

Unusual Location of a Rare Complication of Celiac Disease

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Keywords

Celiac disease · Gastrointestinal cancer · Gluten-free diet

Abstract

Introduction: Celiac disease has been associated with gastrointestinal malignancies, most commonly gastrointestinal lymphoma. Nevertheless, rarer malignancies have also been reported, such as small bowel adenocarcinoma, mainly located in the duodenum or jejunum. **Case Presentation:** We report a case of a female patient with celiac disease with poor adherence to a gluten-free diet who presented with small bowel obstruction due to a primary ileal adenocarcinoma. The patient remains asymptomatic, adherent to the gluten-free diet, and without clinical, biochemical, or imaging evidence of cancer recurrence. **Discussion/Conclusion:** This case should raise awareness about the importance of the gluten-free diet and the early diagnosis and appropriate management of rare small bowel malignant complications of celiac disease, namely, adenocarcinoma.

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Localização incomum de uma complicação rara de doença celíaca

Palavras Chave

Doença celíaca · Neoplasias do tracto gastrointestinal · Dieta isenta em glúten

Resumo

Introdução: A doença celíaca tem sido associada a neoplasias malignas do tracto gastrointestinal, mais frequentemente linfoma gastrointestinal. No entanto, neoplasias malignas mais raras também têm sido relatadas, como o adenocarcinoma do intestino delgado, mais frequentemente localizado no duodeno ou jejuno. **Apresentação do caso:** Trata-se de uma doente com doença celíaca com fraca adesão à dieta isenta em glúten que se apresentou em oclusão do intestino delgado devido a um adenocarcinoma primário do íleo. Durante o seguimento após cirurgia com intenção curativa e quimioterapia adjuvante, a doente permanece assintomática, a cumprir dieta isenta em glúten e sem evidência clínica, bioquímica e imagiológica de recidiva neoplásica. **Discussão/Conclusão:** Este caso deve aumentar a consciencialização sobre a importância da dieta isenta de

Introduction

Celiac disease (CD) is a chronic, multiorgan disease triggered by gluten ingestion in genetically predisposed individuals. It manifests as immune-mediated inflammatory enteropathy associated with specific circulating autoantibodies and human leukocyte antigen haplotypes (HLA-DQ2 or HLA-DQ8) [1].

The prevalence and incidence of CD have increased in recent years, partly due to improved diagnostic tools and thorough screening of high-risk individuals. In Western countries, around 0.6% of the population has a histologically confirmed diagnosis, while serological screening shows a 1% prevalence. With a female-to-male ratio of 1:3 to 1.5:1, it can be diagnosed in any age, with over 70% of new cases occurring in adults [2].

CD presents a wide range of symptoms, making diagnosis difficult. While children often exhibit traditional gastrointestinal symptoms, adults are frequently asymptomatic. Classical manifestations include chronic diarrhea, abdominal pain, and weight loss. However, CD can also present with chronic constipation, abdominal distension, gastroesophageal reflux, and obesity [3].

The most common extraintestinal manifestations are decreased bone mineralization, iron-deficiency anemia, arthralgia, fatigue, and neuropsychiatric manifestations, including gluten ataxia and peripheral neuropathy. CD can also manifest with hypertransaminasemia, oro-dental disorders, infertility, delayed puberty, and short stature [4].

Diagnosis is based on evaluating specific autoantibodies, histopathologic findings of duodenal biopsy specimens, and HLA-DQ2/DQ8 genotyping [5, 6]. Testing should be considered for individuals suspected of having CD and asymptomatic individuals at higher risk.

The primary treatment for CD is maintaining a gluten-free diet (GFD) along with lifelong medical monitoring [6]. Key goals of post-diagnosis monitoring include symptom management, supporting adherence to the GFD, preventive measures (such as vaccinations and dual-energy X-ray absorptiometry), tracking seroconversion, vigilant monitoring for comorbidities, and early identification of complications. For adults, follow-up duodenal biopsies can be considered to assess mucosal healing in the absence of

symptoms after 2 years on a GFD, as this approach seems to be linked to better outcomes [6].

Up to 30% of patients with CD have nonresponsive CD, defined as persistent symptoms, signs, or laboratory abnormalities typical of CD despite 6–12 months on a GFD. This may be associated with dietary indiscretion, slow healing, alternative diagnoses, or refractory CD [7].

Patients with CD, particularly those who are long-standing and untreated, have an increased risk of gastrointestinal malignancies, most commonly gastrointestinal lymphoma [8]. Rarer malignancies have also been reported, such as small bowel adenocarcinoma (SBA), mainly located in the duodenum or jejunum [9]. We present a case of a patient with CD with poor adherence to a GFD who presented with small bowel obstruction due to a primary ileal adenocarcinoma.

Case Presentation

A 59-year-old female presented to our emergency department with a 10-day history of nausea, vomiting, diffuse abdominal pain, and abdominal distension. She also reported a 6-month history of anorexia and involuntary weight loss of 21% (48–38 kg). Her past medical history includes a diagnosis of CD at age of fifteen after investigation for chronic diarrhea. During follow-up visits, she experienced periods of noncompliance with a GFD and loss to follow-up. Recent investigations revealed elevated transglutaminase immunoglobulin A antibody (TTG IgA) levels (35.7 U/mL [normal <20]) and Marsh 3b findings on duodenal biopsies performed 2 months prior. Additionally, the patient has been managing iron deficiency anemia with oral iron supplementation and osteopenia with calcium carbonate plus vitamin D3. She had a history of cholecystectomy following acute cholecystitis, and there was no significant family history of gastrointestinal diseases or autoimmune conditions. On physical examination, she appeared pale, dehydrated, and a 2–3 cm painless tumefaction was detected on the left iliac fossa on deep abdominal palpation. Her normocytic normochromic anemia was stable (hemoglobin level of 10.4 g/dL [normal 12.0–16.0 g/dL]), and other blood parameters including leukocyte and platelet counts and biochemical parameters, namely, carbohydrate antigen 19-9 and carcinoembryonic antigen were unremarkable, except for albumin (2.0 g/dL [normal 3.4–5.0]) and positive TTG IgA (40.7 U/mL) (Table 1.). After a plain abdominal radiograph showing dilated small bowel loops with gas-fluid levels and absent gas in colon and distal bowel suggestive

Table 1. Abnormal laboratory findings upon the patient's admission to our emergency department

Laboratorial variables	Value	Normal range
Hemoglobin, g/dL	10.4	12.0–16.0
Mean corpuscular volume, fL	84.8	83–103
Mean corpuscular hemoglobin, pg	28.8	28–34
Mean corpuscular hemoglobin concentration, g/dL	32.6	32.0–36.0
Albumin, g/dL	2.0	3.4–5.0
Free T4, ng/dL	0.90	0.89–1.76
Thyroid-stimulating hormone, μ UI/L	0.964	0.55–4.78
Total vitamin D 25(OH), ng/mL	27.18	30–100
Tissue transglutaminase IgA antibody, U/mL	40.7	<20

of small bowel obstruction (shown in Fig. 1), an abdominopelvic computed tomography with oral and intravenous contrast was performed, identifying a thickened segment of ileum with parietal enhancement, measuring 4 cm in length and with a maximum thickening of 1.5 cm, with stenotic characteristics, causing proximal bowel dilation (maximum dilation of 8 cm) (shown in Fig. 2). Therefore, we decided to admit the patient to our ward, initiating nutritional optimization and the study of the ileal stenosis. The patient underwent antegrade and retrograde single-balloon-assisted enteroscopy, with progression to approximately 120 cm distal to the pylorus and proximal to ileocecal valve, respectively, without endoscopic abnormalities identified. Endoscopic tattooing was performed at the limit of endoscopic progression. Given the persistence of obstructive symptoms in the absence of a definitive diagnosis, the lack of findings compatible with lymph node involvement or metastatic potential of a possible small bowel neoplasm, and the absence of contraindications for surgery, the patient underwent exploratory laparotomy. During surgery, a stenotic ileal segment was identified, located at an approximate middle distance from the ileocecal valve to the angle of Treitz, proximally to the previously tattooed ileum segment. Enterectomy of the stenotic segment with en bloc removal of regional lymph nodes was performed without complications (shown in Fig. 3). There were no complications during the hospital stay, and the patient was discharged 5 days after surgery. The histopathological examination of the surgical specimen described the presence of a low-grade, infiltrative adenocarcinoma involving the serosa (pT4), without lymphatic permeation, but with venous and perineural invasion. The surgical margins (R0) and all the five resected lymph nodes were tumor-free (pN0) (shown in Fig. 4).



Fig. 1. Posteroanterior erect abdominal radiograph showing gas-fluid levels.

On the immunohistopathological analysis, CDX2 was positive, and DNA mismatch repair (MMR) proteins were present. After completed tumor staging (adding a thoracic computed tomography), a final TNM stage was defined (T4, N0, M0 – IIB), and following multidisciplinary discussion, adjuvant treatment was initiated with



Fig. 2. Coronal view of the abdominopelvic computed tomography (oral and intravenous contrast) exhibiting a segment of ileum thickened and with parietal enhancement, measuring 4 cm in length and with a maximum thickening of 1.5 cm, with stenotic characteristics, causing proximal bowel dilation (maximum dilation of 8 cm).

capecitabine plus oxaliplatin for 6 months (8 cycles) without complications. Six months after finishing adjuvant treatment, the patient remains asymptomatic, adherent to the GFD (TTG IgA <2.0 U/mL), and without clinical, biochemical, or imaging evidence of cancer recurrence.

Discussion

To the best of our knowledge, our clinical case represents one of the very limited number of cases in which a diagnosis of a primary adenocarcinoma as-

sociated with CD is described in a female patient and located in the ileum (Table 2) [10–13]. Small bowel malignant tumors are rare, comprising less than 5% of all gastrointestinal malignancies. Primary SBA represents 25–40% of small bowel malignant tumors, and its incidence appears to be increasing, particularly in the duodenum [14]. In Europe, SBA incidence was estimated as 3,600 new cases/year. The duodenum is the most affected segment, accounting for 55–82% of cases, followed by the jejunum (11–25%) and ileum (7–17%) [9]. SBA is most often diagnosed during the seventh decade with a slight male predominance and a higher incidence in Black patients. The majority of SBA cases are sporadic, but almost 20% are associated with predisposing factors, namely, patients with a diagnosis of colorectal cancer, genetic disorders such as Peutz-Jeghers syndrome or familial adenomatous polyposis, and chronic intestinal inflammatory diseases such as Crohn's disease and CD [9].

Since 1955, there have been many case reports, nationwide studies, and meta-analyses suggesting the association between CD and primary SBA [15, 16]. Although the absolute risk is low (5 per 10,000 CD patients over 10 years), the relative risk is high, with hazard ratios ranging at least 3.05 [8]. The role of the GFD diet as a protective factor for SBA is still a matter of debate. A delay in diagnosis or untreated CD, poor adherence to GFD, and persistent villous atrophy were identified as risk factors for SBA in CD patients. Our case corroborates these observations, as the patient had a long history of CD and poor adherence to GFD. Nevertheless, some patients on a strict GFD are also at risk for SBA [8, 17].

The pathogenic mechanisms of SBA in CD remain unclear. Possible explanations include high cellular turnover related to chronic inflammation, increased intestinal permeability to oncogenic factors, malabsorption of protective factors such as vitamins A and E, and impaired immunogenic surveillance in CD. Additionally, there are few reports suggesting that SBA may arise from adenomatous polyps, as in colonic adenocarcinomas [18, 19]. The large discrepancy in the incidence between SBA and colorectal adenocarcinoma may be explained by lower exposure to carcinogens and different frequencies of common molecular abnormalities present in SBA and colonic adenocarcinomas, reflecting distinct carcinogenesis pathways [9].

The clinical presentation is nonspecific. SBA often presents with a local complication of the tumor, most commonly gastric outlet obstruction in the case of

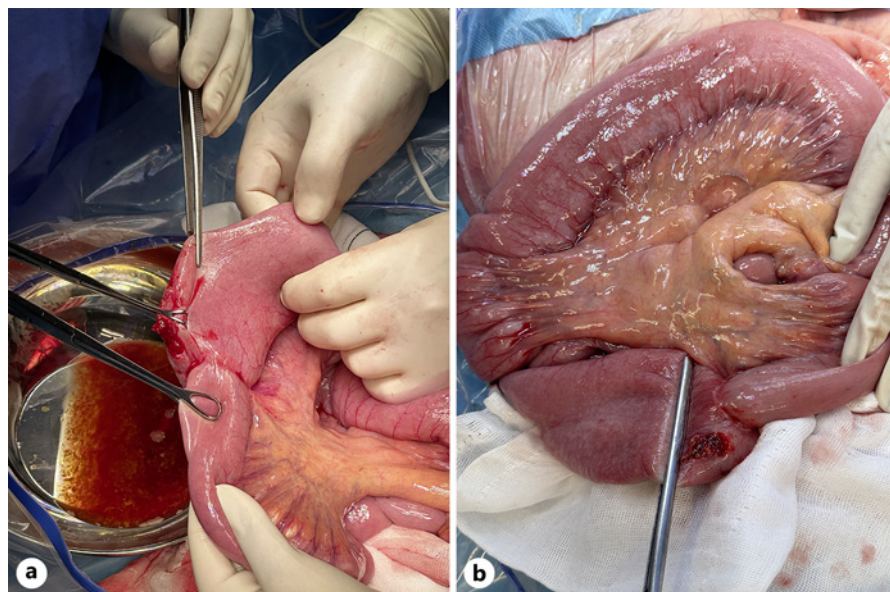


Fig. 3. a, b Ileal stenosis identified during exploratory laparotomy.

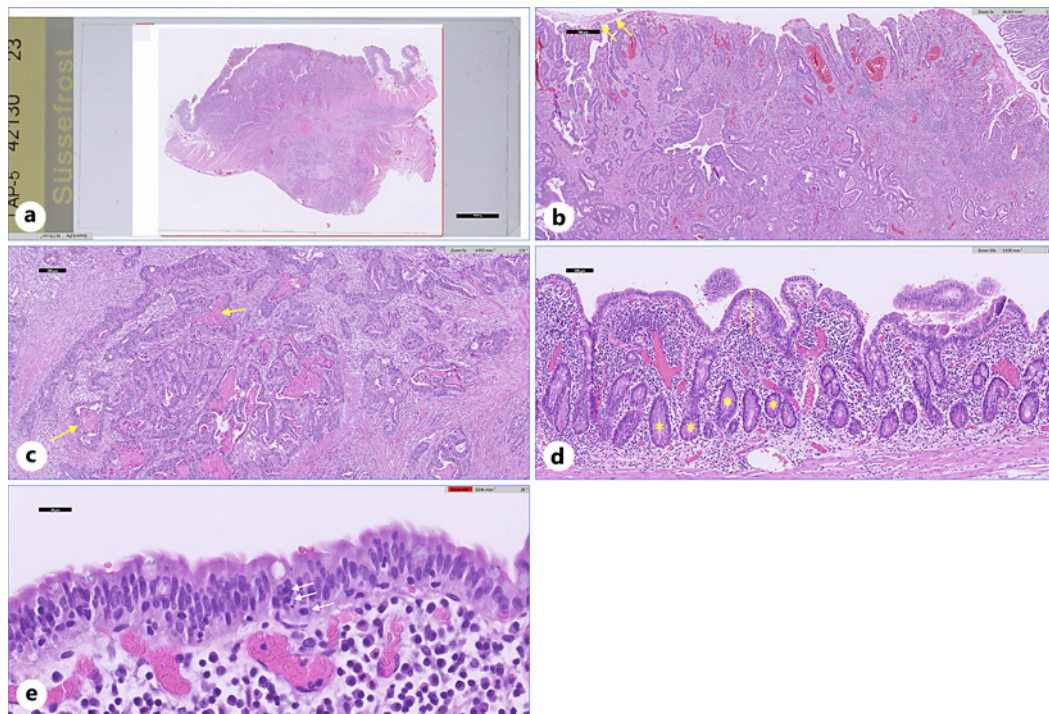


Fig. 4. Histopathology assessment of the surgical specimen. **a** Adenocarcinoma with subserosa involvement (H&E. $\times 2.5$). **b** Ulceration on the surface, highlighted by the yellow arrows (H&E. $\times 20$). **c** Comedonecrosis, identified by the yellow arrows (H&E. $\times 50$). **d** Normal mucosa, short villi (yellow arrow), and crypt hyperplasia (yellow asterisks) (H&E. $\times 100$). **e** Normal mucosa with intraepithelial lymphocytes (white arrows) (H&E. $\times 600$).

duodenal SBA or cramping abdominal pain in the case of jejunal or ileal SBA, as was the case of our patient. Occult gastrointestinal bleeding is another common

presentation for SBA. Jaundice, anorexia, weight loss, or intussusception or perforation have been also described [20].

Table 2. Clinical and pathological features of published cases of CD-associated ileal adenocarcinoma

Study	Sex	Age at CD diagnosis, years	Age at SBA diagnosis, years	CD duration at SBA diagnosis, months	Dietary status at SBA diagnosis	Symptoms at diagnosis of SBA	SBA location	Histological type	SBA grade	SBA stage	Management	Follow-up, months	Outcome
Garrido et al. [10]	F	72	72	0	No GFD	Abdominal pain, nausea, vomiting, weight loss	Ileum	Adenocarcinoma	G3	T4N0M0	Surgery + adjuvant chemotherapy	8	Alive
Rampertab et al. [11]	M	31	21	^a	No GFD	Abdominal pain	Ileum	Adenocarcinoma	G1	T4/N1-2/M0	Surgery ^b	^c	^c
Benhammane et al. [12]	M	46	46	0	No GFD	Abdominal pain and weight loss	Ileum	Adenocarcinoma	G3	T4N1M0	Surgery + adjuvant chemotherapy (CAPOX)	^c	Alive
Benhammane et al. [12]	M	37	37	0	No GFD	Abdominal pain, nausea, vomiting	Ileum	Adenocarcinoma	G2	T2N1M0	Surgery + adjuvant chemotherapy (CAPOX)	56	Alive
Vanoli et al. [13]	F	42	42	0	No GFD	^c	Ileum	Adenocarcinoma	G2	IIA	Surgery ^b	75	Alive
Vanoli et al. [13]	F	41	43	24	Strict GFD	^c	Ileum	Adenocarcinoma	G2	I	Surgery ^b	210	Alive
Vanoli et al. [13]	M	51	51	0	No GFD	^c	Ileum	Adenocarcinoma	G3	IIA	Surgery ^b	113	Alive

CAPOX, capecitabine and oxaliplatin; CD, celiac disease; F, female; GFD, gluten-free diet; M, male; SBA, small bowel adenocarcinoma. ^aCeliac disease was diagnosed after pathology slides from the small bowel adenocarcinoma resection were reviewed. ^bIt is not specified in the original article if additional treatment was performed. ^cNot specified in the original article.

The diagnosis is often delayed after the onset of symptoms because exploration of the small bowel is not as commonly performed as is the study of the upper gastrointestinal tract or the colon. Some studies report the onset time years after CD diagnosis, whereas in some cases, SBA and CD can be diagnosed at the same time [13]. Although the median age at diagnosis for CD patients with SBA is significantly higher than the median age at diagnosis for CD patients without malignancies, patients younger than 50 years at SBA diagnosis might have a higher probability of having CD [8, 21]. In CD patients, the most frequently affected site is the jejunum, as compared to the duodenum and ileum [22].

There is no standardized and validated surveillance strategy recommended for the early diagnosis of SBA following a diagnosis of CD. Due to the nonspecific nature of the presenting symptoms, maintaining a high level of suspicion for early diagnosis and treatment is crucial. In patients with known CD, in the presence of the aforementioned symptoms, SBA must be suspected and investigated. As was performed in our case, a complete diagnostic and staging workup should be done, including complete blood count, biochemistry profile, carbohydrate antigen 19-9, and carcinoembryonic antigen. Depending on the tumor's location and the patient's history, imaging studies (chest, abdomen, and pelvic CT and abdominopelvic and/or cholangiopancreatography magnetic resonance), endoscopic evaluation (upper endoscopy or colonoscopy, push and/or device-assisted enteroscopy, and capsule endoscopy), and biopsy of the lesion for pathologic tissue review should be obtained. MMR or microsatellite instability testing is also recommended for all patients with SBA because MMR/microsatellite instability status can function as a prognostic and/or predictive marker of response to treatment [23].

Considering the rarity of CD-associated SBA, all therapeutic recommendations come from the treatment of sporadic SBA. In line with what was performed in our case, according to the National Comprehensive Cancer Network clinical practice guidelines for SBA, the treatment will differ according to the location and stage of the SBA [23]. The mainstay of treatment of stage I–III resectable SBA consists of surgical resection with en bloc removal of the regional lymph nodes. The type of resection used to treat localized SBA depends on the location of the primary tumor. Given the common local and distant recurrence after surgery, adjuvant chemotherapy (folinic acid + fluorouracil + oxaliplatin; isolated fluo-

rouracil, leucovorin, or capecitabine; or capecitabine + oxaliplatin) is an option, mostly for SBA having high-risk features [23].

The prognosis of SBA is generally poor. SBA is usually diagnosed at an advanced stage (74% in stage III or IV) because of late-presenting symptoms [24]. In a retrospective study evaluating 217 patients with SBA, the median overall survival time was 20 months, and the 5-year overall survival rate was 26%. For localized disease, the 5-year survival was relatively high (85%). However, even in these patients who underwent cancer-directed surgery, 39% subsequently developed disease recurrence, with a median time to recurrence of 25 months, the majority (57%) developing distant metastases [25]. In conclusion, this case is a paradigmatic example about the importance of the adherence of GFD, the early diagnosis and appropriate management of rare small bowel malignant complications of CD, namely, adenocarcinoma.

Statement of Ethics

This case report has been granted an exemption from requiring ethics approval by the Unidade Local de Saúde do Alto Ave Ethics Committee. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tiago Lima Capela: involved in the drafting of the case and in the patient's care. Ana Isabel Ferreira: involved in the patient's care. Joana Magalhães: involved in the patient's care and final approval of the manuscript. Tiago Cúrdia Gonçalves, Bruno Rosa, and José Cotter: involved in the final approval of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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