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Untreated Celiac Disease in a Patient with Dermatitis Herpetiformis Leading to a Small Bowel Carcinoma

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Key Words
Celiac disease · Dermatitis herpetiformis · Small bowel carcinoma

Abstract
Usually, celiac disease has a benign course, though the overall morbidity and mortality have increased. Treatment with a gluten-free diet restores the damaged intestinal mucosa. In rare cases a small bowel adenocarcinoma develops. Unfortunately, the clinical presentation is not always recognized and prognosis is bad. We present a 69-year-old man with a history of dermatitis herpetiformis who presented to our tertiary center for a second opinion for a suspected gastric motility disorder. This diagnosis was based on the combination of upper abdominal pain for over 2 years and repetitive episodes of vomiting. Immediately after referral, celiac disease was diagnosed and a gluten-free diet was started. In the next half year of follow-up, additional anemia and weight loss developed and eventually a small bowel adenocarcinoma was diagnosed. Revision of a small bowel follow-through, which had been performed 2 years earlier, showed that the tube had been positioned just distal from the process. Therefore, this diagnosis had not been made at that time. Unfortunately, curative therapy was not possible and the patient died a few months later. In conclusion, all patients with dermatitis herpetiformis have a gluten-sensitive enteropathy and should be treated with a gluten-free diet. Next to this it is important to notice that patients with celiac disease have an increased risk of developing a small bowel malignancy. Unexplained upper abdominal pain, weight loss and anemia should lead to additional investigations to exclude a small bowel malignancy in these patients. At last, the diagnosis of a small bowel carcinoma is difficult. Together with the radiologist, the optimal techniques for visualization of this malignancy should be considered.

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Introduction

Celiac disease is an inflammatory disorder in which the small intestine is damaged as a result of an excessive autoimmune response to gluten. Treatment consisting of a lifelong gluten-free diet restores the intestinal architecture. Once treated, celiac disease in general runs a benign course. However, the overall morbidity and mortality is moderately elevated in comparison to the general population. This is caused by the development of a number of associated disorders such as autoimmune diseases (hypothyroidism, diabetes, autoimmune hepatitis, alopecia), osteoporosis and inflammatory bowel disease [1–3].

One of the complications of celiac disease, with the largest implication for the patient's survival, is the development of small bowel malignancies. Most studies report an increased risk of non-Hodgkin lymphoma in celiac disease, though the risk for the individual patient is still very low [2]. Some evidence suggests that a gluten-free diet may reduce lymphoma risk [4, 5], though two case-control studies that screened for silent, i.e. untreated, celiac disease in lymphoma patients reported a less clear clinical association than perhaps thought [6, 7].

In addition, patients with celiac disease are at risk of developing a small bowel carcinoma [1, 8, 9]. Small bowel carcinomas are often overlooked in part because of their low prevalence, but also because diagnostic techniques such as video capsule and enteroscopy have only been recently developed. Most small bowel cancers are adenocarcinomas located between the duodenum and the ligament of Treitz [10, 11]. Surgical resection is the key therapy to obtain a good survival, but despite these measures the prognosis is dismal, with a 5-year survival rate of approximately 28% [12]. Earlier detection favors the chance of a good prognosis. It is unclear though whether earlier detection of celiac disease prevents the development of small bowel carcinoma.

In this case report we want to raise the clinicians' awareness for this silent killer in celiac disease and present the pitfalls in the clinical recognition as well as diagnosis of a small bowel adenocarcinoma.

Case Report

A 69-year-old male was referred to our tertiary center for a second opinion for a gastric motility disorder. His medical history revealed a dermatitis herpetiformis diagnosed 15 years previously which responded to Dapsone. In the two preceding years, he had been investigated in another center because of prolonged upper abdominal pain and vomiting. Initially anemia (Hb 7.6 mmol/l) attributed to a benign ventricular ulcer were diagnosed and treated. Due to persisting complaints, additional investigations were performed. Laboratory parameters were normal and a duodenoscopy, duodenal biopsies, an abdominal ultrasound, colonoscopy, an abdominal CT scan and a small bowel enteroclysis showed no abnormalities apart from a raised but decreasing ESR (from 76 to 59 mm/h) and a diverticular colon. Just prior to referral to our center, he developed severe vomiting and gastric retention. A motility disorder was considered and metoclopramide and erythromycin were prescribed.

The patient was referred to our tertiary center for further analysis. Apart from vomiting and pain following meals he had no other symptoms. A few years earlier his BMI had decreased from obese to normal. Since then, his weight had been stable over the last year. Physical examination showed no abnormalities. Laboratory investigations showed a slightly raised ESR (25 mm/h), increased ALT

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(127 U/l) and vitamin B12 deficiency. Revision of the small bowel follow-through and CT scan did not show any abnormalities. A new duodenoscopy was performed (**fig. 1**a). Duodenal histology showed partial villous atrophy (Marsh 3a), and celiac disease was diagnosed. The patient was referred to a dietician to start a gluten-free diet and vitamin B12 therapy was initiated.

For almost half a year, the patient was free of complaints. Then his upper abdominal pain resumed. New duodenal biopsies excluded refractory celiac disease. Upon follow-up he suffered from involuntary weight loss. Three months later he presented with a palpable mass in the abdomen and anemia (Hb 6.9 mmol/l). A video capsule followed by a single balloon enteroscopy revealed a large process at the duodenal-jejunal junction (fig. 1b, c). The lesion appeared to be a poorly differentiated adenocarcinoma, partly of the signet cell type. A CT scan suggested mesenterial infiltration in close relation to the stomach and several enlarged lymph nodes. Laparotomy demonstrated an unresectable process with a close relation to the gastric wall, left kidney, aorta and pancreas. In view of these findings and given the unresectability, a palliative gastrojejunostomy was made.

After surgery, the patient's condition did not improve. A second CT showed an increase of the tumor mass and lymph node enlargement within 4 weeks. The patient died 2 months later.

Discussion

This case report gives rise to three important key messages of which we should be more aware in patients with (untreated) celiac disease.

The first message concerns the fact that all patients with dermatitis herpetiformis have a gluten-sensitive enteropathy and that they should be advised to follow a gluten-free diet [13, 14]. We present a patient with long-existing dermatitis herpetiformis who developed a small bowel carcinoma 15 years after initial presentation. Our patient was never advised to follow a gluten-free diet, and in retrospect this may have been a contributing factor to the increased risk of small bowel carcinoma. The risk in dermatitis herpetiformis of developing additional autoimmune diseases is comparable with that in celiac disease, though the risk for developing a lymphoma is increased [15, 16]. Especially patients with dermatitis herpetiformis and autoimmune thyroiditis have a stronger predisposition to develop malignancies [16].

The second message underlines the importance of considering a small bowel adenocarcinoma in patients with (untreated) celiac disease who present with unexplained abdominal pain. However the problem is that patients often present with nonspecific complaints and that the awareness of the possibility of a small bowel adenocarcinoma is low because of the overall low incidence. In the spectrum of all possible malignancies, small bowel adenocarcinoma represents less than 0.5% of the cases. Only 2.5% of cancers in the digestive tract arise in the small bowel, of which 30–40% present as an adenocarcinoma [10]. Why the small intestine is relatively protected against adenocarcinoma in comparison to the colon is unknown. Several hypotheses have been postulated, but all remain to be proven. Possible factors protecting the small bowel include a rapid turnover of the small intestine mucosal cells, a fast transit time and thus short exposure of the small bowel to food and possible carcinogens, a small bacterial load in the small intestine, a well-developed IgA-mediated immune system and an increased (protective) alkaline content of the small bowel [17]. More recently, Sanders et al. demonstrated that the small bowel produces less endogenous reactive oxidative species than the colon, resulting in a decrease in oxidative stress [18]. In (untreated) celiac disease the ongoing inflammatory reaction together with a more permeable mucosal membrane to

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carcinogens and bacteria and the inability of the damaged epithelial cells to produce antioxidant enzymes may promote a malignant transformation [19]. Treatment of a small bowel adenocarcinoma is difficult and only based on surgical resection, with a 5-year survival of 32.5% in case of resection [11]. There are some retrospective studies that suggest a benefit in survival after chemotherapy in patients with advanced small bowel adenocarcinoma [20, 21], though until now there are no specific guidelines because of the lack of randomized clinical trials. As such, it has a poor prognosis.

At last, the diagnosis can easily be missed on conventional radiological investigations [22]. In the present case, the radiologists had not been made aware of the suspicion of a small bowel carcinoma. As a consequence, during the small bowel enteroclysis the tube was positioned just distal from the ligament of Treitz and thus distal from the malignant process. Since small bowel carcinoma in celiac disease often presents in the proximal small bowel, a position proximal from the ligament of Treitz is preferable. With knowledge of the diagnosis, a second revision of the small bowel enteroclysis, which had been performed 2 years earlier, demonstrated a subtle process close to the ligament of Treitz (**fig. 2**).

Conclusion

In conclusion, all patients with dermatitis herpetiformis should be regarded as celiac disease patients and a gluten-free diet should be advised. It is unclear though whether this will prevent the development of a small bowel malignancy. Also, we should be aware of the high risk of a small bowel carcinoma in celiac disease patients although a malignancy of the small intestine is rare. Unexplained upper abdominal pain, weight loss and anemia should lead to additional investigations to exclude a small bowel malignancy in these patients. At last, the diagnosis of a small bowel carcinoma is difficult. When considering this malignancy, one should make the radiologist aware of this suspicion. As a result, the most specific visualization techniques should be used.

Disclosure Statement

The authors declare that they have no competing interests.

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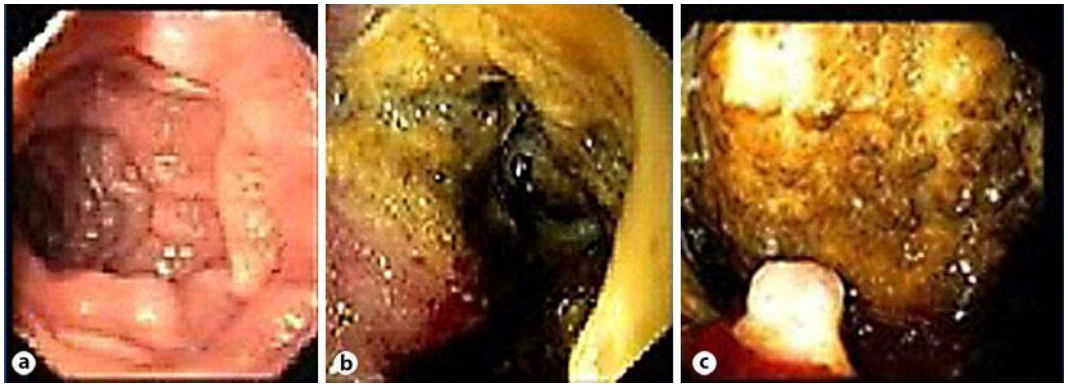

Fig. 1. a The first duodenoscopy after referral to our center did not show any macroscopic alterations. Biopsies showed partial villous atrophy (Marsh 3a) and the diagnosis of celiac disease was set. **b**, **c** After 6 months abdominal pain developed again. A single balloon enteroscopy showed a large tumorous mass at the junction of the duodenum and the jejunum in which no further normal mucosa of the small intestine was recognized.

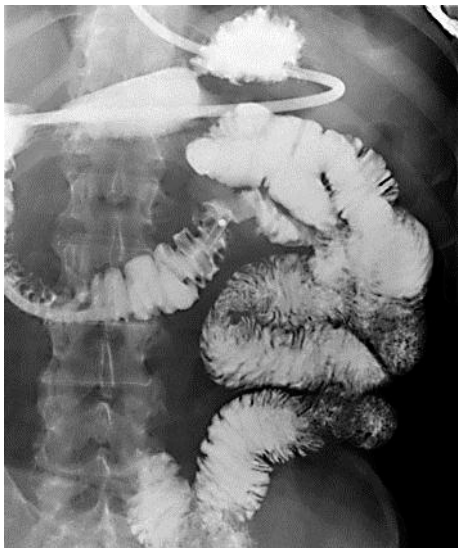

Fig. 2. A second revision of the small bowel enteroclysis, which had been performed 2 years earlier, demonstrated a subtle process close to the ligament of Treitz.

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