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Celiac disease associated with B-cell lymphoma

B hücreli lenfomanın eşlik ettiği çölyak olgusu

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Celiac disease is a gluten-induced enteropathy controlled by gluten restriction. Celiac disease is occasionally associated with T-cell lymphoma. We report a case with celiac disease who presented with duodenal ulcer-like symptoms and endoscopic findings. The persistent symptoms despite a strict diet led to the suspicion of an associated malignancy. Intensive evaluation revealed a case with celiac disease associated with B-cell lymphoma. Although B-cell lymphoma is rare, it should be kept in mind especially in female patients with persistent symptoms and refractory celiac disease.

Key words: Lymphoma, celiac, B cell lymphoma, duodenal ulcer

Çölyak hastalığı, gluten kısıtlaması ile kontrol altına alınan gluten enteropatisidir. Zaman zaman T hücreli lenfomaya yol açar. Duodenal ülser benzeri semptom ve bulgulara yol açan bir çölyak hastası sunduk. Sıkı diyete rağmen semptomların devam etmesi malignite şüphesi doğurdu. Yoğun araştırmalarla çölyak hastalığı ile birlikte B hücreli lenfoma teşhisi konuldu. B hücreli lenfoma nadir olmasına rağmen, özellikle persistan semptomlu retrakter çölyak hastalığı olan kadınlarda akılda tutulmalıdır.

Anahtar kelimeler: Lenfoma, çölyak hastalığı, B hücreli lenfoma, duodenal ülser

INTRODUCTION

Celiac disease is a gluten-induced enteropathy characterized by diffuse damage of the proximal small intestinal mucosa. It is usually a self-limited disease controlled by a gluten- free diet; however, a notable complication of celiac disease is the development of malignancies (1, 2). T-cell lymphoma constitutes 50% of all malignancies in individuals with celiac disease (3). On the contrary, B-cell intestinal lymphoma associated with celiac disease has been reported rarely (4). We report a case of a 28-year-old female with celiac disease and marginal zone extranodal B-cell lymphoma who presented with duodenal ulcer-like symptoms and endoscopic findings.

CASE REPORT

A 28-year-old female had been evaluated for complaints of dyspepsia, epigastric pain and diarrhea in another medical center. The first endoscopic evaluation had shown gastritis and duodenal ulcerations associated with *Helicobacter pylori (H. pylori)* infection. She had been diagnosed with peptic ulcer disease and treated for *H. pylori* with triple therapy. Two months later, endoscopic findings were persistent and duodenal biopsies were taken; however, they were not diagnostic. Although *H. pylori* was successfully eradicated, the patient's complaints persisted. Laboratory investigations were as follows: white blood cell (WBC): 5,600 mm3; hemoglobin (Hb): 13.5 g/dl; platelets: 234,000/mm3; and sedimentation rate: 15 mm/h. Biochemical tests were within normal ranges except for slightly low total protein (5.9 g/dl) and globulin levels (2.4 g/dl). A third endoscopic evaluation suggested Crohn's disease or intestinal lymphoma, prominent with several ulcerations in the duodenum; however, biopsy was not diagnostic.

She was then referred to our clinic and upper and lower gastrointestinal (GI) endoscopies were repeated. On the upper GI endoscopy, similar erosi-

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ons and ulcerations were persistent in the duodenal bulb and the second part of the duodenum (Figure 1). Several biopsies were taken; however, pathology could not differentiate between celiac disease and intestinal lymphoma. There was regional villous atrophy. Inflammation that was present in all the duodenal biopsies appeared to be composed of a mixture of plasma cells, lymphocytes and eosinophils. The majority of immune cells were kappa-restricted IgA-positive B cells (CD20+) and plasma cells. The CD3 stain highlighted the scattered T lymphocytes throughout the lamina propria. These findings were suspicious, but not diagnostic, of involvement by mucosa-associated lymphoid tissue (MALT) lymphoma. Histological assessment of *H. pylori* in the gastric biopsy specimen by Giemsa stain was negative. Endosonographic evaluation showed increased wall thickness in the duodenum suggesting diffuse infiltration (Figure 2). Colonoscopy was apparently normal but biopsy of the terminal ileum showed blunted villi and a kappa-restricted population of B-cell and plasma cell predominant immune cell infiltration to the mucosa, which were suspicious for MALT lymphoma involving the terminal ileum. Her anti-endomysial antibody and anti-gliadin antibody were also highly positive (anti-tissue transglutaminase IgA: 7200 RU/ml [N: <20] and antigliadin IgA: 40 RU/ml [N: < 25]). She was placed on a gluten-free diet for two months and the endoscopic evaluation was repeated. There was no regression in duodenal ulcerative lesions; however, this biopsy proved the association of celiac disease and B-cell lymphoma in this case (Figure 3a and 3b).

Radiological screening showed a nodule in the lung, but biopsy established it as only reactive lymphoid tissue. A further staging work-up demonstrated the presence of retroperitoneal lymphadenopathy. Chemotherapy with anti-CD20 monoclonal antibody was initiated. After six months, the duodenal lesions disappeared, all symptoms resolved and remission was achieved. The follow-up endoscopy and duodenal biopsy revealed prominent findings of celiac disease (Figure 4).

DISCUSSION

We report herein a female who presented with peptic ulcer-like symptoms and endoscopic findings who was then diagnosed with extranodal marginal zone B-cell lymphoma associated with celiac disease. Celiac disease can have multiple hematological manifestations. The risk of malignant lymphoma development in celiac disease is increased 50- to 100-fold compared to that of the general population (5, 6). Lymphomas associated

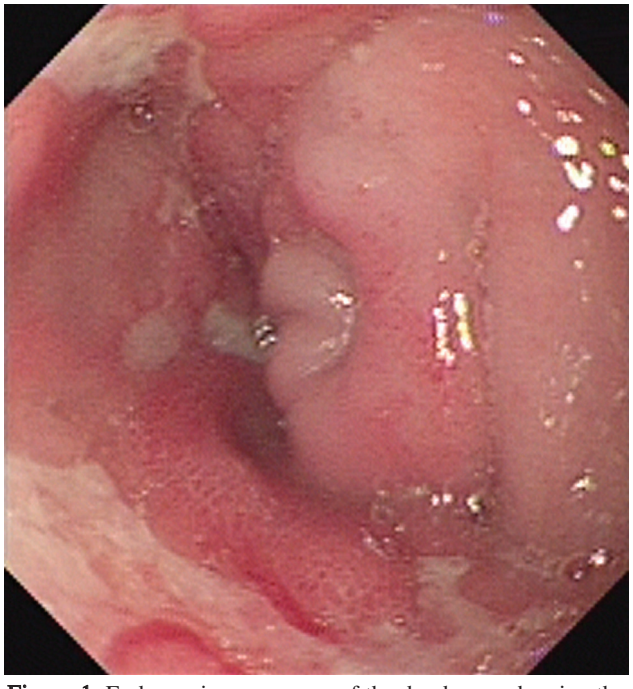

Figure 1. Endoscopic appearance of the duodenum showing the ulcerative lesions.

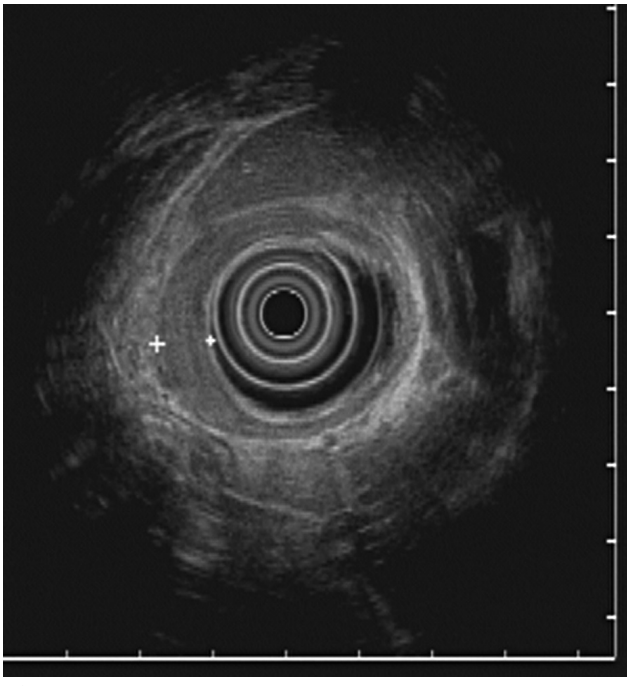

Figure 2. Endosonographic appearance of duodenal mucosa showing increased wall thickness suggesting mucosal cell infiltration.

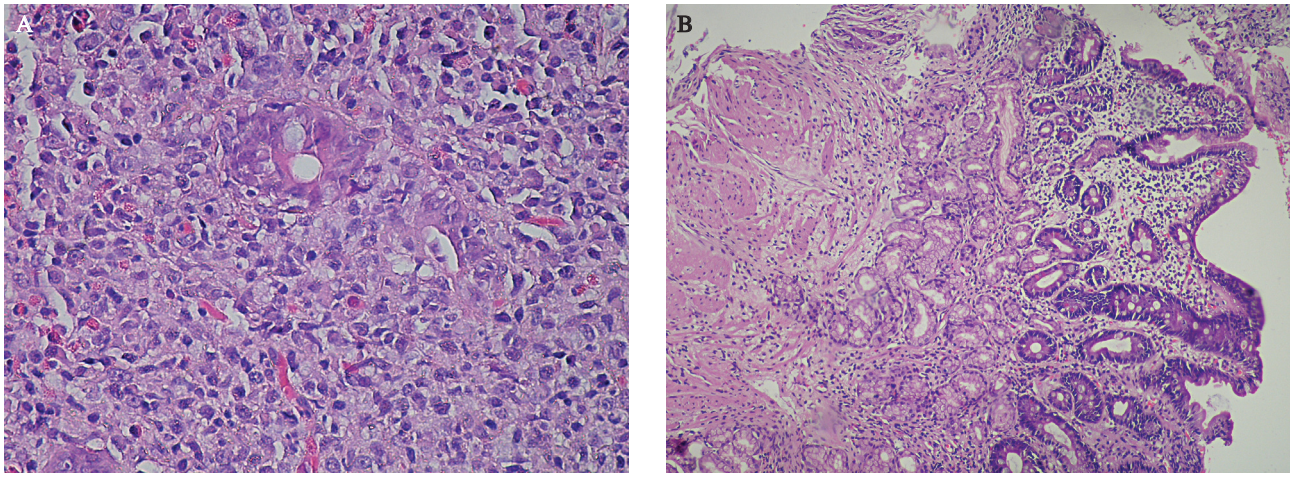

Figure 3. Duodenal biopsy showing the lymphocytic infiltration of the mucosa **(A)** (hematoxylin & eosin stain, x40) and villous atrophy **(B)**.

with celiac disease are heterogeneous and their diagnosis is difficult. The association between celiac disease and the otherwise uncommon enteropathy-type T-cell lymphoma has been emphasized in the literature (7). However, intestinal B-cell lymphoma associated with celiac disease has been described in only a few case reports (8-10). In a prospective study, 166 patients with celiac disease were followed for a period of up to 25 years; of the 13 intestinal lymphoma cases, only 2 (15%) were B-cell intestinal lymphomas (9). In a multi-center study including 653 patients with lymphoma, celiac disease was diagnosed in 6 patients and 3 were of B-cell origin (7).

Low-grade lymphoma arising in MALT of the duodenum is a very rare entity (10). Furthermore, lymphoma that arises in the presence of enteropathy is commonly from T lymphocytes. However, Smedby et al. (11) reported recently that lymphomas complicating celiac disease are indeed not only of the enteropathy-type T-cell lymphoma. They found a remarkable aggregation of female sex, celiac disease, and B-cell lymphoma in a large population study. Our case is representative of this association and emphasizes the necessity of intense search for an accurate diagnosis. The diagnosis of diffuse large B-cell lymphoma is usually straightforward while low-grade B-cell lymphoma of MALT-type may be difficult to diagnose and distinguish from reactive lymphoproliferations. In addition, initial presentation of celiac disease with peptic ulcer-like symptoms and duodenal ulcerations is very rare. As in this case, repeated biopsies are sometimes needed to investigate the characteristic immunohistochemical profile of lymphoproliferations in the mucosa. The initial biopsies of this case revealed increased lymphocytes in all biopsy samples; however, Dutcher bodies were evident in many plasma cells. Immunohistochemical staining confirmed the presence of more kappa-restricted plasma cells than would be expected for a reactive process. Repeated biopsies proved this to be a case with B-cell lymphoma.

Celiac disease is a gluten-induced enteropathy controlled by gluten restriction. The disease may

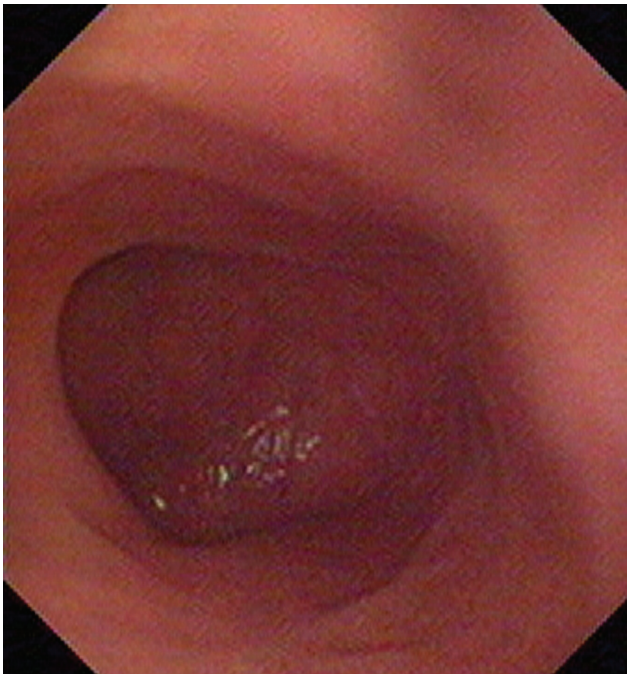

Figure 4. Endoscopic appearance of the duodenum after chemotherapy. Mucosal scalloping and atrophy were prominent and typical for celiac disease.

present with intestinal lymphoma in the initial presentation. The presence of persistent symptoms such as abdominal pain, weight loss and malaise associated with endoscopic findings in patients with celiac disease, despite their maintaining a strict gluten-free diet, should raise a suspicion of malignancy. Follow-up of the patients and intense investigations are necessary for an accurate diagnosis. This case emphasizes that although B-cell lymphoma is rare, it should be kept in mind especially in female patients with refractory celiac disease.

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