



# Remission of primary low-grade gastric lymphomas of the mucosa-associated lymphoid tissue type in immunocompromised pediatric patients

Yasuharu Ohno, Taichirou Kosaka, Izumi Muraoka, Takashi Kanematsu, Akira Tsuru, Eiichi Kinoshita, Hiroyuki Moriuchi

Yasuharu Ohno, Taichirou Kosaka, Izumi Muraoka, Takashi Kanematsu, Division of Pediatric Surgery, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Akira Tsuru, Eiichi Kinoshita, Hiroyuki Moriuchi, Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Correspondence to: Yasuharu Ohno MD, PhD, Department of Pediatric Surgery, Saitama Medical School Hospital, 38 Morohongo, Moroyama, Iruma, Saitama, 350-0495, Japan. ohno\_y@saitama-med.ac.jp

Telephone: +81-49-2761654 Fax: +81-49-2761654

Received: 2005-10-26 Accepted: 2006-01-14

## Abstract

We report the remission of primary gastric lymphoma of the mucosa-associated lymphoid tissue (MALT) type in two immunocompromised pediatric patients. Patient 1, a 14-year-old boy in an immunocompromised state of unknown cause, complained of repeated abdominal pain. Examinations revealed gastric MALT with local invasion and lymph node involvement. Serum anti-*Helicobacter pylori* (*H. pylori*) antibody was positive. *H. pylori* eradication was abandoned due to its adverse effects. The MALT lesion spontaneously regressed over the next 24 months without any treatment for lymphoma. Patient 2, a 6-year-old boy, underwent cord blood transplantation for the treatment of adrenoleukodystrophy. He was administered immunosuppressants for graft-versus-host disease after transplantation. Nausea and hematochezia appeared and further examinations revealed gastric MALT with *H. pylori* gastritis. Treatment consisting of medication for the *H. pylori* infection alone eradicated the *H. pylori* and completely resolved the patient's MALT lesion, as well. Patients 1 and 2 were followed up over periods of 10 years and 3 years, respectively, without any signs of relapse. In conclusion, gastric lymphoma of the MALT type can be cured by conservative treatment even in immunocompromised pediatric patients.

© 2006 The WJG Press. All rights reserved.

**Key words:** Pediatric gastric lymphoma; Mucosa-associated lymphoid tissue; Immunocompromised states

Ohno Y, Kosaka T, Muraoka I, Kanematsu T, Tsuru A, Kinoshita E, Moriuchi H. Remission of primary low-grade

gastric lymphomas of the mucosa-associated lymphoid tissue type in immunocompromised pediatric patients. *World J Gastroenterol* 2006; 12(16): 2625-2628

<http://www.wjgnet.com/1007-9327/12/2625.asp>

## INTRODUCTION

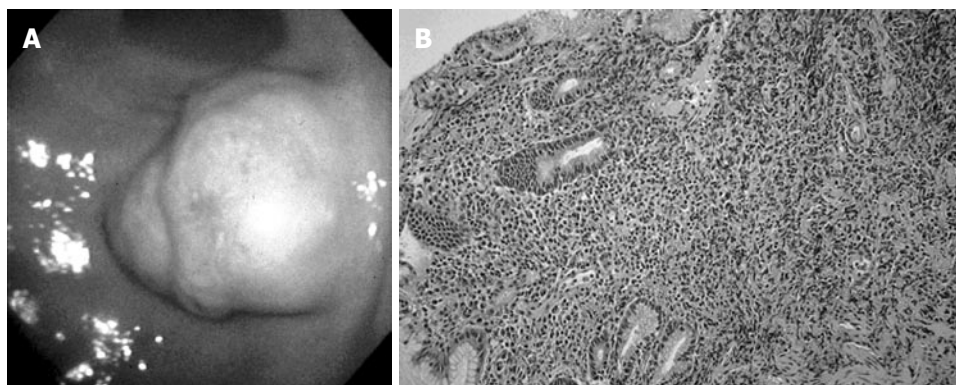
The stomach is one of the most common sites of extranodal malignant lymphomas. Since the first report by Isaacson and Wright in 1983, the concept of low-grade gastric B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT) type has become widely accepted<sup>[1]</sup>. Studies from the 1990s have established that the development of low-grade gastric lymphoma of the MALT type is strongly associated with chronic gastritis caused by *Helicobacter pylori*<sup>[2-4]</sup>. Low-grade gastric lymphoma of the MALT type occurs commonly in middle and old age but rarely in children<sup>[5,6]</sup>. The first long-term follow-up of a pediatric patient with *H. pylori*-associated gastric lymphoma of the MALT type was reported in 1995<sup>[7]</sup>. The present report describes the development of primary gastric lymphomas of the MALT type in two pediatric patients in immunocompromised states followed by tumor regression with conservative treatment.

## CASE REPORT

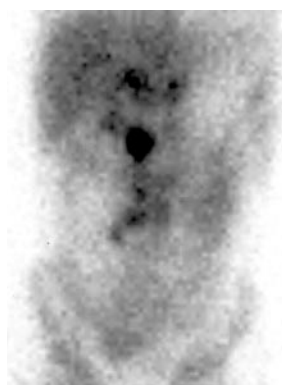
### Patient 1

A 14-year-old boy complained of repeated abdominal pain. Upper gastrointestinal endoscopy revealed a tumor-like lesion in the stomach and the patient was referred to our hospital. The patient had a history of autoimmune hemolytic anemia at the age of 1 year and measles infection at 2 years. Thereafter, he developed systemic lymphadenopathy and hyper-gamma-globulinemia. He had been administered oral prednisone from the age of 5 years onward based on a putative diagnosis of immunoblastic lymphadenopathy.

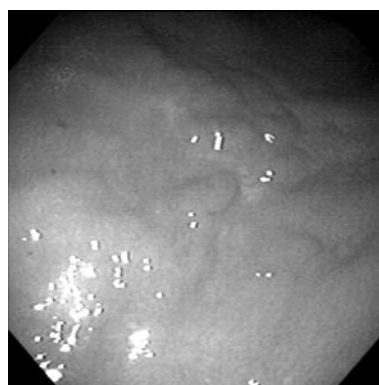
A tender mass, hen-egg in size, was discovered in the epigastrium upon admission. Endoscopy revealed a polypoid lesion in the posterior wall of the lower corpus of the stomach. The mass was diagnosed as a low-grade gastric lymphoma of the MALT type based on examination of a biopsy specimen (Figure 1). The



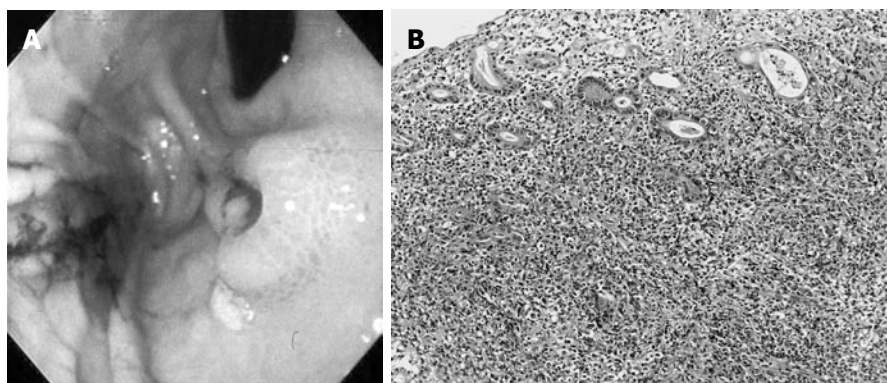
**Figure 1** Mucosa-associated lymphoid tissue lymphoma in Patient 1. **A:** A polypoid lesion on the posterior wall of the lower corpus of the stomach, suggesting the existence of lymphoproliferative disease; **B:** The histological features show characteristic appearance of low-grade gastric lymphomas of the mucosa-associated lymphoid tissue type with a diffuse infiltrate of centrocyte-like cells and the formation of lymphoepithelial lesions (H & E, original magnification x10).



**Figure 2** Gallium scintigraphy in Patient 1 shows an abnormal accumulation of the nuclide in the para-aortic lymph nodes.



**Figure 3** Twenty-four months later, an area of partly whitish rugged mucosa appeared at the site previously occupied by the mucosa-associated lymphoid tissue lymphoma in Patient 1.



**Figure 4** Mucosa-associated lymphoid tissue lymphoma in Patient 2. **A:** An ulcerated lesion on the anterior wall of the upper corpus before eradication; **B:** The histological features show the appearance of low-grade gastric lymphomas of the mucosa-associated lymphoid tissue type similar to that found in Patient 1 (H & E, original magnification x10).

biopsy also confirmed an invasion to the duodenum. Both computed tomography and Gallium scintigraphy strongly suggested metastases to the para-aortic lymph nodes (Figure 2).

Fearing that a complete, en bloc removal of such an advanced tumor would be too invasive in an immunocompromised patient, the authors opted for a watch-and-wait strategy. The patient's serum was positive for anti-*H. pylori* antibody, but *H. pylori* eradication had to be abandoned due to its adverse effects. Thankfully, the MALT lesion spontaneously regressed over the next 24 mo without any treatment for lymphoma (Figure 3). As the MALT lesion grew less serious, an abdominal pain gradually disappeared. The patient has been followed up for 10 years and continues to do well with no signs of relapse as of this writing.

#### Patient 2

A 6-year-old boy was referred to our department with

a complaint of nausea with hematochezia. He had been diagnosed with adrenoleukodystrophy at the age of 5 years and underwent cord blood transplantation for the treatment of the condition at that time. After the transplantation he was administered oral immunosuppressants, including methylprednisolone and FK506, for graft-versus-host disease.

Upper gastrointestinal endoscopy revealed an ulcerated lesion in the anterior wall of the upper corpus of the stomach. The mass was diagnosed as a low-grade gastric lymphoma of the MALT type associated with *H. pylori* gastritis, based on an examination of a biopsy specimen (Figure 4). Neither local invasion nor lymph node involvement was present on diagnostic modalities. When the dosages of the immunosuppressants were tapered he was additionally treated for the *H. pylori* infection using a proton pump inhibitor combined with clarithromycin and amoxicillin according to international guidelines<sup>[8]</sup>. The treatment not only eradicated the *H. pylori*, but brought

about a complete remission of the MALT lesion as well (Figure 5). The patient has been followed up for 3 years and continues to do well without any signs of relapse as of this writing.

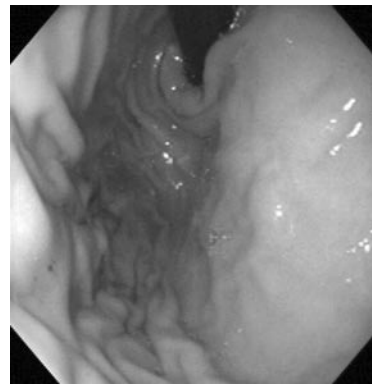
## DISCUSSION

Primary low-grade gastric B-cell lymphoma of the MALT type is generally defined as an extranodal lymphoma characterized by an infiltration of the mucosa by centrocyte-like B-cells with formation of lymphoepithelial lesions<sup>[9]</sup>. Gastric lymphoma of the MALT type is thought to be derived from chronic gastritis caused by *H pylori*<sup>[2-4]</sup>. *H pylori* infection has been documented in up to 90% of patients with low-grade gastric lymphoma of the MALT type. At first, it has been believed that the MALT acquired in response to *H pylori* infection provides the background on which unidentified factors act and then lead to the development of lymphoma. However, the immune response of B-cell lymphomas of MALT type to *H pylori* antigen is proved to occur only with the presence of T cells on the culture<sup>[10,11]</sup>. Furthermore, the cellular proliferation of low-grade gastric B-cell lymphomas of MALT type to *H pylori* seems to be dependent on *H pylori*-specific T cells and their products, rather than the bacteria themselves<sup>[11]</sup>. The inhibitive action against such a mechanism would break down in immunocompromised state so that B-cell lymphomas of MALT type may develop even in *H pylori* infected children.

*H pylori* eradication is now established to be effective in reducing primary gastric lymphomas of the MALT type and is well accepted as an initial therapy for patients with localized low-grade gastric lymphomas. Remission rates in the recent literature range from 60% to 80%, though recurrence can be expected in some 5% of cases<sup>[12-15]</sup>. As described above, authors addressed the contributions of the persistent exposure to *H pylori* antigen and the presence of *H pylori*-specific T cells in the pathogenesis of lymphomas of MALT type. With the eradication of *H pylori*, chronic inflammation decreases and the density of submucosal lymphocytes dramatically declines<sup>[7]</sup>. Thus, the cessation of exposure to *H pylori* antigen due to either the spontaneous cure of *H pylori* or the result of the eradication might progress the tumor regression through the immunologic response.

The major negative predictive factor of tumor response to anti-*H pylori* treatment in patients with primary low-grade gastric lymphoma of the MALT type is involvement of the regional lymph nodes. The depth of the tumor infiltration in the gastric wall correlates with the involvement of the regional lymph nodes and with the degree of tumor malignancy<sup>[16-18]</sup>.

Primary gastric lymphoma of the MALT type has been documented in liver, heart, and kidney transplant recipients<sup>[19-22]</sup>. The development of these post-transplantation lymphomas of the MALT type appears to be closely related to the abnormal response of the dysregulated host immune system. Post-transplantation lymphoma of the MALT type is also associated with *H pylori* infection and is usually of an Epstein-Barr Virus-negative, B-cell origin. A combination of treatments to



**Figure 5** Two months after eradication therapy in Patient 2, an area of glossy whitish mucosa appeared at the site previously occupied by the low-grade gastric lymphoma of the mucosa-associated lymphoid tissue type.

minimize immunosuppression and eradicate *H pylori* frees most patients from disease<sup>[21-23]</sup>.

Primary gastric malignant tumors are very rare in children, as are most lymphomas. The majority of primary gastric lymphomas are high-grade non-Hodgkin's lymphomas of B-cell origin. To our knowledge, the literature has not reported significant numbers of primary gastric lymphomas of the MALT type in children<sup>[7,24-26]</sup>. The clinicopathological features in pediatric cases are considered to be similar to those observed in adults.

In this report we have described the complete remission of primary gastric lymphomas of the MALT type in two pediatric patients under an immunocompromised state. In patient 1, an advanced gastric lymphoma of the MALT type with duodenal invasion and lymph node involvement regressed spontaneously without any treatment. This experience prompts us to question whether regional lymph node involvement is a negative predictive factor of the tumor response, as described above. Anti-*H pylori* treatment with minimization of immunosuppression was satisfactory in our second patient. To the best of our knowledge, patient 2 is the first reported case of primary gastric lymphoma of the MALT type occurring in a post-cord blood transplantation setting.

In conclusion, the authors propose that low-grade gastric lymphoma of the MALT type can be cured by conservative treatment even in immunocompromised pediatric patients. A watch-and-wait strategy combined with *H pylori* eradication and close follow-up should be an option before attempting more aggressive treatments, even in cases with advanced disease.

## REFERENCES

- 1 **Harris NL**, Isaacson PG. What are the criteria for distinguishing MALT from non-MALT lymphoma at extranodal sites? *Am J Clin Pathol* 1999; **111**: S126-S132
- 2 **Harris NL**, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; **17**: 3835-3849
- 3 **Horstmann M**, Erttmann R, Winkler K. Relapse of MALT lymphoma associated with *Helicobacter pylori* after antibiotic treatment. *Lancet* 1994; **343**: 1098-1099
- 4 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176
- 5 **Gold BD**. *Helicobacter pylori* infection in children. *Curr Probl*

- Pediatr Adolesc Health Care* 2001; **31**: 247-266
- 6 **Blecker U**. Helicobacter pylori-associated gastroduodenal disease in childhood. *South Med J* 1997; **90**: 570-576; quiz 577
- 7 **Blecker U**, McKeithan TW, Hart J, Kirschner BS. Resolution of Helicobacter pylori-associated gastric lymphoproliferative disease in a child. *Gastroenterology* 1995; **109**: 973-977
- 8 **Malfertheiner P**, Mégraud F, O'Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of Helicobacter pylori infection--the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002; **16**: 167-180
- 9 **Jaśkiewicz K**, Kobierska G. Lymphoid aggregates in gastric biopsies: relationship to other mucosal lesions. *Arch Immunol Ther Exp (Warsz)* 2000; **48**: 201-204
- 10 **Elitsur Y**, Jackman S, Keerthy S, Lawrence Z, Maynard VL, Triest WE. T and B cell repertoire in gastric lymph follicles in children with Helicobacter pylori infection. *Pediatr Pathol Mol Med* 2002; **21**: 31-39
- 11 **Hussell T**, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. *Lancet* 1993; **342**: 571-574
- 12 **Fischbach W**, Goebeler-Kolve ME, Dragosics B, Greiner A, Stolte M. 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**: 34-37
- 13 **Stolte M**, Bayerdörffer E, Morgner A, Alpen B, Wündisch T, Thiede C, Neubauer A. Helicobacter and gastric MALT lymphoma. *Gut* 2002; **50** Suppl 3: III19-III24
- 14 **Steinbach G**, Ford R, Globel G, Sample D, Hagemeister FB, Lynch PM, McLaughlin PW, Rodriguez MA, Romaguera JE, Sarris AH, Younes A, Luthra R, Manning JT, Johnson CM, Lahoti S, Shen Y, Lee JE, Winn RJ, Genta RM, Graham DY, Cabanillas FF. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. *Ann Intern Med* 1999; **131**: 88-95
- 15 **Thiede C**, Morgner A, Alpen B, Wündisch T, Herrmann J, Ritter M, Ehninger G, Stolte M, Bayerdörffer E, Neubauer A. What role does Helicobacter pylori eradication play in gastric MALT and gastric MALT lymphoma? *Gastroenterology* 1997; **113**: S61-64
- 16 **Levy M**, Copie-Bergman C, Traulle C, Lavergne-Slove A, Brousse N, Flejou JF, de Mascarel A, Hemery F, Gaulard P, Delchier JC. Conservative treatment of primary gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue: predictive factors of response and outcome. *Am J Gastroenterol* 2002; **97**: 292-297
- 17 **Ruskone-Fourmestreaux A**, Lavergne A, Aegerter PH, Megraud F, Palazzo L, de Mascarel A, Molina T, Rambaud JL. Predictive factors for regression of gastric MALT lymphoma after anti-Helicobacter pylori treatment. *Gut* 2001; **48**: 297-303
- 18 **Nakamura S**, Matsumoto T, Suekane H, Takeshita M, Hizawa K, Kawasaki M, Yao T, Tsuneyoshi M, Iida M, Fujishima M. Predictive value of endoscopic ultrasonography for regression of gastric low grade and high grade MALT lymphomas after eradication of Helicobacter pylori. *Gut* 2001; **48**: 454-460
- 19 **Aull MJ**, Buell JF, Peddi VR, Trofe J, Beebe TM, Hanaway MJ, Roy-Chaudhury P, Alloway RR, First MR, Woodle ES. MALToma: a Helicobacter pylori-associated malignancy in transplant patients: a report from the Israel Penn International Transplant Tumor Registry with a review of published literature. *Transplantation* 2003; **75**: 225-228
- 20 **Shehab TM**, Hsi ED, Poterucha JJ, Gunaratnam NT, Fontana RJ. Helicobacter pylori-associated gastric MALT lymphoma in liver transplant recipients. *Transplantation* 2001; **71**: 1172-1175
- 21 **Hsi ED**, Singleton TP, Swinnen L, Dunphy CH, Alkan S. Mucosa-associated lymphoid tissue-type lymphomas occurring in post-transplantation patients. *Am J Surg Pathol* 2000; **24**: 100-106
- 22 **Wotherspoon AC**, Diss TC, Pan L, Singh N, Whelan J, Isaacson PG. Low grade gastric B-cell lymphoma of mucosa associated lymphoid tissue in immunocompromised patients. *Histopathology* 1996; **28**: 129-134
- 23 **Boissonnat P**, El Bekkali Y, Salles G, Dumortier J, Roussoulières A, Sebbag L, Gare J, Robin J, Ninet J, Bastien O. Regression of gastric lymphoma of mucosa associated with lymphoid tissue (MALT) following cardiac transplantation. *J Heart Lung Transplant* 2002; **21**: 1044-1045
- 24 **Mo JQ**, Dimashkieh H, Mallery SR, Swerdlow SH, Bove KE. MALT Lymphoma in Children: Case Report and Review of the Literature. *Pediatr Dev Pathol* 2004; **7**: 407-413
- 25 **Kurugoglu S**, Mihmanli I, Celkan T, Aki H, Aksoy H, Korman U. Radiological features in paediatric primary gastric MALT lymphoma and association with Helicobacter pylori. *Pediatr Radiol* 2002; **32**: 82-87
- 26 **Ashorn P**, Lähde PL, Ruuska T, Mäkipernaa A. Gastric lymphoma in an 11-year-old boy: a case report. *Med Pediatr Oncol* 1994; **22**: 66-67

S- Editor Wang J L- Editor Zhang JZ E- Editor Bi L