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Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pitfalls and management

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Gastrointestinal lymphoma is the most common form of extranodal lymphoma, accounting for 30%–40% of cases. The most commonly involved site is the stomach (60%–75% of cases), followed by the small bowel, ileum, cecum, colon and rectum. The most common histological subtypes are diffuse large B-cell lymphoma (DLBCL) and marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT). *Helicobacter pylori* infection has been implicated in the pathogenesis of MALT gastric lymphoma, but its role in gastric diffuse large B-cell non-Hodgkin's lymphoma (NHL) is controversial. The therapeutic approach for patients with gastric NHL has been revised over the last 10 years. Conservative treatment with anthracycline-based chemotherapy alone or in combination with involved-field radiotherapy has replaced gastrectomy as standard therapy in cases with DLBCL. Additionally, MALT lymphomas are mainly treated with antibiotics alone, which can induce lasting remissions in those cases associated with *H. pylori* infection. Nevertheless, various therapeutic aspects for primary gastric lymphomas are still controversial and several questions remain unanswered. Among others, the role of rituximab, consolidation radiotherapy as well as *H. pylori* eradication in histological aggressive subtypes warrants better clarification.

Key words: diffuse large B-cell lymphomas, extranodal lymphomas, *Helicobacter pylori* infection, mucosa-associated lymphoid tissue, primary gastric lymphomas

introduction

The term primary extranodal non-Hodgkin's lymphoma (PE-NHL) refers to lymphomas which present with disease at any organ or tissue other than lymph nodes or spleen; the symptoms at initial presentation are caused mainly from extranodal involvement and after routine staging procedures, the extranodal involvement remains the clinically dominant site of the disease. PE-NHL comprise ∼25%–40% of non-Hodgkin's lymphoma (NHL) and may occur at any organ [1, 2].

Primary non-Hodgkin's lymphoma of the gastrointestinal tract is the most commonly involved extranodal site and represents 10%–15% of all NHL cases and 30%–40% of all extranodal sites [3]. The most commonly involved site is the stomach (60%–75% of cases), followed by the small bowel, ileum, cecum, colon and rectum [4, 5]. All histological categories of nodal lymphomas may also arise in the gastrointestinal (GI), but the main two histological subtypes (>90% of cases) are mucosa-associated lymphoid tissue (MALT) NHL and diffuse large B-cell (DLBC) NHL (Table 1).

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Primary gastric non-Hodgkin's lymphoma (PG-NHL) is localized in the stomach, with or without perigastric and/or abdominal lymph node involvement, and constitutes 20%–30% of all PE-NHL. PG-NHL shows an incidence of 1 per 100 000 of the population in Western countries, but the incidence is progressively increasing. Any histological subtype can arise in the stomach, but the main two histological subtypes (>90% of cases) are MALT NHL and DLBC NHL. *Helicobacter pylori* infection has been implicated in the pathogenesis of MALT PG-NHL [6, 7], but its role in gastric DLBC NHL is controversial [8].

The present review summarizes the clinical presentation, diagnostic work-up and management of patients with primary gastric lymphomas.

diagnosis and staging

Clinical presentation of PG-NHL is not specific and varied, with abdominal pain being the most common symptom followed by dyspepsia, vomiting nausea and anorexia. Weight loss is common, but it is mainly associated with the localization of the disease. Gastric bleeding as presenting symptom occurs in 20%–30% of patients, while gastric occlusion and perforation are less common [4]. Bone marrow involvement, elevated lactate dehydrogenase (LDH) and B symptoms are less

Table 1. Distribution of the main histological types (according to the REAL classification) in the Greek and German study for gastrointestinal non-Hodgkin's lymphoma [4, 5]

Histological type	Greek study (128 patients) frequency (%)	German study (371 patients) frequency (%)
Diffuse large B-cell lymphoma	45	59
With MALT component	9	14
Without MALT component	36	45
MALT lymphoma of the marginal zone	48	38
Follicular lymphoma	2	0.5
Mantle cell lymphoma	1	1
Peripheral T-cell lymphoma	4	1.5

REAL, Revised European-American Lymphoma; MALT, mucosa-associated lymphoid tissue.

common in gastric compared with nodal lymphomas. Endoscopy usually reveals nonspecific gastritis or peptic ulcer with mass lesions being unusual [9]. Occasionally, PG-NHL can present as a multifocal stomach disease with numerous clonally identical foci in macroscopically unaffected tissue [10]. Therefore, gastric mapping of unaffected mucosa is crucially recommended in order to establish diagnosis. Gastric MALT lymphoma is characterized by the presence of lymphoepithelial lesions that are formed by invasion of single glands by aggregates of neoplastic cells with centrocyte morphology [11], in contrast to aggressive lymphoma where lymphoma-infiltrating cells show a centroblastic morphology [12].

Staging work-up for PG-NHL include complete hematological biochemical examinations (including LDH and β2-microglobulin), computerized tomography (CT) of chest, abdomen and pelvis and bone marrow aspiration and biopsy. Upper GI endoscopy and multiple biopsies from stomach, duodenum, gastroesophageal junction and from abnormal-appearing lesions are required. An endoscopic ultrasound should be carried out to determine the depth of invasion and the presence of perigastric nodes. Examination of the pharynx by an otorhinolaryngologist should be carried out to exclude infiltration of Waldeyer ring that is occasionally associated with PG-NHL [13, 14]. In addition to routine histology and immunohistochemistry, cytogenetic studies should be carried out. FISH for the detection of three specific MALT-related translocations is recommended. The pertinent genotypic evaluations should be carried out at the time of diagnosis to guide treatment decisions. Histochemistry (Genta stain or Warthin–Starry stain) and breath test should be carried out to determine the presence of an active *H. pylori* infection. If histology is negative, serology should be undertaken to identify truly negative *H. pylori* gastric MALT NHL which is ∼10% of the cases.

Positron emission tomography (PET) scan bears a documented diagnostic value only for DLBCLs but is controversial for MALT lymphomas, which are frequently reported as PET negative due to their indolent behavior and small tumor volume of disease [15, 16].

The Ann-Arbor classification system [17] is not easily applied to GI tract lymphomas and although alternative staging systems have been proposed, the problem of 'staging' a PG-NHL is controversial even today. The use of different staging systems combined with the variability in staging procedures hamper meaningful comparisons of published series. However, factors that have consistently been associated with poor prognosis in these series are involvement of paraortic (versus local) lymph nodes, serosal penetration and intestinal (versus gastric) origin. An International Workshop in 1994, during the fifth International Conference on Malignant Lymphoma, proposed a modification to Blackledge's system, known as 'Lugano staging' which examines separately local spreading to neighboring anatomic sites [18]. More recently, in 2003, a modified tumor–node–metastasis classification system—the Paris staging system—was proposed in order to describe more efficiently (i) the depth of tumor infiltration, (ii) extent of nodal involvement and (iii) extent of local tissue infiltration by lymphoma [19] (Table 2).

PG MALT lymphomas

Isaacson and Wright [20] first observed in 1983 that primary low-grade gastric B-cell lymphoma and immunoproliferative small intestinal disease share histological characteristics more similar to MALT than those of peripheral lymph nodes. Gastric MALT lymphomas represent the vast majority of the three different types of marginal zone B-cell lymphomas (MZBCLs) according to the Revised European-American Lymphoma (REAL) classification [21]. MALT lymphomas comprise 50% of PG-NHL and are often multifocal. They occur predominantly in individuals >50 years, with a peak in the seventh decade, but cases have been reported in younger patients (third decade or even earlier). In ∼90% of cases, a strong association between chronic *H. pylori* infection and MALT gastric lymphoma has been found [22]. It is accepted that gastric MALT lymphomas arise from MALT acquired as a consequence of *H. pylori* infection and the bacterial infection plays a crucial role in the genesis and development of this tumor [23]. *H. pylori* can be demonstrated in the gastric mucosa of most cases with gastric MALT lymphomas [6]. In addition, epidemiological studies have demonstrated the association between *H. pylori* infection and development of gastric lymphoma [24, 25]. Nevertheless, host immune responses play a less well-defined role in MALT lymphoma formation as indicated by the fact that only a minority of *H. pylori*-infected patients will eventually develop lymphoma.

As with other MZBCL, the cells of PG MALT are typically CD20 positive and express surface and, to a lesser extent, cytoplasmic immunoglobulin (Ig) showing light chain restriction. Most cases express IgM and a few IgA or IgG, but IgD expression is rare. In ∼50% of cases, they aberrantly express CD43. In addition, MALT lymphomas contain moderately high concentrations of CD3+ and CD5+ T cells, but in the majority of cases the lymphoma cells themselves are CD5 negative.

Three translocations, t(11;18)(q21;q21), t(1;14)(p22;q32) and t(14;18)(q32;q21), are specifically associated with MALT lymphomas and the genes involved have been characterized. Although these three translocations involve different genes, they all converge on the activation of the same nuclear factor

Table 2. Comparison of 'Lugano' and 'Paris' staging system for primary GI lymphomas

Lougano staging system [18]	TNM Paris system [19]	Lymphoma extension
Stage I	T1–3 N0 M0	Lymphoma confined to GI tract. Single primary site or noncontiguous lesions.
Stage I1	T1m N0 M0	Confined to mucosa
Stage I2: infiltrating the gastric wall up to the serosa	T1sm N0 M0	Lymphoma infiltrates the submucosa
	T2 N0 M0	Lymphoma infiltrates muscularis propria or subserosa
	T3 N0 M0	Lymphoma penetrates serosa
Stage II	T1–3 N1–2 M0	Lymphoma extending to abdominal lymph nodes
Stage II1	T1–3 N1 M0	Involvement of local (paragastric) lymph nodes
Stage II2	T1–3 N2 M0	Involvement of distant (mesenteric, para-aortic, paracaval, pelvic, inguinal) lymph nodes
Stage IIE	T4 N0–2 M0	Infiltration of adjacent organs or tissues by direct infiltration
Stage IV: extranodal involvement	T1–4 N3 M0	Spread to extraabdominal lymph nodes
or concomitant supradiaphragmatic nodal involvement	T1–4 N0–3 M1	Noncontinuous involvement of separate site in GI tract (e.g. stomach and rectum)
	T1–4 N0–3 M2	Noncontinuous involvement of other organs (e.g. tonsils, parotid gland, ocular adnexa, liver and spleen) or tissues (e.g. peritoneum and pleura)
	T1–4 N0–3 M0–2 B0	Bone marrow not involved
	T1–4 N0–3 M0–2 B1	Lymphomas infiltrates bone marrow
A		Presence of systemic symptoms (fever, night sweats and weight loss >10% BW)
B		Absence of systemic symptoms
X		Bulky mass (lesion of 10 cm or more in the longest diameter)

GI, gastrointestinal; TNM, tumor–node–metastasis; BM, body weight.

kB (NF-kB) oncogenic pathway [23]. Translocation t(11;18), very common in gastric MALT lymphomas as well as MALT lymphomas at other anatomic sites (30% of MALT lymphomas) [26], results in a chimeric fusion between *AP12* and *MALT1* genes [27, 28]. This translocation is not seen in *H. pylori* gastritis and its presence is associated with extension of the disease outside the stomach (regional lymph nodes and/or distal sites) [29]. The t(11;18)(q21;q21) translocation as well as the t(1;14)(p22;q32) can identify cases that will not respond to *H. Pylori* eradication [30].

In *H. Pylori*-associated gastritis and at the early stages of MALT lymphoma, development antigens expressed by *H. pylori* in conjunction with antigen-specific T cells activate the antigen receptor of polyclonal B cells and lead to the interaction of BCL10 and MALT1 proteins and consequently the activation of NF-kB pathway. During the long course of a chronic infection and persistent antigenic stimulation, a subclone may acquire one of the MALT lymphoma-specific translocations and develop a growth advantage. As a result, constitutive activation of NF-kB pathway occurs independently of *H. pylori* infection and the eradication of the bacterium does not reverse the disease process [23]. The scoring system proposed by Wotherspoon et al. [22] reflects this spectrum of proliferation from polyclonal to monoclonal state.

High-grade MALT lymphomas are equivalent to DLBCL in the REAL classification [21] and they have probably transformed from low-grade MALT lymphomas as they share common clone-specific *Ig* heavy chain gene rearrangements with low-grade lesions [31].

treatment of early stage gastric MALT lymphomas

antibiotic therapy

More than 20 studies have shown a high rate of complete remission (CR) of low-grade MALT lymphomas confined to the stomach following eradication of *H. pylori* with antibiotics [32–36]. Therefore, antibiotic treatment is a reasonable initial treatment in low-grade gastric MALT lymphoma provided thorough hematological and endoscopic follow-up takes place. Thorough endoscopic follow-up is recommended because initial diagnostic gastric biopsies do not exclude the coexistence of aggressive lymphoma which requires cytotoxic chemotherapy. Breath test 2 months after treatment to confirm *H. pylori* eradication and repeat endoscopies with biopsies every 6 months for 2 years and then annually to document remission of the lymphoma are recommended. Despite the fact that eradication of *H. pylori* may take place within 1 month of completion of drug therapy, disappearance of lymphoma may take several months and histologic CR may be delayed up to 18 months. When remission occurs, it appears to be stable. If relapse occurs, it is usually associated with *H. pylori* reinfection. Indications also exist that stage I patients with minimal histological lymphoma residuals after *H. pylori* eradication show a favorable course when treated only by regular follow-up with endoscopies and multiple biopsies without administration of oncological therapy, suggesting the potential role of watch and wait strategy in these patients [37, 38]. In patients with histological CR, lymphoma clone can be detected by PCR analysis of the rearranged *Ig* gene on postremission gastric

biopsies in 50% of the cases. This group should be observed closely, whereas long-term negative PCR may indicate cure of the disease [39].

therapy of cases refractory to antibiotics or *H. Pylori* negative

There are no treatment guidelines for the management of patients who show unresponsiveness to antibiotics or for the subset of *H. pylori*-negative cases. This latter group of patients usually does not respond to antibiotics. A choice can be made between conventional therapeutic approaches.

Radiation therapy (RT) alone is a reasonable treatment option in patients with early-stage (stages I and II) gastric MALT lymphomas refractory to antibiotics. Two small prospective series have shown a 100% complete response rate following RT with a median dose of 30 Gy. The first study by Yahalom [40] from Memorial Sloan-Kettering Cancer Center demonstrated only one treatment failure at a median follow-up of 18 months, whereas the one from Schechter et al. [41] showed no treatment failure at a median follow-up of 27 months. Additionally, Tsang et al. [42] reported on 85 patients with MALT lymphoma (17 patients with gastric MALT NHL) receiving RT alone that up to 90% of patients attained a CR with excellent 5-year progression free and overall survival (OS) rates of 98% and 77%, respectively. With the recent evolvement of CT radiotherapy planning, advanced techniques such as three-dimensional conformal radiotherapy and intensity modulated radiotherapy have facilitated the determination of the clinical target volume, thereby reducing the toxicity that is related to the irradiation of normal gastric mucosa and of nearby organs (especially the left kidney). However, side-effects of RT are encountered, most frequently anorexia, nausea and vomiting. Although with the standard dose (30–35 Gy), no delayed toxicity (such as peptic ulcers or GI haemorrhaging) has been reported; the long-term effects of RT on the structure and function of the gastric mucosa remain to be clarified.

There is no consensus regarding the role of adjuvant chemotherapy after antibiotic treatment. The role of chemotherapeutic agents such as alkylating agents, nucleoside analogues or combination chemotherapy for gastric MALT lymphomas refractory to antibiotics has been tested, but only limited data especially on untreated patients with localized disease exist to date. Recently, Nakamura et al. [43] reported CR rates of 89% after oral monotherapy with cyclophosphamide 100 mg/day on patients with gastric MALT NHL, refractory to antibiotic therapy. In this study, the results were comparable to the results achieved after RT; hence, oral monotherapy with cyclophosphamide might also be a suitable second-line therapeutic option after failure of *H. pylori* eradication therapy. The role of the translocation t(11;18) for the prediction of response to chemotherapy is yet under investigation. Recent data support that for oral alkylating agents such as chlorambucil or cyclophhosphamide, the presence of this translocation in gastric MALT NHL is predictive of resistance [44]. CR rates after 1 and 8 years were 42% and 8% for t(11;18)-positive and 89% for t(11;18)-negative patients, respectively ($P = 0.0003$, 8 years). Hence, oral alkylating agents might only be administered in patients without the translocation t(11;18). Nucleoside analogue named cladribine or 2-chlorodeoxyadenosine has been tested in a phase II study in patients with gastric ($n = 19$) and no-gastric MALT NHL at any stage [45]. Patients had to be chemotherapy naive, not responding to *H. pylori* eradication therapy in case of gastric NHL or suffering from relapse after RT. 2-Chlorodeoxyadenosine was administered at a dose of 0.12 mg/kg body weight by i.v. infusion over 2 h on days 1–5 and was repeated every 4 weeks. All patients responded to treatment after a median number of four cycles, and 84% achieved CR including all patients with gastric NHL. Three patients with gastric NHL have relapsed locally after 13, 18 and 22 months and were salvaged with RT. Grade 3 or 4 toxicity World Health Organisation (WHO) is observed in 38% of patients including mainly leukocytopenia, a herpes zoster in one patient and cardiac toxicity in another. In addition, Streubel et al. [46] have shown that the presence of the translocation t(11;18) does not adversely affect the response to 2-chlorodeoxyadenosine chemotherapy. Therefore, 2-chlorodeoxyadenosine can be considered as an effective and relatively safe drug and seems to be a good therapeutic option for patients with gastric MALT NHL being *H. pylori* negative or unresponsive to eradication therapy.

The efficacy of rituximab (monoclonal anti-CD20 antibody) in patients with gastric MALT NHL has not been extensively evaluated. Martinelli et al. [47] reported on 27 patients with gastric MALT NHL, refractory or not eligible for antibiotic therapy, who were treated with rituximab monotherapy at doses of 375 mg/m^2 once weekly for 4 weeks. Forty-six percent of patients had a pathological and clinical CR and 31% had a partial response (PR). With a median follow-up of 33 months, only two patients relapsed whereas there was no association between t(11;18) (q21;21) translocation by FISH and response to treatment. Nevertheless, extrapolating data from randomized studies showing survival advantage in patients with low-grade NHL when rituximab is added to the treatment, we can assume that rituximab is reasonable therapeutic option in patients with gastric MALT NHL refractory to the first-line treatment or in *H. pylori*-negative patients.

In the past, gastrectomy was the treatment of choice in patients with PG-NHL. However, the high morbidity rates associated with this procedure led to attempts to preserve the organ using radiation and combination chemotherapy approaches. Aviles et al. [48] reported the results of a three-arm randomized trial in patients with gastric MALT lymphomas treated in Mexico. They randomized 241 patients to surgery (total gastrectomy) alone versus radiation (30 Gy to the entire abdomen, increased to 40 Gy for the upper abdomen only) alone or chemotherapy [three cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-21 followed by four cycles COP-14] alone with median follow-up of 7.5 years. All patients in the three arms achieved CR. Event free survival (EFS) was significantly inferior in radiation (52%) and surgery (52%) arms compared with the chemotherapy arm (87%) ($P < 0.01$). The 5-year OS tended to be superior in the chemotherapy-treated group (87%) versus the surgery (80%) and RT (75%) arms but this did not reach significance ($P = 0.4$) probably due to the lack of power. The authors concluded that chemotherapy

is an effective and well-tolerated treatment for patients with gastric MALT lymphoma. Although this study investigated the role of surgery versus radiation versus chemotherapy as primary treatment of gastric MALT lymphoma, it provides some evidence that combination chemotherapy is more efficacious and durable than radiation in patients with gastric MALT lymphoma who have failed *H. pylori* eradication or for the subset of *H. pylori*-negative cases. In addition, in the German Multicenter Study Group trial, patients with low-grade gastric lymphomas who were treated with surgery and radiation or radiation and COP regimen (six cycles) had equal rates of EFS and 5-year OS (83% and 80%, respectively) [49]. Taken together, these results indicate that organ preservation with chemotherapy combined with radiation can yield equal results to surgery plus radiation in this group of patients.

The addition of rituximab to anthracycline-based combination chemotherapy has not been extensively tested in patients with relapsed gastric MALT lymphomas. In a small retrospective study by Raderer et al. [50], 26 patients with relapsed MALT NHL were treated with rituximab plus CHOP or CNOP. Twenty of 26 patients (77%) achieved a CR and six patients a PR. Toxic effects were mainly hematological, with WHO grade leukocytopenia occurring in 20% of patients. With a median follow-up of 19 months (range 10–45), all patients were alive: 22 were in ongoing remission, while four relapsed between 12 and 19 months after treatment. A clinical trial conducted by the International Extranodal Lymphoma Study Group is currently evaluating the activity of the combination of rituximab and chemotherapy in MALT NHL.

On the basis of combination of the published data, we recommend an algorithm for the treatment of low-grade MALT lymphomas of the stomach. *H. pylori*-positive patients with stage I should have an initial treatment of *H. Pylori* eradication. If *H. Pylori* infection is persistent, reeradication should be attempted. Close follow-up with upper endoscopy and biopsies every 3–6 months is recommended. If complete regression of macroscopic disease is not attained after 12 months, patients should receive radiation alone or rituximab or single-agent chemotherapy if RT is contraindicated. These therapies should be instituted more quickly in patients with progressive disease after antibiotic treatment. In patients with macroscopic remission but with minimal lymphoma histological residuals, watchful waiting with regular endoscopies and multiple biopsies (every 3 months) should be considered. *H. pylori*-negative patients, as well as patients with stage II or/and with t(11;18) translocation should receive antibiotic treatment in addition to close follow-up with endoscopy every 3 months. Combined chemotherapy alone or plus radiation should be initiated if no regression is seen. Nevertheless, the issue is open and further studies are needed to determine the optimal therapy of patients with gastric MALT lymphomas refractory to antibiotics.

treatment of advanced stage gastric MALT NHL

Gastric MALT lymphomas rarely present at advanced stage. Similar to other categories of indolent lymphomas, chemotherapy is not curative and asymptomatic patients can be observed without treatment. Indications for therapy include candidacy for a clinical trial, symptoms, GI bleeding, threatened end-organ function, bulky disease, steady progression and patient preference. Chemotherapy (single-agent or combination regimens) is the treatment of choice in most cases [51]. Locoregional RT is utilized in specific cases such as superior vena cava syndrome. If there is evidence of recurrence, endoscopy is recommended. Management of recurrent cases is similar to follicular lymphomas. Platinum analogues have shown promise [52].

practice points in primary gastric MALT lymphomas

- The t(11;18) translocation as well as the translocation t(1;14)(p22;q32) can identify cases that will not respond to *H. Pylori* eradication.
- Antibiotic treatment is a reasonable initial treatment in low-grade gastric MALT lymphoma provided that thorough hematological and endoscopic follow-up takes place.
- Thorough endoscopic follow-up is recommended because initial diagnostic gastric biopsies do not exclude the coexistence of aggressive lymphoma which requires cytotoxic chemotherapy.
- Radiotherapy alone or rituximab or single-agent chemotherapy should be used for the treatment of patients who fail to response to antibiotics or for the subset of *H. pylori*-negative cases.

DLBCL of the stomach

DLBCL of the stomach is an aggressive lymphoma that might arise *de novo* or from MALT lymphoma transformation. This malignancy constitutes 40%–70% of all gastric lymphomas [4, 5]. High-grade lymphomas bearing the same Ig light chain restriction and identical rearranged *Ig* gene with coexistent low-grade MALT lymphoma represent transformed cases [31, 53]. Foci of DLBCL may be seen in MALT lymphomas but the extent of this high-grade component varies from a small proportion of transformed blasts with the indolent MALT lymphoma to a dominant large cell component with only small residual foci of MALT lymphoma. The differentiation of the latter group from *de novo* large cell lymphomas becomes very difficult. DLBCLs with germinal center-like phenotype (bcl6- and CD10 positive and a proportion bcl2 positive) are not confused with transformed MALT lymphomas. Transformed MALT lymphomas are CD10- and bcl2 negative and bcl6 positive [54]. In most cases, however, immunophenotype as well as molecular genetics cannot reliably distinguish transformed MALT from PG-DLBCL. However, the differentiation between transformed MALT and *de novo* PG-DLBCL is not clinically important since the two entities behave similarly [55]. PG-DLBCL occurs more frequently in males, with median age range of occurrence of 50–60 years [4, 5, 56]. Clinical presentation is similar to that of gastric cancer. The majority of patients report epigastric pain (70% of cases) or dyspepsia (30%). Weight loss is observed in 40% of patients,

more frequently as a result of dyspepsia and less often as a B symptom. Bleeding and perforation are rare at the time of diagnosis. No risk factors have been clearly demonstrated in patients with PG-DLBCL. However, there is some evidence that atrophic gastritis, especially in the setting of immunodeficiency, may be a risk factor for this neoplasm [57].

The role of *H. Pylori* infection in PG-DLBCL is controversial. This bacterium is detected in 35% of DLBCL of the stomach, mainly in cases with concomitant MALT areas (65% versus 15%) [58]. This suggests that most DLBCL may arise from long-standing *H. pylori*-associated MALT lymphomas. In contrast to early reports, recent data have supported that *H. pylori* eradication results in durable histological CR in 50%–63% of patients with gastric DLBCL with concomitant MALT areas [8]. These findings suggest that, at least in the initial phase, high-grade transformation is not necessarily associated with the loss of *H. pylori* dependence.

treatment of DLBCL of the stomach

Treatment of choice for DLBCL irrespective of anatomic site of the lesion is rituximab plus anthracycline-based combination chemotherapy: epirubicin, or adriamycin or mitoxantrone combined with cyclophosphamide, vincristine and prednisone (CHOP, CEOP or CNOP regimen). Although the impact of the addition of rituximab to chemotherapy regimens has not been tested in large clinical trials in patients with PG-DLBCL [59], treatment must include rituximab due to its proven therapeutic benefit in DLBCL [60, 61]. Complications of chemotherapy include gastric outlet obstruction and bleeding while gastric perforation is rare. Therefore, irrespective of the role of gastrectomy as primary treatment of patients with DLBCL of the stomach which as explained below remains controversial, the role of surgical consultant remains essential in the management of DLBCL of the stomach.

The role of surgery in the management of PG-DLBCL is controversial. Many previous studies have suggested that gastrectomy, particularly in stages I and II patients, significantly improves survival [62–65]. In addition, complications such as perforation, obstruction and hemorrhage can be prevented or treated with surgery. However, these complications are rare. Several studies have shown that patients undergoing gastrectomy have a better outcome compared with those having incomplete resection or biopsy alone [66–68]. It is unclear, however, whether the improved outcome is related to low tumor burden which allows complete resection, similarly to low LDH, or the surgery itself. Contrary to the aforementioned reports, other studies have shown that the extent of surgery (excision or biopsy) has no impact on outcome of GI lymphomas [3, 69, 70]. The excellent results obtained with the use of combination chemotherapy, sometimes combined with radiation, have challenged the role of gastrectomy in the management of patients with PG-DLBCL [71, 72]. Some retrospective and prospective studies suggested that conservative nonsurgical treatment achieves equal or better results than gastrectomy (reviewed recently by Ferreri and Montalban [73]). In our study, patients treated with surgery plus chemotherapy had similar OS and disease-free survival after 38 months of median follow-up with patients treated with chemotherapy alone [5]. In addition, a small prospective randomized trial comparing patients with PG-DLBCL treated with combination chemotherapy alone or with surgical resection followed by chemotherapy concluded that gastrectomy is unnecessary (10-year survival rates 96% and 91%, respectively) [74]. However, the question is open and further prospective trials are required to determine the optimal management of this disease.

The role of consolidation radiotherapy is debated. In retrospective studies, the addition of RT was associated with a lower local relapse rate compared with chemotherapy alone [75]. In a prospective study, the combination of six cycles of CHOP-14 followed by involved-field RT (40 Gy) has been associated with a survival rate at 42 months of 91% [76]. Further prospective randomized trials are required in order to answer the question about the role of RT in the treatment of PG-DLBCL.

In addition to chemotherapy, *H. pylori* eradication with antibiotic therapy should always be carried out in localized or extensive PG-DLBCL, especially in cases of PG-DLBCL with concomitant low-grade MALT component [77]. Although PG-DLBCL with MALT component appeared to be independent of the *H. Pylori* antigen drive, two recent studies showed that 60% of patients with PG-DLBCL with MALT areas achieved histological CR after *H. Pylori* eradication, which have been maintained after long follow-up [78, 79].

The choice of treatment for patients with relapsed or refractory disease depends on patient's age, performance status, extension of relapse and previous therapies. At present, high-dose therapy followed by autologous stem-cell transplantation is the treatment of choice for patients in whom chemosensitivity to some kind of salvage treatment is still present. However, only young patients with good performance status and without comorbidities are candidates for this therapy. Gastrectomy can be a suitable approach in elderly patients who experience relapse limited to the gastric wall and exhibit clear contraindications to chemotherapy. Finally, new combinations of chemotherapeutic regimens, immunotherapy and radioimmunotherapy should be tested in prospective phase II trials on patients with relapsed or refractory PG-DLBCL.

practice points in PG-DLBCL

- The treatment of choice is combination of rituximab plus chemotherapy with anthracycline-based regimens (CHOP, CEOP and CNOP).
- The role of gastrectomy is limited in localized disease due to the similar effectiveness of organ-preserving chemotherapy treatment, alone or in combination with radiation.
- *H. pylori* eradication with antibiotic therapy should always be carried out in localized or extensive disease, especially in cases with concomitant low-grade MALT component.

conclusions

In conclusion, the therapeutic approach for patients with PG-NHL has been revised over the last 10 years. It is widely

accepted that MALT lymphomas are mainly treated with *H. pylori*-eradicating antibiotics, which can induce lasting remissions in those cases associated with *H. pylori* infection. Conservative treatment with anthracycline-based chemotherapy alone or in combination with involved-field RT has replaced gastrectomy as treatment of choice in patients with DLBCL. Nevertheless, various therapeutic aspects for PG-NHL are still controversial and several questions remain unanswered. Among others, the role of rituximab, consolidation RT as well as *H. pylori* eradication in histological aggressive subtypes warrants further investigation.

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