STOMACH

Successful antibiotic treatment of *Helicobacter pylori* negative gastric mucosa associated lymphoid tissue lymphomas

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Background and aims: The role of antibiotic treatment in early stage gastric mucosa associated lymphoid tissue (MALT) lymphoma not associated with *Helicobacter pylori* infection has not been investigated.
Patients and methods: Six patients with localised gastric MALT lymphoma underwent antibiotic treatment with clarithromycin, metronidazole, and pantoprazole. Staging, including endosonography plus gastroscopy, computed tomography of the thorax and abdomen, colonoscopy, magnetic resonance imaging of the salivary glands, and bone marrow biopsy were performed to rule out distant spread of the disease. In addition, MALT specific genetic changes, including reverse transcriptase-polymerase chain reaction for t(11;18)(q21;q21), were tested in all patients. *H pylori* infection was ruled out by histology, urease breath test, serology, and stool antigen testing.
Results: All six patients had MALT lymphoma restricted to the stomach, and no evidence of infection with *H pylori* was found. Only one patient tested positive for t(11;18)(q21;q21) while the remaining five displayed no genetic aberrations. Following antibiotic treatment, endoscopic controls were performed every three months. Five patients responded with lymphoma regression between three and nine months following antibiotic treatment (one partial remission and four complete responses). One patient had stable disease for 12 months and was then referred for chemotherapy.
Conclusions: Patients with early stage gastric MALT lymphoma negative for *H pylori* might still benefit from antibiotic treatment as the sole treatment modality.

Mucosa associated lymphoid tissue (MALT) lymphoma of the stomach is associated with *Helicobacter pylori* infection in the large majority of patients.[1] The decisive role of *H pylori* in the development of gastric MALT lymphoma has resulted in attempts to treat gastric MALT lymphoma using antibiotic eradication of the bacteria. Following pioneering work published by Wotherspoon and colleagues,[2] a large number of studies have clearly shown the benefit of *H pylori* eradication as the standard treatment for patients with early stage *H pylori* associated gastric MALT lymphoma, resulting in response rates of 70–80%[3] in selected patients. Based on current knowledge, patients treated solely with *H pylori* eradication have an excellent long term outcome, as evidenced by sustained complete remissions after eradication and a very low rate of relapse.[4]

In patients with *H pylori* associated gastric MALT lymphoma, risk factors predictive of lymphoma regression following antibiotic treatment have been published in recent years. The first investigation on this topic defined restriction of the lymphoma to the mucosa and submucosa as a positive predictive factor, as opposed to more advanced stages.[5] In addition, the presence of an underlying autoimmune disease[6] and probably monoclonal immunoglobulin production by lymphoma cells[7] have been reported as adverse prognostic indicators.

The most extensively studied prognostic factor however is the presence of t(11;18)(q21;q21) in gastric MALT lymphoma. It occurs exclusively in MALT lymphoma and is found in 24% of patients with gastric MALT lymphoma.[7] According to recent findings, it identifies patients whose lymphoma will not regress following antibiotic treatment.[8 9] In the largest series to date, Liu and colleagues[9] investigated 111 patients and found t(11;18)(q21;q21) in 42/63 non-responders but in only 2/48 patients responding to antibiotic treatment.

In addition to the data published on t(11;18)(q21;q21), a small series by Taji *et al* has recently suggested that the presence of trisomy 3 may also predict non-response of the lymphoma to *H pylori* eradication.[10] Also, nuclear expression of nuclear factor κB or BCL10 have been reported to be predictive of a *H pylori* independent status for gastric MALT lymphoma.[11]

In 5–10% of patients with gastric MALT lymphoma, however, no evidence of *H pylori* infection can be demonstrated. As this cohort of patients is very rare, only limited clinical data have been published to date. A multicentre analysis to characterise MALT lymphoma in such patients has shown a higher rate of t(11;18)(q21;q21) than in patients with *H pylori* infection,[12] with 9/17 cases (53%) being positive. According to this study, *H pylori* eradication was performed in 5/17 cases, and none had responded to treatment. These patients, however, had either been positive for t(11;18)(q21;q21) or were followed for only a short time, suggesting that the conclusions from this series cannot be extrapolated to all patients with *H pylori* negative MALT lymphoma.

These facts, together with a report including three patients with *H pylori* negative MALT lymphomas arising in the rectum who responded to antibiotic treatment,[13] have prompted us to treat six patients with early stage *H pylori* negative gastric MALT lymphoma with *H pylori* eradication.

PATIENTS AND METHODS

From December 2003, patients with localised gastric lymphoma who tested negative for *H pylori* were given antibiotic treatment. Eight cases of *H pylori* negative gastric MALT

Abbreviations: MALT, mucosa associated lymphoid tissue; CT, computed tomography; CR, complete remission; PR, partial remission

lymphoma were referred to our institution but two had advanced disease beyond the stomach and were given chemotherapy. Thus six consecutive patients (one female, five males) with histologically verified MALT lymphoma of the stomach were studied. Histological diagnosis of MALT lymphoma was performed according to the criteria outlined in the WHO classification,[14] and histological assessment was performed by a reference haematopathologist (AC). Immunological phenotyping on paraffin sections was done for demonstration of light chain restriction and the phenotype CD20+CD5−CD10−cyclinD1− which, in the context of the microscopic appearance, is consistent with MALT lymphoma. None of the patients had evidence of *H pylori* infection, as judged by histology, urease breath test, serological testing, or stool antigen testing, and no evidence of *Helicobacter heilmannii* (HH) infection was present.

Staging consisted of endosonography, gastroscopy plus multiple biopsies, enteroclysma (computed tomography (CT)), enteroscopy, CT of the thorax and abdomen, magnetic resonance imaging of the lachrymal and salivary glands, colonoscopy with multiple biopsies, and a bone marrow biopsy. In all patients, routine assessment of MALT lymphoma associated genetic aberrations was performed on biopsy samples. The presence of t(11;18)(q21;q21) was evaluated by reverse transcriptase-polymerase chain reaction while t(14;18)(q32;q21) involving *IGH/MALT1*, t(1;14)(p22;q32), and trisomies 3 and 18 were assessed by FISH, as previously published.[15]

After obtaining informed consent, patients were given antibiotic treatment with clarithromycin 2×500 mg for seven days and metronidazole 2×500 mg for seven days, while pantoprazole was administered at a dose of 2×40 mg as continuous therapy during the observation period (that is, for a minimum of 12 months).

Patients were followed by regular endoscopies with histological assessment of biopsy samples every three months following antibiotic treatment for assessment of response, and CT of the thorax and abdomen was also performed every three months to rule out distant spread of the disease.

RESULTS

All six patients had MALT lymphoma without transformation to diffuse large B cell lymphoma, and staging showed restriction of the disease to the stomach (stage I) in all cases. In two patients, endosonography showed restriction of the lymphoma to the mucosa and submucosa while the remaining four cases had involvement of the whole gastric wall. Five patients were diagnosed with MALT lymphoma due to unspecific epigastric pain leading to gastroscopy, while in one patient anaemia due to chronic bleeding was the leading symptom. Ulcerated lesions were present in three patients. Testing for the presence of an underlying autoimmune disease was negative in all patients. In five patients, none of the genetic changes investigated was present, while one was positive for t(11;18)(q21;q21).

All patients underwent antibiotic treatment as scheduled. Regular endoscopic follow up showed response of the lymphoma in five of our patients, with four achieving complete remission (CR) between three and nine months after eradication, one patient developing partial remission (PR) after six months, while one patient had stable disease for 12 months before being referred for chemotherapy. In all patients, responses were verified by at least 2–4 additional endoscopies to rule out sampling bias. Interestingly, the patient with evidence of t(11;18)(q21;q21) developed a CR three months after eradication, which is ongoing after a follow up of 12 months. After a follow up of 12, 16, 18, 19, and 19 months, respectively, all six patients are alive, and four remain in CR. One patient relapsed in the stomach 14 months after initial CR.

DISCUSSION

These data suggest that patients with early stage gastric MALT lymphoma may still benefit from antibiotic treatment even in the absence of *H pylori* infection. In fact, four patients had a CR, one a PR, and one stable disease. The latter patient was referred for chemotherapy after 12 months of stable disease. In view of the interval of stable disease, however, one might speculate that a wait and see strategy for a longer time could have been applied as patients with *H pylori* positive gastric MALT lymphoma have been reported to achieve delayed remission following antibiotic therapy. Our data are in contrast with other series, and a definite explanation for our findings is lacking. Of interest is the fact that only one of the six patients was found to be positive for t(11;18)(q21;q21). This percentage is lower than expected compared with recent data reporting that approximately 50% of *H pylori* negative gastric MALT lymphomas are positive.[12] However, this patient also responded to treatment, with a CR of the lymphoma in spite of the fact that t(11;18)(q21;q21) has been demonstrated as the most significant prognostic factor for non-response.

To date, a definite explanation for our findings is still lacking but one might speculate that bacteria other than *H pylori* might be involved in the development of gastric MALT lymphoma. Based on current knowledge, however, only highly specialised bacteria such as *H pylori* or *H heilmannii* have been demonstrated to be able to survive in the gastric environment. Nevertheless, one cannot rule out the possibility that hitherto undetected bacterial agents capable of surviving in the stomach might play a role in the development of the rare *H pylori* negative gastric MALT lymphomas. If this assumption is indeed correct, one might expect response to broad spectrum antibiotic therapy, as evidenced in our patients. The rarity of *H pylori* negative gastric MALT lymphoma, however, would require a large scale effort to identify such bacteria. While *Campylobacter jejuni* has been implicated in the development of a special form of MALT lymphoma arising in the small intestine (IPSID),[16] to date it has not been found in primary gastric MALT lymphomas. In addition, it is not endemic in the Austrian population, and none of the patients related episodes of severe diarrhoea or prolonged stays abroad in the last five years. That a primary gastric MALT lymphoma was indeed present in all of our patients was demonstrated by the stringent staging routine used (including enteroscopy to evaluate the small bowel), which failed to detect additional lymphoma foci outside the stomach. Therefore, the hypothesis of a non-gastric bacterial infection leading to development of gastric MALT lymphoma seems highly unlikely.

As MALT lymphoma is an immunologically driven disease to some extent, an additional hypothesis might focus on potential immunomodulatory effects of the antibiotic agents used. In fact, macrolides such as clarithromycin, which formed part of our triple therapy, have repeatedly been implicated as having immunomodulatory and anti-inflammatory properties,[17] which might result in an as yet undiscovered effects against MALT lymphomas.

Our findings suggest that *H pylori* negative patients with stage I gastric MALT lymphoma should be given the chance of antibiotic therapy as initial treatment, provided that regular follow up is performed.

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Conflict of interest: None declared.

REFERENCES

1 **Isaacson PG**. Gastric MALT-lymphoma: from concept to cure. *Ann Oncol* 1999;**10**:637–45.
2 **Wotherspoon AC**, 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.
3 **Raderer M**, Isaacson PG. Extranodal lymphoma of MALT-type: Perspective at the beginning of the 21st century. *Expert Rev Anticancer Ther* 2001;**1**:53–64.
4 **Fischbach W**, Goebeler-Kolve M, Dragosics B, *et al*. Long-term outcome of patients with gastric marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive Helicobacter pylori eradication therapy: experience from a large prospective series. *Gut* 2004;**53**:34–7.
5 **Sackmann M**, Morgner A, Rudolph B, *et al*. Regression of gastric MALT-lymphoma after eradication of Helicobacter pylori is predicted by endosonographic staging. MALT Lymphoma Study Group. *Gastroenterology* 1997;**113**:1087–90.
6 **Raderer M**, Österreicher C, Machold K, *et al*. Impaired response of gastric MALT lymphoma to Helicobacter pylori eradication in patients with autoimmune disease. *Ann Oncol* 2001;**12**:937–9.
7 **Wöhrer S**, Streubel B, Bartsch R, *et al*. Monoclonal immunoglobulin production is a frequent event in patients with mucosa assocoiated lymphoid tissue lymphoma. *Clin Cancer Res* 2004;**10**:7179–81.
8 **Liu H**, Ye H, Ruskone-Fourmestraux A, *et al*. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. *Gastroenterology* 2002;**122**:1286–94.
9 **Liu H**, Ye H, Ruskone Fourmestraux A, *et al*. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to Helicobacter pylori eradication therapy. *Lancet* 2001;**357**:39–40.
10 **Taji S**, Nomura K, Matsumoto Y, *et al*. Trisomy 3 may predict a poor response to Helicobacter pylori eradication therapy. *World J Gastroenterol* 2005;**11**:89–93.
11 **Yeh KH**, Kuo SH, Chen LT, *et al*. Nuclear expression of BCL10 or nuclear factor kappa B helps predict Helicobacter pylori-independent status of low-grade gastric mucosa-associated lymphoid tissue lymphomas with or without t(11;18)(q21;q21). *Blood* 2005;**106**:1037–41.
12 **Ye H**, Liu H, Raderer M, *et al*. High incidence of t(11;18)(q21;q21) in Helicobacter pylori-negative gastric MALT-lymphoma. *Blood* 2003;**101**:2547–50.
13 **Nakase H**, Okazaki K, Ohana M, *et al*. The possible involvement of micro-organisms other than Helicobacter pylori in the development of rectal MALT lymphoma in H.pylori-negative patients. *Endoscopy* 2002;**34**:343–6.
14 **Isaacson PG**, Müller-Hermelink HK, Piris MA, *et al*. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In:In: Jaffe ES, Harris NL, Stein H, *et al*. *World Health Organization classificationof tumours: tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press, 2001:157–60.
15 **Streubel B**, Simonitsch-Klupp I, Müllauer L, *et al*. Variable frequencies of MALT-lymphoma associated genetic aberrations in MALT lymphomas of different sites. *Leukemia* 2004;**18**:1722–6.
16 **Lecuit M**, Abachin E, Martin A, *et al*. Immunoproliferative small intestinal disease associated with Campylobacter jejuni. *N Engl J Med* 2004;**350**:239–48.
17 **Amsden GW**. Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimcrob Chemother* 2005;**55**:10–21.

EDITOR'S QUIZ: GI SNAPSHOT

Cholestatic hepatitis with marked thrombocytopenia

Clinical presentation

A 54 year old woman was admitted because of abnormal liver laboratory tests (serum bilirubin 3.0 mg/dl, alanine aminotransferase 492 U/l, aspartate aminotransferase 186 U/l, alkaline phosphatase 199 U/l, and gamma glutamyl transferase (GGT) 154 U/l), associated with normosideric anaemia (haemoglobin 9.0 g/dl, red blood cells 3.1 T/l). The patient's history was unremarkable for liver disease. On physical examination she was pale without stigmata of chronic liver disease or lymphadenopathy. Abdominal ultrasound was uneventful. The patient was consuming anti-inflammatory drugs, statins, and used hormonal replacement therapy. Metabolic, toxic, and viral (hepatitis B virus, hepatitis C virus, cytomegalovirus) causes were ruled out and magnetic resonance cholangiography did not reveal pathology of the biliary ducts. Test for antismooth muscle antibodies was positive. The patient was asked to stop taking potentially hepatotoxic drugs, and following moderate improvement in laboratory tests was discharged for further ambulatory surveillance. After six weeks she was readmitted because of fever and persistence of hepatitis with aggravating cholestasis (alkaline phosphatase 457 U/l, GGT 1062 U/l). Her regular blood counts revealed fluctuating thrombocytopenia ranging from 55 to 16 g/l, associated with moderate anaemia and leukopenia. Corticosteroids normalised the temperature but had no definitive effect on hepatic or haematological parameters.

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Question

What further diagnostic examinations would you suggest?
See page 648 for answer
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