CASE REPORT

Free perforation of primary small bowel lymphoma in a patient with celiac sprue and dermatitis herpetiformis

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ABSTRACT

Small bowel lymphomas are rare and constitute approximately 1% of the malignant gastrointestinal tumors. However, the risk of malignant disease in adult celiac disease is about 8–10%, and non-Hodgkin lymphoma is the most common. In the literature, cases with celiac disease and small bowel lymphoma have been reported, but the emphasis on emergency surgery is extremely rare. We herein present a case of primary small intestinal lymphoma diagnosed after surgery in a 55-year-old male patient who presented to our emergency department with findings of gastrointestinal perforation and had a history of celiac disease and dermatitis herpetiformis. The purpose of this report is to review this situation briefly and discuss it in the light of literature.

Keywords: Celiac disease; dermatitis herpetiformis; free perforation; gluten; intestinal lymphoma; non-Hodgkin lymphoma; small bowel lymphoma; small bowel perforation.

INTRODUCTION

Small bowel malignancies are very rare. The small intestine has three-quarters of the length of the digestive tract, but small bowel malignancies account for approximately 1–5% of gastrointestinal cancers. Lymphomas encompass 15% of small bowel malignancies[1] and are most commonly seen in the ileum. Among the risk factors related to the development of small bowel lymphomas, there exists celiac disease, as well as dermatitis herpetiformis.

Celiac disease is an autoimmune disease characterized by gluten intolerance and damage to small intestinal villi.[2] The risk of small bowel tumors increases in celiac disease. Lymphoma develops most frequently; however, adenocarcinoma may rarely develop.[3] Dermatitis herpetiformis is a chronic, polymorphic and itchy skin disease that often develops in patients with latent gluten-sensitive enteropathy.[4] The interesting connection between celiac disease and dermatitis herpetiformis has been revealed by understanding that lymphoma may be the first clinical manifestation of the celiac disease or aggravate dermatitis herpetiformis.[5–8]

We herein present a case of primary small intestinal lymphoma diagnosed after surgery in a 55-year-old male patient who presented to our emergency department with free perforation findings and had a history of celiac disease and dermatitis herpetiformis. The purpose of this report is to review this situation briefly and discuss it in the light of literature.

CASE REPORT

A 55-year-old male was admitted to our emergency service with complaints of abdominal pain, nausea and vomiting, and absence of gas-feces discharge for one day. He had a 35-year history of celiac sprue and dermatitis herpetiformis with compliance to a gluten-free diet strictly. His medical history also included arterial hypertension. On physical examination, the abdomen was distended, and there exist defense musculaire and rebound tenderness upon palpation of the abdomen.

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The bowel sounds were hypoactive. Digital rectal examination revealed an empty rectum. White blood cell count was 11.2 10^3/μL. A computed tomography (CT) of the abdomen showed that there was a wall thickening of 15 mm measured at the thickest part consistent with diffuse mucosal edema in the jejunal loops of the small intestine. At the umbilical level, free air densities were observed on the anterior abdominal wall (Fig. 1). At the laparotomy, there was a perforation area of 0.5 cm in the antimesenteric side of the jejunum 50 cm distal to the ligament of Treitz (Fig. 2a). Jejunal loops of approximately 50 cm, including this perforation area, were edematous and inflamed. These small bowel loops were resected and an end-to-end anastomosis was performed.

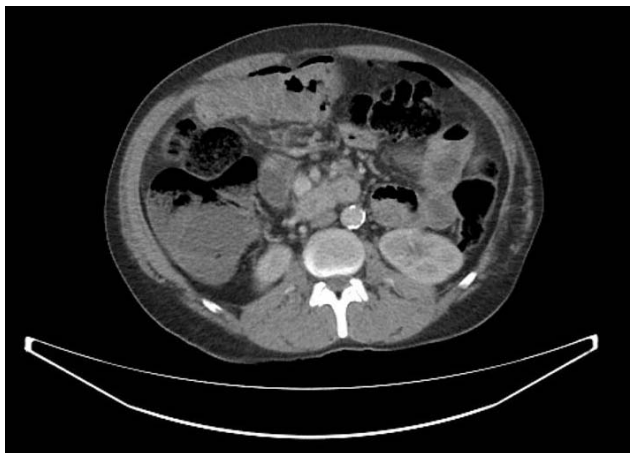


Figure 1. An axial CT section showing a wall thickening of 15 mm measured at the thickest part consistent with diffuse mucosal edema in the jejunal loops of the small intestine, and free air densities at the umbilical level on the anterior abdominal wall.

In the pathological examination, macroscopically, 6x2.5x2 cm ulcerated lesion with irregular borders and incised face similar to fish meat was observed in the area corresponding to the perforated region (Fig. 2b). There was no tumor at the surgical margins. Histopathological microscopic examination showed that the small bowel mucosa was completely ulcerated in the defined area. In this area, tumor formation consisting of atypical lymphoid cells with hyperchromatic nuclei, a few nucleoli and narrow basophilic cytoplasm was remarkable throughout the wall (Fig. 3a). This tumor infiltrated the entire wall but did not reach the serosa. Many atypical mitosis, lymphovascular invasion, and desmoplastic reactions were observed. It was morphologically compatible with non-Hodgkin lymphoma (NHL). Immunohistochemical examinations revealed CD10, CD19, CD20 and bcl6 negativity. However, CD3 (Fig. 3b), CD4 (Fig. 3c) and CD43 expressions were positive, and focally positive immunoreactivity to CD5 was determined. These findings were reported as T-cell NHL.

The patient was discharged seven days after the surgery without any problem. After the surgery, chemotherapy was planned to be added to the treatment, and he was referred

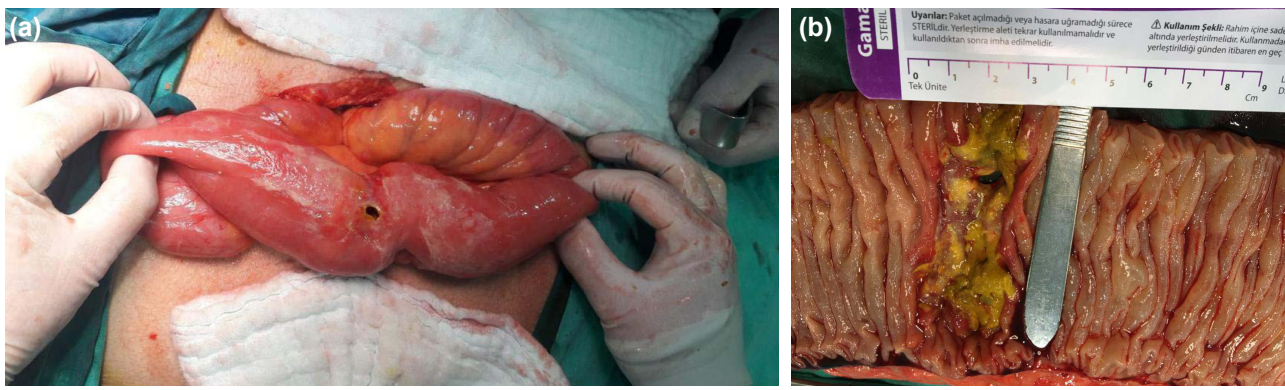


Figure 2. (a) A perforation area of 0.5 cm in the antimesenteric side of the jejunum 50 cm distal to the ligament of Treitz. **(b)** Macroscopically, 6x2.5x2 cm ulcerated lesion with irregular borders and incised face similar to fish meat in the area corresponding to the perforated region.

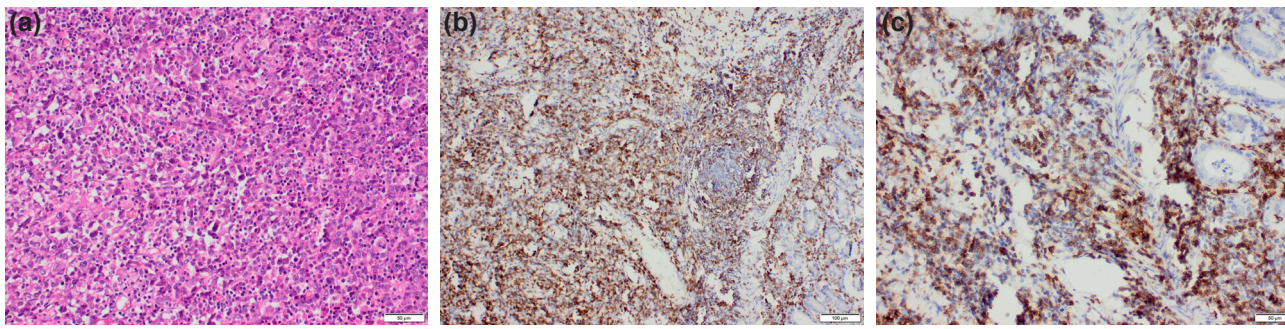


Figure 3. (a) Tumor formation consisting of atypical lymphoid cells with hyperchromatic nuclei, a few nucleoli and narrow basophilic cytoplasm throughout the wall (H&E, x 200). **(b)** Malignant lymphocytes showing positive immunohistochemical staining for CD3 (x100). **(c)** Malignant lymphocytes showing positive immunohistochemical staining for CD4 (x200).

to the department of medical oncology. However, the patient died of a heart attack on the 45th postoperative day. The patient's consent was obtained for this study.

DISCUSSION

Lymphomas are simply the malignant transformation of normal lymphoid cells in lymphoid tissues. This condition occurs predominantly in the lymph nodes (nodal lymphoma), but more rarely may occur in organs containing lymphoid tissue (extra-nodal lymphoma). Of these extra-nodal areas, the gastrointestinal tract (GIT) is an important area. GIT involvement during the natural course of lymphomas occurs in two different ways. The cases where malignant transformation predominantly and primarily arises from GIT are called primary gastrointestinal lymphomas and their treatment is directed to the localized area. In a patient who has been previously diagnosed with nodal lymphoma, GIT may be involved and they can be defined as secondary gastrointestinal lymphomas. Whether GIT involvement is primary or secondary, GIT involvement is predominantly in the form of NHL, and Hodgkin's disease is very rare. Gastrointestinal lymphomas develop from T or B cells. They encompass Burkitt lymphomas, mantle cell lymphomas, diffuse large B cell lymphomas, and mucosa-associated lymphoid tissue (MALT) lymphomas. In the presented case, the T-cell NHL was detected.

Primary NHLs occupy approximately 1–4% of all GIT neoplasms, while GIT involvement in secondary NHLs may reach up to 10% in the early stages of the disease and 60% in terminal periods. In summary, GIT is an important system that is affected during lymphomas. Forty percent of lymphomas can be grouped as indolent (survival is expressed in years), 55% as aggressive (survival is expressed in months) and 5% as very aggressive (survival is expressed in weeks). When the distribution within GIT was examined, the stomach was the first with 75%, followed by involvement of the small bowel (9%), ileocecal region (7%), rectum (2%), colon (1%) and multiple bowel regions (6%).[9] The most common sites of small bowel lymphomas are the ileum (60–65%), jejunum (20–25%) and duodenum (6–8%), respectively. They usually settle in multiple foci, and 15% of cases have skip lesions.[10] Lymphoma, which aggravates celiac disease, is frequently seen in the jejunum.[11,12] In our patient, the lymphoma involved the jejunum.

Celiac disease is an autoimmune disease associated with gluten and shows genetic transmission.[13,14] Celiac disease is seen with a frequency of 0.5–1% in various countries of the world[14] and is more common in women, but the association with small bowel tumor is more common in men.[3] Our case was a 55-year-old man with small bowel lymphoma concerning celiac disease, as reported in the literature. The risk of small bowel tumor increases approximately 60–80 times in celiac disease.[15] Small bowel lymphoma is approximately 10 times more common than adenocarcinoma.[16] The number of cases with celiac disease and small bowel NHL is relatively low in the literature.[3] Additionally, intestinal lymphoma may aggravate dermatitis herpetiformis.[17,18] In our patient, celiac disease was diagnosed 35 years before presenting with an acute abdomen due to a perforating lymphoma while on a gluten-free diet. In the same way, the diagnosis of dermatitis herpetiformis was established in this patient with small bowel lymphoma before the clinical picture of an acute abdomen.

The symptomatology of celiac disease varies, and patients may present with various symptoms. Gastrointestinal symptoms include diarrhea and abdominal pain, whereas extra-gastrointestinal ones are chronic anemia, increased liver function tests, arthritis, osteoporosis, skin disorders, and neurologic abnormalities. Sometimes, patients with celiac disease may be asymptomatic for a long time and may present with findings related only to small bowel mass before the diagnosis of celiac disease.[3] In the patient reported here, dermatitis herpetiformis, which is an accompanying clinical entity of celiac disease, was evident. Small bowel malignancies usually manifest themselves with gastrointestinal discomforts. Among the most common presenting symptoms are abdominal pain (75%), losing weight (28%), intestinal obstruction (25%), and hemorrhage (24%). Diagnosis is mostly delayed if the clinical presentation at the time of admission does not include a condition requiring urgent intervention, such as obstruction, hemorrhage or free perforation. Ten percent of patients with small intestine malignancies have bowel perforation at the time of admission to the emergency department. Intestinal perforation mostly arises from lymphoma or sarcoma. Our patient had a small bowel perforation as the first clinical presentation of his NHL. He admitted to the emergency room with an acute abdomen requiring surgical intervention. The patient had exploratory laparotomy and we did not clinically suspect small bowel lymphoma before surgery.

The diagnostic workup begins with a detailed history of the patient and a physical examination. Laboratory analysis should include complete blood count, serum electrolytes, and liver function tests. Since the risk of tumor development is high in celiac disease, the use of noninvasive imaging methods, such as CT and MRI, as well as endoscopic examinations, is important in early diagnosis. CT scan has a sensitivity of 80% for the detection of small intestinal lesions and if CT or MR enterography is carried out, this rate increases to 85% to 95%.[19,20] Our patient's preoperative CT scan showed a wall thickening with diffuse mucosal edema in the jejunal loops and free air densities at the umbilical level. In our case, there was an abdominal pain localized around the umbilicus, which started abruptly one day ago, and preoperative radiographic imaging methods indicating perforation of a hollow viscus with intraabdominal free air were applied. MRI has an important role in the differential diagnosis of benign and malignant lesions and in the characterization of the mass. Concomitant diffusion-weighted imaging increases the efficiency of accurate diagnosis. Endoscopy is a very useful diagnostic tool for the detection of proximal small intestinal malignancies, such as

those in the duodenum and for obtaining biopsies from these lesions. Double balloon enteroscopy is a method used to detect small bowel malignancies located beyond the ligament of Treitz. Video capsule endoscopy is a noninvasive method that is increasingly used in advanced referral centers for visualization of the small intestine. In patients with signs of upper or lower digestive system bleeding or bowel obstruction, if there is no diagnosis yet, but if there is a high degree of clinical suspicion, then exploratory celiotomy should be performed and surgeon-assisted intraoperative endoscopy can provide visualization of all segments of the small bowel to the finest detail. Diagnostic laparoscopy is also a useful method for visualization of the peritoneal cavity and for obtaining multiple biopsies, even without gastrointestinal complications.

Celiac disease progresses with atrophy and fissures, and these pathological changes are more commonly seen in intestinal villi secondary to autoimmune changes and chronic inflammation, and rarely, polyp development, ulceration, benign stenosis secondary to chronic inflammation, and malignant masses can be seen.[21] On the other hand, small bowel lymphomas can be seen as a polypoid, infiltrative or exophytic mass. Accompanying mesenteric lymphadenopathy is more common in lymphoma. In our case, there was no lesion causing luminal narrowing and obstruction, but diffuse mucosal edema and wall thickening were observed in the jejunal loops. Macroscopically, 6x2.5x2 cm ulcerated lesion with irregular borders and an incised face reminiscent of fish meat was observed in the perforated region. Besides, in this patient who developed free perforation, there was no granuloma or vasculitis, which is one of the pathognomonic signs of Crohn's disease.[22]

Studies have shown that small bowel malignancies may occur in celiac disease.[11,12,15] Most of these small intestinal malignancies consist of lymphomas, but there has also been an increase in the incidence of small intestinal carcinoma.[23] Small bowel lymphomas may invade the mucosa, causing ulceration and sometimes bleeding or perforation, whereas expansive growth may result in obstruction of the intestine. The development of an ulcer in the mucosa of the small intestine is a concern for the development of a possible lymphoma in celiac disease. However, perforation due to malignant ulcers in the digestive tract is extremely rare in celiac disease. The estimated free perforation development rate is approximately 1–2%.[24] This rate is similar to the incidence of free perforation of the small intestine of 1.5% in Crohn's disease.[22] Any region within the digestive system is a potential candidate for this free perforation complication in celiac disease. This ominous complication may emerge unexpectedly, even in stable celiac disease, after visibly adapting to a gluten-free diet for many years. This case report describes a patient with stable celiac disease and dermatitis herpetiformis. The first clinical manifestation of lymphoma in celiac disease was a free perforation in the small intestine. Lymphoma occurred despite our patient surviving on a gluten-free diet. Free perforation developed unexpectedly, mostly as the first clinical presentation of the lymphoma in celiac disease. Small bowel perforation in celiac disease is an inauspicious clinical manifestation frequently regarded as an ominous forerunner of lymphoma in celiac disease.

The centrepiece of management for celiac disease is a gluten-free diet, which involves evasion of the gluten-containing cereals wheat, rye, and barley. Allowed cereals encompass rice, oats, buckwheat, corn, millet, and quinoa. A patient diagnosed with celiac disease will benefit from a consultation with a dietician who can assist in appropriate food selection and prevention. The basis of the treatment of dermatitis herpetiformis is a strict gluten-free diet that is healthy, which may prevent the development of lymphoma and other diseases related to gluten-induced enteropathy and malabsorption.[25–27] Strict adherence to a gluten-free diet is critical for clinical improvement of the disease and histological healing of the small intestine. However, the definite effects of certain dietary treatments on the prevention of different complications of the celiac disease still deserve further investigation. Strict adherence to a gluten-free diet may not provide complete protection against the risk of lymphoma in celiac disease.

Patients with no complications due to small bowel lymphoma should be treated with chemotherapy, similar to patients with systemic lymphoma.[28] However, systemic chemotherapy is contraindicated in patients with small bowel lymphoma where severe complications, such as hemorrhage, obstruction and perforation develop and require immediate medical or surgical intervention if the patient's general condition and concomitant systemic diseases permit an operation. During laparotomy, a tumor-containing segment of the small intestine is resected, and other small bowel loops should be carefully examined to avoid overlooking potential skip lesions if any. Unlike other primary small intestinal cancers, extensive mesenteric excision is not required. The remaining lymph nodes are managed with systemic chemotherapy after the patient is discharged. In our patient, emergent exploratory laparotomy revealed a 0.5-cm perforation over the jejunum. Partial small bowel resection with end-to-end anastomosis was done. Chemoradiation may be preferred in patients who cannot withstand cytotoxic systemic chemotherapy. However, the complication rates of radiation therapy are high for tumor necrosis, hemorrhage and intestinal perforation.

Conclusion

In conclusion, considering the difficulties in the diagnosis of small bowel tumors, it should be kept in mind that a small bowel perforation that we encountered during surgery may belong to a small bowel lymphoma and complications that may arise from this tumor should be well known. Small intestine malignancies are rarely seen as a cause of free perforation and can be delayed in diagnosis. The diagnostic value of imaging modalities is limited in patients with small intestinal lymphoma. In such cases, surgical intervention may always be necessary for both diagnosis and treatment. In our patient, the diagnosis of small bowel lymphoma was made by exploratory laparotomy only after free perforation developed.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: H.B., Z.T.; Design: H.B., Z.T.; Supervision: H.B., Z.T.; Resource: H.B., Z.T.; Materials: H.B., Z.T.; Data: H.B., Z.T.; Analysis: H.B., Z.T.; Literature search: H.B., Z.T.; Writing: H.B., Z.T.; Critical revision: H.B., Z.T.

Conflict of Interest: None declared.

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OLGU SUNUMU - *ÖZET*

Çölyak hastalığı ve dermatitis herpetiformisi olan bir hastada primer ince bağırsak lenfomasının serbest perforasyonu

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İnce bağırsak lenfomaları oldukça nadir görülmekte olup gastrointestinal malign tümörlerin yaklaşık %1'ini oluşturmaktadır. Ancak, erişkin çölyak hastalığında malign hastalık riski yaklaşık %8–10 arasındadır ve en sık non-Hodgkin lenfoma gelişmektedir. Literatürde çölyak hastalığı ve ince bağırsak lenfomasının birlikte görüldüğü olgular bildirilmekle birlikte acil cerrahi gereksinimi üzerine vurgu son derece nadirdir. Biz bu olgu sunumunda gastrointestinal perforasyon bulguları ile acil servisimize başvuran ve özgeçmişinde çölyak hastalığı ve dermatitis herpetiformis öyküsü bulunan 55 yaşındaki bir erkek hastada operasyon sonrası tanısı konulan primer ince bağırsak lenfomasını sunuyoruz. Bu sunumun amacı, bu klinik durumu kısaca gözden geçirmek ve literatür ışığında tartışmaktır.

Anahtar sözcükler: Bağırsak lenfoması; çölyak hastalığı; dermatitis herpetiformis; gluten; ince bağırsak lenfoması; ince bağırsak perforasyonu; Non-Hodgkin lenfoma; serbest perforasyon.

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