CASE REPORT

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Extranodal marginal zone B-cell lymphoma of the gastrointestinal tract sparing only the esophagus: A case report

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Lymphomas presented in any organ or tissue other than lymph nodes or the spleen are considered primary extranodal non-Hodgkin's lymphomas, and the most common non-Hodgkin's lymphomas are of the gastrointestinal tract. The most common histological subtypes are marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue and diffuse large B-cell lymphoma, and typically only one to two organs are affected. Patients present with a wide variety of vague complaints, making early diagnosis problematic. Herein, we report the case of a 76-year-old male with extranodal marginal zone B-cell lymphoma involving the entire gastrointestinal tract, sparing only the esophagus, who was Helicobacter pylori-negative. He underwent six courses of chemotherapy with R-CHOP regimen, and achieved complete remission.

Key words: Extranodal marginal zone B-cell lymphoma, gastrointestinal tract, mucosa-associated lymphoid tissue

Özefagus hariç tüm gastrointestinal sistemi tutan ekstranodal marjinal zon B-hücreli lenfoma: Vaka sunumu

Lenf bezlerini veya dalağı tutmaksızın herhangi bir organ tutulumu ile prezente olan lenfomalar primer ekstranodal non-Hodgkin lenfomalar olarak kabul edilir ve gastrointestinal sistemde en sık görülen lenfoma tipidir. En sık görülen histolojik alt tipleri mukoza ilişkili lenfoid dokunun marjinal zon B-hücreli lenfoması ve diffüz büyük B hücreli lenfomadır, ve tipik olarak bir ya da iki organ tutulumu ile seyrederler. Hastalar çok çeşitli silik semptomlar ile prezente olurlar ve bu nedenle erken tanıda problemlerle karşılaşılabilir. Burada, Helikobakter pylori negatif olan 76 yaşındaki erkek hastada, özefagus hariç tüm gastrointestinal sistemi tutan ekstranodal marjinal zon B-hücreli lenfoma hastası sunulmuştur. Hasta 6 kür R-CHOP kemoterapisi almıştır ve halen tam remisyonda izlenmektedir.

Anahtar kelimeler: Ekstranodal marjinal zon B-hücreli lenfoma, gastrointestinal system, mukoza ilişkili lenfoid doku

INTRODUCTION

Lymphomas that present with disease in any organ or tissue other than the lymph nodes or the spleen are considered primary extranodal non-Hodgkin's lymphomas (NHLs), and the most common NHLs are of the gastrointestinal (GI) tract (1). The most common histological subtypes are marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) and diffuse large B-cell lymphoma (1). MALT lymphomas are the second most frequently encountered type of GI NHL, the first being diffuse large B-cell lymphoma (2). Patients present with a wide variety of vague

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complaints, making early diagnosis problematic (3). In the present report, we describe a case of extranodal marginal zone B-cell lymphoma involving the entire GI tract, sparing only the esophagus.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

CASE REPORT

A 76-year-old male presented with a two-month history of postprandial fullness and epigastric pain. He described passage of tarry stools on two separate occasions in the past two months, as well as a significant weight loss (5 kg). He also complained of generalized weakness and dizziness. The patient denied any family history of colon cancer, familial polyposis, or hereditary non-polyposis colon cancer (HNPCC). The physical examination revealed mild tenderness in the epigastric region without peritoneal signs. Other physical findings were unremarkable. Laboratory blood tests revealed: white cell count 8280/mm^3 (62.5% segmented neutrophils, 30.4% lymphocytes, 4.3% monocytes, 2.4% eosinophils, 0.4% basophils), red cell count 5140000/mm^3, hemoglobin 14.5 g/dl, and platelet count 218000/mm^3. Electrolytes and tests of renal and liver functions were within normal limits.

Esophagogastroduodenoscopy (EGD) (Figure 1-A) revealed diffuse giant folds on the greater curvature of almost the entire gastric body. Patchy hyperemia was detected on the rugae, and no impairment of distensibility of the stomach was noted. Multiple small polypoid lesions with intact mucosal surface were also identified in the duodenum. Biopsy of the stomach was performed, and campylobacter-like organism (CLO) test was negative.

Colonoscopy (Figure 1-B) revealed multiple 0.5-1.0 cm polypoid lesions with intact mucosa located from the rectum to the ascending colon and terminal ileum. Endoscopic mucosal resection (EMR) biopsy was performed. Small bowel series (Figure 1-C) revealed diffuse mucosal thickening of the stomach, with extension into the second portion of the duodenum. Multiple small round filling defects were found in the jejunum, ileum and ascending colon. Contrast was noted to pass into the colon. Abdominal computed tomography (CT) (Figure 1-D) disclosed diffuse thickening of the gastric rugae with extensive lymphadenopathy over the para-aortic region and mesentery. Thickened bowel wall and multiple small round filling defects of the duodenum, jejunum and ileum were identified.

Histopathological examination of biopsies of the stomach (Figures 2-A, B) and colon both showed dense lymphocytic infiltrates in the lamina propria. The lymphocytes were small and centrocyte-like, with occasional mitoses. Lymphoepithelial lesions were evident.

Immunohistochemical staining (Figures 2-C, D) of the biopsies was positive for CD45 and CD20, but negative for CD5 and CD3. Examination of a bone-marrow aspirate disclosed normal tissue without malignancy. Therefore, low-grade extranodal marginal zone B-cell lymphoma involving the entire GI tract and sparing only the esophagus was diagnosed. Ann Arbor classification system staging was IIE, and the International Prognostic Index (IPI) score was 2.

Because the patient was not infected by *Helicobacter pylori (H. pylori),* he underwent six courses of chemotherapy with R-CHOP regimen adjusted to his body surface area (600 mg rituximab, 960 mg cyclophosphamide, 80 mg adriamycin, 2 mg vincristine, and 16 mg betamethasone) every 3-4 weeks. One month after the last course of chemotherapy, both EGD and colonoscopy (Figures 1E, F) revealed marked regression of the rugae and polypoid lesions. Biopsies of stomach and colon revealed chronic inflammation without centrocyte-like lymphocytes or lymphoepithelial lesions. There was no evidence of residual malignancy.

DISCUSSION

Although multi-focal extranodal marginal zone B-cell lymphoma of the GI tract is well-recognized, and up to 10% of patients may fall into this category (1-3), in most patients, only two organs are usually affected, for example, the stomach and small intestine, the stomach and large intestine, the small and large intestines, or the jejunum and ileum. To our knowledge, extranodal marginal zone B-cell lymphoma simultaneously and continuously occurring throughout the GI tract and comprising more than a hundred lesions, sparing only the esophagus, has not been reported. In addition, this patient had no *H. pylori* infection.

Lymphoma of the GI tract is the most common form of extranodal lymphoma, and accounts for 30%-40% of cases (4). The stomach is the most commonly involved site (60%-75% of cases), follo-

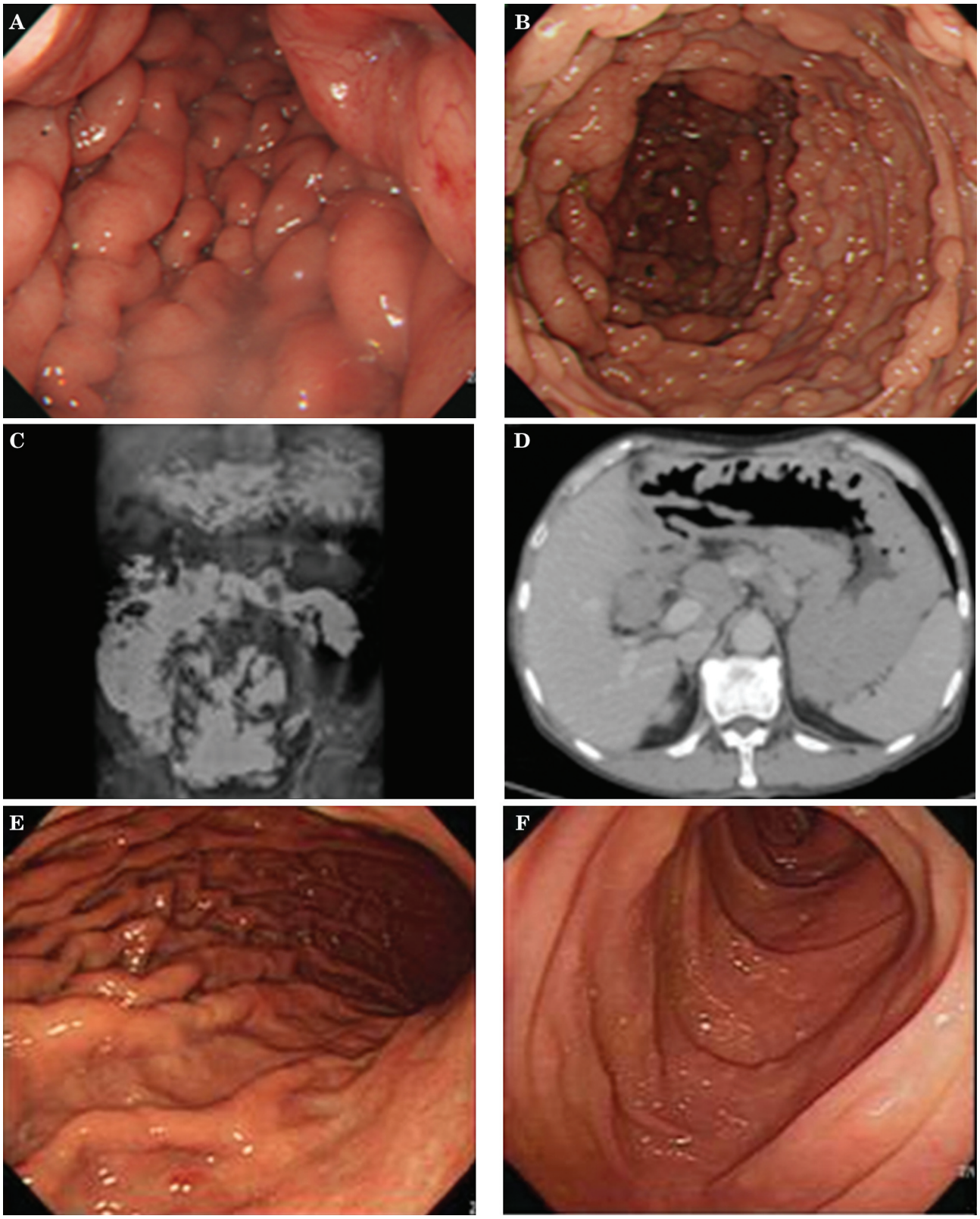

Figure 1. A) Esophagogastroduodenoscopy (EGD) revealed diffuse giant folds on the greater curvature of the entire gastric body and patchy hyperemia on the rugae. **B)** Colonoscopy revealed multiple 0.5-1.0 cm polypoid lesions with intact mucosa from the rectum to the ileum. **C)** Small bowel series revealed diffuse mucosal thickening in the stomach with extension into the duodenum. Multiple small round filling defects were noted in the jejunum, ileum and ascending colon. **D)** Abdominal computed tomography disclosed diffuse thickening of the gastric rugae, with extensive para-aortic and mesenteric lymphadenopathy. After six courses of chemotherapy, EGD revealed marked regression of the rugae **(E)**, and colonoscopy revealed marked regression of the polypoid lesions **(F)**.

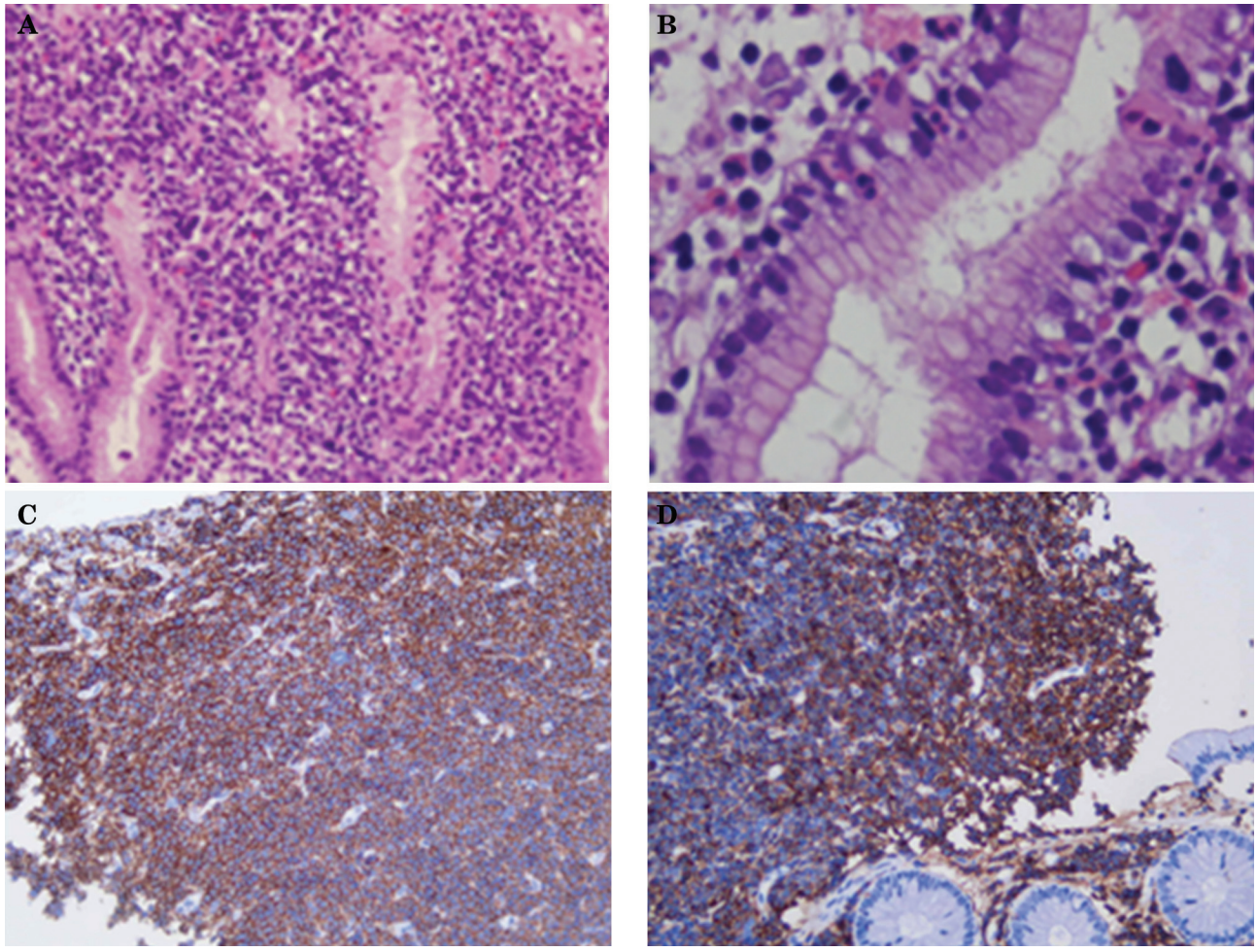

Figure 2. A) Histological examination of a stomach biopsy specimen revealed dense lymphocytic infiltrates in the lamina propria (H&E x40). **B)** Lymphocytes were small and centrocyte-like, with occasional mitoses, and lymphoepithelial lesions were evident (H&E x100). **C, D)** Immunohistochemical staining was positive for CD45 (C) and CD20 **(D)**.

wed by the small bowel, ileum, cecum, colon, and rectum; involvement of the esophagus is rare (4). Approximately one-half to two-thirds of GI NHLs are diffuse large B-cell lymphomas (1). In the early 1990s, the term marginal zone lymphoma was proposed in the Revised European American Lymphoma (REAL) classification to encompass two apparently closely related lymphoma subtypes, namely the "low-grade extranodal marginal zone B-cell lymphoma", currently named "MALT lymphoma", and the "nodal marginal zone B-cell lymphoma", also known as "monocytoid lymphoma" (2).

MALT lymphomas arise in a distinct subtype of B-cells that are associated with mucosal immunity. A characteristic of MALT lymphomas is the presence of lymphoid follicles and a diffuse infiltrate of lymphocytes occupying the marginal zone and infiltrating the crypt epithelium to form lymphoepithelial lesions (5). The immunophenotype is that of typical marginal zone B-cells ($CD20^+$, $CD21^+$, $CD35^+$, IgM^+, IgD^-) (6). Notably, the neoplastic cells are $CD5^-$, $CD10^-$ and cyclin-D1-negative (6). A t(11;18)(q21;q21) translocation is found in 30-40% of MALT lymphoma cases, and patients are more likely to be *H. pylori*-negative, less likely to respond to *H. pylori* eradication, and more likely to have widely disseminated disease (7). In addition, gastric MALT lymphoma with t(1;14) is also unlikely to respond to *H. pylori* eradication therapy (7).

The connection between *H. pylori* and gastric MALT lymphoma is well-established (8). *H. pylori* infection causes an immunological response, leading to chronic gastritis with formation of lymphoid follicles within the stomach. This accumulation of lymphoid tissue in the stomach establishes the conditions from which low-grade gastric MALT

lymphoma emerges (8). *H. pylori* can be identified in the gastric mucosa of more than 90% of patients with gastric MALT lymphomas (8). Regression of MALT lymphomas in response to *H. pylori* eradication strengthens the theory of a cause and effect relationship (8).

Clinically, MALT lymphomas behave as an indolent disease with a prolonged clinical course, and patients have long disease-free intervals and overall survival, and as a result, MALT lymphomas are known as "pseudolymphomas" (4). There are few published reports of MALT lymphomas similar to that seen in our patient in which the entire GI tract with the exception of the esophagus was affected. Our patient was not infected by *H. pylori,* and therefore, eradication did not have a role in the treatment. Because of multiple polypoid lesions in almost the entire GI tract, neither surgery nor radiation therapy was possible; thus, chemotherapy was administered.

The optimal management of extranodal marginal zone B-cell lymphomas has not yet been clearly defined, especially in *H. pylori*-negative MALT lymphomas and refractory B-cell lymphomas (1,7). Although chemotherapy with CHOP may not be an optimal regimen, it is the standard treatment for patients with aggressive lymphomas (9). Rituximab, a monoclonal antibody that attacks CD20 receptors on the surface of lymphoma cells, in combination with CHOP chemotherapy, has emerged as a new treatment for *H. pylori*-negative gastric MALT lymphomas and refractory B-cell lymphomas (9,10), as well as extranodal marginal zone B-cell lymphomas (11). In our patient, more than a hundred extranodal marginal zone B-cell lymphoma lesions were identified in almost the entire GI tract, including the stomach, small intestine and large intestine. In addition, the patient was not infected by *H. pylori,* so it was not possible to treat by targeting *H. pylori.* Thus, it was likely that combined immuno-chemotherapy would have better efficacy than conventional chemotherapy. After explaining the pros and cons of the various therapies, the patient decided to receive combined immuno-chemotherapy, and after six courses, his condition was ameliorated.

In conclusion, extranodal marginal zone B-cell lymphoma involving the entire GI tract is rare. In most cases, gastric MALT lymphomas are associated with *H. pylori,* and therapy revolves around eradication of *H. pylori.* Chemotherapy with R-CHOP regimen has been shown to be an effective treatment.

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