Commentary

See article on page 297

Helicobacter pylori associated gastric B cell MALT lymphoma: predictive factors for regression

Experimental data have extended the knowledge of the mere association of gastric mucosa associated lymphoid tissue (MALT) lymphoma and infection with *Helicobacter pylori*. The acquisition of MALT in the stomach is a direct consequence of the infection; thus MALT in the stomach is formed as an immunological defence system to control local infection caused by *H pylori*. Lymphomas arising from gastric MALT show several specific features: they arise from the marginal zone of the lymphoid follicle, they consist of centrocyte-like cells, and lymphoepithelial destruction must be present in order to establish the diagnosis of gastric MALT lymphoma.[1 2] The genetic events that lead to clonal evolution and, finally, malignant transformation also show that MALT lymphomas have specific features not known from nodal lymphomas—for example, the translocation t(11;18). Data concerning other genetic events like rearrangements of oncogenes such as *bcl-2* (translocation t(14;18) in follicular lymphoma), *c-my* (translocation t(8;14) in Burkitt's lymphoma), or *bcl-l* (translocation t(11;14) in small cell lymphoma/chronic lymphocytic leukaemia) have not been reported to be significantly associated with gastric MALT lymphoma. Furthermore, numerical chromosomal abnormalities—that is, trisomy 3, 7, or 12—have not been reported to be consistently involved in the cases analysed.[3–7] In contrast, the translocation t(11;18) has been associated with marginal zone B cell lymphomas. Ott *et al* reported that up to 40% of low grade MALT lymphomas of different mucosal sites showed the translocation t(11;18)(q2l;q2l).[8] The recently identified genes involved in this translocation APJ2 (apoptosis inhibitor gene 2 on chromosome 11) and MLT (MALT lymphoma translocation gene on chromosome 18) have not been fully functionally classified.[9 10] It has been reported that lymphomas responding to *H pylori* therapy are t(11;18) negative,[11] thus this translocation may be associated with more advanced disease. In keeping with these data, Dierlamm and colleagues[10] demonstrated that t(11;18) occurs predominantly in more advanced low grade lymphomas. Thus t(11;18) may be a clonal marker of lymphoma progression.

The perception that growth of the genetically altered lymphoid cell and of the low grade MALT lymphoma is modulated in vitro by *H pylori* related factors,[12 13] and that cure of the infection may influence tumour growth leading to lymphoma remission started a revolution in the treatment of low grade gastric MALT lymphomas by eradicating *H pylori*. Up to now, it has been shown in more than 200 published patients that cure of *H pylori* infection in patients with low grade MALT lymphoma at an early clinical stage is associated with complete remission in approximately 77% (median remission value).[14–19]

In this issue of *Gut*, Ruskoné-Fourmestraux *et al* pointed out that the percentage of tumour regression after eradication of *H pylori* varied markedly in different studies, from 41% to 100% (see page 297). In their own study, the overall complete remission rate was 43% and concerned all localised tumours in stages I_E and II_{E1}, irrespective of their *H pylori* status. Thus they asked two important questions: what are the predictive factors of lymphoma remission? How can patients be defined that benefit most from antibiotic treatment?

To provide the best therapeutic approach, a careful diagnostic workup of the patient is mandatory. In the study of Ruskoné-Fourmestraux *et al*, the authors suggested considering five main factors: (1) establishment of malignancy (low grade/high grade) using the histological criteria of diagnosis[1 2]; (2) *H pylori* status; (3) demographic features; (4) depth of tumour infiltration as well as the modality of its evaluation; and (5) follow up of patients. Patients could then be allocated into different treatment groups in accordance with stage and risk. In the clinical management of lymphoma, it is important to make this distinction early on.

With reference to (1), we know that the value of any lymphoma classification and its impact on the determination of treatment depends largely on its histopathological reproducibility. Gastric MALT lymphomas are difficult to grade, and disagreement can occur among pathologists. The appearance of diffuse large cell lymphoma in patients with low grade MALT lymphoma is usually associated with an accelerated clinical course and shorter survival. Despite anecdotal case reports[20–23] it is recognised that high grade lymphomas do not generally respond to attempts at *H pylori* eradication. It is therefore recommended that a sufficient number of biopsy specimens at different mucosal sites are taken because gastric MALT lymphoma is often multifocal, and that an experienced pathologist reviews the slides to minimise the possibility of high grade lymphoma.

Another factor that adversely affects response to antibacterial treatment is lack of *H pylori* infection. As reported by Ruskoné-Fourmestraux *et al*, 10 patients were *H pylori* negative and none (23% of all cases) showed lymphoma remission—that is, 40% of all non-responders. The authors stressed that the absence of *H pylori* on histological gastric biopsies does not necessarily imply the absence of recent *H pylori* infection.[24] Therefore, in clinical practice, serological testing is strongly recommended in cases of negative histology. Systemic eradication of the bacteria in patients with low grade gastric MALT lymphoma, irrespective of *H pylori* status, is therefore of doubtful interest. Not only is *H pylori* status in these patients important, but in addition the distribution of gastritis is probably related to the different clinical courses of these lymphomas. Steinbach and colleagues[25] postulated that proximal localised MALT lymphomas may be either *H pylori* gastritis associated or *H pylori* independent autoimmune gastritis associated, which is generally proximal in distribution. Therefore, *H pylori* positivity and distal or diffuse MALT tumours seem to be positive predictive factors of response to antibiotic treatment.

The demographic data presented by Ruskoné-Fourmestraux *et al* do not surprise us. We know from epidemiological studies that gastric lymphoma occurs predominantly in individuals over 50 years of age, with a peak in the seventh decade, but it can occur at any age. The male:female ratio is approximately 1.7:1. Despite the fact

that treatment responders were statistically younger and female, the demographic features do not represent a strong predictive factor concerning treatment outcome.

One of the most important points, also emphasised by Ruskoné-Fourmestraux *et al*, is the exact determination of the initial clinical tumour stage and modality of its evaluation. Biopsy specimens taken at endoscopy may provide histological diagnosis but depth of infiltration by the lymphoma cannot be evaluated. Endoscopic ultrasonography (EUS), introduced almost 20 years ago, has been shown to reliably differentiate the layers of the gastric wall if it is used by an experienced investigator. The clinical stage is determined in accordance with the Musshoff classification, as proposed in 1977.[26] In 1994, this staging system was refined with emphasis on separate description of local penetration into neighbouring structures. The subdivision in stage III and IV disease was taken together and considered as widely disseminated disease. Further subdivision of stage I into stage I_1 (infiltration of the mucosa±submucosa) and I_2 (infiltration of the muscularis and/or (sub)serosa) has also been proposed. The Musshoff staging system is simple and has been shown to provide important prognostic information. Ruskoné-Fourmestraux *et al* showed that EUS has a much higher sensitivity in distinguishing stage I_E from stage II_{E1} lymphoma compared with computed tomography. With EUS 15 patients were identified as having stage II_{E1} lymphoma whereas only nine patients were identified using CT scan. Furthermore, analysing the response data according to depth of infiltration, the overall response rate (43%) changed: it was therefore highest for the mucosa-type El_1 (78%) and then decreased markedly to 43%, 20%, and 25% for the submucosa, muscularis propria, and serosa (I_{E2}). In type II_{E1} lymphomas (nodal involvement) identified by EUS, no response was noted. The overall remission rate therefore increased to 79% if nodal involvement was absent, which was the only remaining predictive factor of complete lymphoma remission based on a multivariate analysis of their patients.

Sackmann *et al* in 1997[27] showed that lymphoma staging by echoendoscopy helps to predict the response of low grade gastric MALT lymphoma to treatment of *H pylori.* Actuarial analysis of the probability of complete remission of MALT lymphoma revealed a significant difference between patients characterised by echoendoscopy as stage I_{E1} compared with those with higher stages. In patients with II_{E1} the probability of complete remission was 60% (12%) (mean (SEM)) at six months, 79% (12%) at 12 months, and reached 100% at 14 months after the start of therapy compared with 0% over the follow up period in patients with higher stages. Therefore, in carefully selected *H pylori* positive patients without any lymph node involvement assessed by EUS, complete remission of gastric MALT lymphoma can be reached in almost 80% of cases after one year.

Another unclarified issue about gastric MALT lymphomas is the appropriate duration of observation before diagnosis of treatment failure in I_E disease. In this study complete lymphoma remission was noted after a median period of six months (range 2–18), which is similar to the periods reported elsewhere. However, some lymphomas do regress after 18 months or even later. Steinbach and colleagues[25] concluded that most *H pylori* positive patients with stage I_{E1} lymphoma attained complete remission within approximately 12 months (range 3–13 months). In light of these data, reports of lymphoma relapses after successful treatment and complete lymphoma remission have to be discussed critically. Such relapses, especially the early ones after 12–15 months, must be distinguished from an occult residual disease. Ruskoné-Fourmestraux *et al* suggested that in order to prevent this possible sampling error bias as false negative biopsy findings, it is worth confirming complete remission in at least three controls at intervals of four months during the first two years of follow up.

To answer the question initially asked, it seems critical to obtain a histopathological diagnosis by an experienced pathologist and to evaluate *H pylori* status. Furthermore, it is necessary to perform clinical tumour staging, including endoscopic ultrasonography to define the depth of lymphoma infiltration, and to exclude II_{E1} disease. Patients that fulfill all of these criteria, that are younger, and have a distal or diffuse lymphoma probably represent the group that will benefit most from eradication therapy. The probability of remission of MALT lymphoma may then increase up to 100% under a strict staging and follow up protocol. Treatment failure might first be defined after one year of follow up.

As many questions about *H pylori* dependent and *H pylori* independent mechanisms in lymphomagenesis are not yet answered, it is still advisable to enroll gastric MALT lymphoma patients in clinical trials.

A MORGNER
E BAYERDÖRFFER

Medical Department I for Gastroenterology, Haematology and Oncology, University Hospital Carl-Gustav-Carus, Fetscherstr 74, 01307 Dresden, Germany

A NEUBAUER

Centre for Internal Medicine, University of Marburg, Baldinger Strasse, 35033 Marburg, Germany

M STOLTE

Institute for Pathologie, Klinikum Bayreuth, Preuschwitzer Str 101, 95445 Bayreuth, Germany

Correspondence to: Professor E Bayerdörffer. bayerdoerffer@t-online.de

1 Isaacson PG, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. *Histopathology* 1987;**11**:44–9.
2 Wotherspoon, Hidalgo CO, Falzon MR, *et al*. *Helicobacter pylori* associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991;**338**:1175–6.
3 Banerjee SK, Weston AP, Persons DL, *et al.* Non-random loss of chromosome 3 during transition of Helicobacter pylori-associated MALT to B cell MALT lymphoma revealed by fluorescence in situ hybridization. *Cancer Lett* 1997;**121**:83–90.
4 Chan WY, Wong N, Bik-Wan Chan A, *et al.* Consistent copy number gain in chromosome 12 in primary diffuse large cell lymphomas of the stomach. *Am J Pathol* 1998;**152**:11–6.
5 Clark HM, Jones DB, Wright DH. Cytogenetic and molecular studies of t(14;18) and t(14;19) in nodal and extra-nodal B-cell lymphoma. *J Pathol* 1992;**166**:129-37.
6 Horsman D, Gascoyne R, Klasa R, *et al.* t(11;18)(q2l;q2l.l): a recurring translocation in lymphomas of mucosa-associated lymphoid tissue (MALT). *Genes Chrom Cancer* 1992;**7**:74–80.
7 Sol6 F, Woessner S, Florensa L, *et al.* Frequent involvement of chromosomes 1, 3, 7, and 8 in splenic marginal zone B-cell Lymphoma. *Br J Cancer* 1997;**98**:446–9.
8 Ott G, Katzenberger T, Greiner A, *et al.* The t(11;18)(q2l;q2l) chromosome translocation is a frequent and specific aberration in low-grade but not high-grade malignant non-Hodgkin's lymphoma of the mucosa-associated lymphoid tissue (MALT-)type. *Cancer Res* 1997;**57**:3944–8.
9 Akagi T, Motegi M, Tamura A, *et al.* A novel gene, MALT1 at 18q2l, is involved in t(11;18)(q2l;q2l) found in low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *Oncogene* 1999;**18**:5785–94.
10 Dierlamm J, Baens M, Wlodarska I, *et al.* The apoptosis inhibitor gene AP12 and a novel 18q, MLT, are recurrently rearranged in the t(l 1;18)(q2l;q2l) associated with mucosa-associated lymphoid tissue lymphoma. *Blood* 1999;**93**:3601–9.
11 Alpen B, Dieriamm J, Marynen P, *et al.* Translocation t(l1;18) absent in early gastric marginal zone B-cell lymphoma of MALT type responding to eradication *of Helicobacter pylori* infection. *Blood* 2000;**95**:4014.
12 Hussell T, Isaacson PG, Crabtree JE, *et al.* The response of cells from low-grade gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori. Lancet* 1993;**342**:571–4.
13 Hussell T, Isaacson PG, Crabtree JE, *et al.* Helicobacter pylori-specific tumour infiltrating T-cells provide contact dependent help for the growth of malignant B-cells in low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *J Pathol* 1996;**178**:122–7.
14 Roggero E, Zucca E, Pinofti G, *et al.* Eradication of *Helicobacter pylori* infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *Ann Intern Med* 1995;**122**:767–9.
15 Wotherspoon, Doglioni C, Diss TC, *et al*. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori. Lancet* 1993;**342**:575–7.
16 Bayerdörffer E, Neubauer A, Rudolph B, *et al*. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. *Lancet* 1995;**345**:1591–4.
17 Savio A, Franzin G, Wotherspoon, *et al.* Diagnosis and post-treatment follow-up of *Helicobacter pylori* gastric lymphoma of mucosa-associated

lymphoid tissue; histology, polymerase chain reaction or both? *Blood* 1996; **87**:1255–60.
18 Stolte M. *Helicobacter pylori* and gastric MALT lymphoma. *Lancet* 1992;**339**:745–6.
19 Knobbier A, Thiede C, Morgner A, *et al.* Cure of *Helicobacter pylori* infection and duration of remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *J Natl Cancer lnst* 1997;**89**:1350–5.
20 Boot H, de Jong D, van Heerde P, *et al.* Role of *Helicobacter pylori* eradication in high-grade MALT lymphoma. *Lancet* 1995;**346**:448–9.
21 Seymour JF, Anderson RP, Bhathal PS. Regression of gastric lymphoma with therapy of *Helicobacter pylori* infection. *Ann Intern Med* 1997;**127**:247.
22 Ng WW, Lam CP, Chau WK, *et al.* Regression of high-grade gastric mucosa-associated lymphoid tissue lymphoma with *Helicobacter pylori* after triple antibiotic therapy. *Gastrointest Endosc* 2000;**51**:93–6.
23 Morgner A, Miehlke, S, Fischbach W, *et al.* Complete remission of gastric high-grade B cell MALT lymphoma after cure of *Helicobacter pylori* infection. *Gut* 1999;**45**(suppl 111):A73 (09/23).
24 Eck M, Greiner A, Schmausser B, *et al.* Evaluation of *Helicobacter pylori in* gastric MALT-type lymphoma: differences between histologic and serologic diagnosis. *Mod Pathol* 1999;**12**:1148–51.
25 Steinbach G, Ford R, Glober G, *et al.* Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. *Ann Intern Med* 1999;**131**:88–95.
26 Musshoff K. Klinische Stadieneinteilung der Nicht-Hodgkin-Lymphome. *Strahlentherapie* 1977;**153**:218–21.
27 Sackmann M, Morgner A, Rudolph B, *et al.* Regression of gastric MALT lymphoma after eradication of *Helicobacter pylori* is predicted by endosonographic staging. *Gastroenterology* 1997;**113**:1087–90.