presented with a bulky tumour of the gastric body was treated with a polychemotherapy CHOP regimen (cyclophosphamide, hydroxyldaunomycin, oncovin, and prednisone) +radiation therapy. Complete remission was obtained in six patients including four treated with cyclophosphamide, with a follow up ranging from 1·5–7 years.

The eight patients with stage IV disease received cyclophosphamide. All these patients are alive after a follow up ranging from 1 to 7·5 years. Four are in a first complete remission and one in partial remission. Three relapsed at 6 years (n=2) and 7 years (n=1). One of these latter patients (no 13) was operated on for an obstructive small bowel relapse and in this patient, as in the two others, gastroscopy and chest computed tomography showed both lung and gastric recurrences. All three patients who relapsed responded again to cyclophosphamide. Repeated gastric biopsies did not show progression to a higher grade lymphoma in any of the patients.

Chemotherapy was well tolerated and no cases of myelodysplastic syndromes were observed despite follow up exceeding two years in seven patients treated with alkylating agents.

Discussion

All the patients we studied fulfilled the histological and immunocytological criteria established by Isaacson *et al* for the diagnosis of low grade B cell lymphoma of MALT.[13 14] Histological examination showed small and medium sized lymphoid cells (centrocyte like cells) invading gastric glands to form characteristic lymphoepithelial lesions. In some cases, the proliferation surrounded and sometimes invaded reactive B cell follicles. Immunohistochemical studies showed a B cell origin of the lymphoma, as well as the IgM+ve, IgD−ve, CD 5−ve phenotype.

The clinical presentation of our patients confirmed previous reports of the non-specific nature of digestive symptoms, clinical indolence, and the slow course in low grade gastric MALT lymphoma.[12 13] All the patients had complained of chronic epigastric pain for years before diagnosis and eight had a past history of recurrent gastric ulcer, gastrointestinal bleeding, or gastritis. The endoscopic aspect of the gastric lesions was clearly suggestive of malignancy in only half the patients. In the remaining cases, the endoscopist described erythematous gastritis, small nodules or thickening and erosions of gastric folds suggestive of a benign condition. This explains how the disease can be misdiagnosed over a long period and stresses the need for biopsy specimens whatever the type of gastric lesion. In patient 9, endosonography showed that there was no relationship between the endoscopic aspect and the locoregional extension of the lymphoma. Although the endoscopic changes were minimal (only mild thickening of gastric folds), endosonography disclosed massive infiltration of the gastric wall associated with an enlargement of regional lymph nodes. This observation illustrates the usefulness of endosonography in the staging of low grade gastric lymphoma.[21]

The chronic nature of the symptoms, the benign appearance of the gastric lesions on endoscopy, and the equivocal histological aspect of the lesions account for the fact that numerous MALT lymphomas were considered 'pseudolymphomas'[4 7] until the monoclonal nature of the proliferation could be routinely shown by immunochemistry. In our series, two patients (nos 3 and 9) were diagnosed as having pseudolymphomas 3 and 10 years respectively before the diagnosis of MALT lymphoma. In both cases a review of previous biopsy specimens showed the presence of lympho-epithelial lesions clearly indicative of malignancy.[15 22] This typical lesion was also present on the surgical specimen from patient 10 who had undergone surgery for a 'bleeding ulcer' seven years before the definitive diagnosis.

Our results show that low grade gastric MALT lymphoma can be readily diagnosed on the basis of biopsy specimens. Lympho-epithelial lesions are observed on fixed tissues and immunohistochemical studies of fixed tissues can help to show these lesions with the aid of anti-cytokeratin or -epithelial membrane antibodies. Finally, immunohistochemical analysis of frozen tissue sections clearly shows the monoclonal nature and B cell phenotype of the proliferation, together with the peculiar IgM+ve, IgD−ve, CD 5−ve phenotype of the tumoural cells, indicative of the MALT origin of the proliferation.

One of the most important findings in our

study was the high frequency of extragastric locations of MALT lymphomas, present in half the patients (8 of 16). Interestingly, they generally affected other mucosal sites (lung, n=7; parotid, n=1; small bowel, n=1) and usually spared the peripheral lymph nodes, spleen, and bone marrow. Involvement of other mucosal sites preceded, coincided with, or followed the manifestations of the gastric lymphoma. These findings were unexpected, as most of previously published clinicopathological studies have shown that low grade B cell gastric lymphoma is a disease process confined to the stomach for years.[17 23] However, recent studies showed that malt lymphomas, whatever the organ involved, were susceptible to spread to or to recur in other mucosal sites.[13 24 25] Although the exact frequency of extragastric localisation remains to be determined prospectively in a larger series, our observations suggest that this possibility has to be taken into account in the choice of the staging procedure and therapeutic strategy.

In previously published studies, most authors recommended surgery, arguing that low grade gastric MALT lymphomas were localised, solitary lesions that could be excised completely[4 6 7 13 24] and that endoscopic biopsy specimens could miss small foci of high grade, B cell lymphomas.[26] However, in our series half the patients had a stage IV lymphoma. Among the eight with stage I disease, five had tumoural involvement of the stomach which would have required total gastrectomy, a procedure with a high morbidity rate and one that is not justified with a well tolerated, slowly progressing disease. Moreover, in one patient (no 10), the lymphoma relapsed after partial gastrectomy. We therefore favoured conservative treatment with cyclophosphamide monochemotherapy.

All the patients with stage I disease responded to therapy, and a complete remission was obtained in those (n=4) treated for at least one year. In the eight stage IV patients in whom the follow up was of specially long duration (median 6 years), a complete remission was initially obtained with cyclophosphamide in every case and patients whose disease recurred several years after the initial treatment remained sensitive to monochemotherapy. Moreover, in contrast with a recent report,[25] no cases of conversion to a high grade lymphoma were observed. Although cyclophosphamide was well tolerated in our patients, the risk of developing a myelodysplastic syndrome cannot be excluded. However, this long term toxicity of alkylating agents has been shown to be related to the intensity of therapy given[27] and is very unlikely to occur with the low doses needed to treat our patients. Thus, in our experience, monochemotherapy is appropriate for low grade, gastric MALT lymphomas.

In conclusion, our findings show that low grade, gastric MALT lymphoma can always be diagnosed on the basis of both fixed and fresh endoscopic biopsy specimens. Extragastric involvement seems to be frequent, usually affecting other mucosal sites and particularly the lung. Cyclophosphamide monochemotherapy procures complete remission, with only slight morbidity, and remains effective against relapses.

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