CASE REPORT

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A Challenging Diagnosis of Jejunal Adenocarcinoma in a Celiac Patient: Case Report and Systematic Review of the Literature

Angelo Zullo[1], Vincenzo De Francesco[2], Raffaele Manta[3], Lorenzo Ridola[4], Roberto Lorenzetti[1]

1) Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome;
2) Section of Gastroenterology, Riuniti Hospitals, Foggia;
3) Gastroenterology Unit, Nuovo Ospedale Civile Sant'Agostino-Estense, Baggiovara-Modena;
4) Gastroenterology Unit, Sapienza University of Rome, Polo Pontino, Latina, Italy

Address for correspondence:
Dr. **Angelo Zullo**
Gastroenterologia ed Endoscopia Digestive
PTP Nuovo Regina Margherita
Via Emilio Morosini, 30
00153 Rome, Italy
angelozullo66@yahoo.it

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ABSTRACT

Celiac disease (CD) is a common and chronic disorder requiring a long-life gluten-free diet. There is evidence that asymptomatic or subclinical presentation of CD has increased in the last decades, so that several cases are diagnosed during adulthood or even in the elderly. Celiac disease patients are at an increased risk of developing malignancies, particularly when the disease is diagnosed in the elderly. We describe a case of a challenging diagnosis of small bowel adenocarcinoma which developed in a patient with CD discovered only in the elderly. We also performed a systematic review of the literature. A tailored follow-up in a sub-group of CD patients at an increased risk of developing intestinal adenocarcinoma could be implemented.

Key words: Celiac disease – adenocarcinoma – small bowel – videocapsule endoscopy.

Abbreviations: CD: Celiac disease; GP: General Practitioner; FOBT: faecal occult blood test; EMA: anti-endomysial antibodies; tTG: anti-tissue transglutaminase antibodies; Hgb: hemoglobin; VCE: videocapsule endoscopy.

INTRODUCTION

Celiac disease (CD) is a common, chronic disorder, which develops in genetically predisposed subjects as an immunological reaction to some prolamines introduced with a diet [1]. A lifelong gluten-free diet is the mainstay treatment achieving a regression of intestinal lesions and resolution of symptoms in the majority of patients [2]. Although primarily affecting the small bowel, different extra-intestinal manifestations may develop [3]. Moreover, CD patients are at an increased risk of some malignancies, including lymphoma and adenocarcinoma of the small intestine [4]. We describe a case of a challenging diagnosis of small bowel adenocarcinoma developed in a patient with CD discovered only in the elderly. A systematic review of the literature on this topic was also performed.

CASE REPORT

A 77-year-old woman was referred to our open-access Endoscopy Unit in February 2012 for a colonoscopy due to mild rectal bleeding episodes in the previous months. No laboratory tests were available. She was suffering from arterial hypertension, successfully treated with lisinopril. No relevant diseases were present in her past medical history. She was not a smoker and neither an alcohol consumer. The patient complained of long-lasting vague abdominal symptoms (sporadic mild pain, bloating) with normal bowel habit (1-2 movements daily), diagnosed as irritable bowel syndrome by her General Practitioner (GP). Despite the fact that colorectal cancer had been diagnosed in her sister at the age of 58 years, she had never performed a colonoscopy screening. During a complete colonoscopy, which was performed with adequate bowel preparation, a 10 mm polyp in the transverse colon was removed by snare polypectomy, and hemorrhoids were detected. The histological assessment revealed tubular adenoma with low-grade dysplasia.

One year later, in March 2013, the patient complained of progressive asthenia and laboratory tests revealed a severe anemia

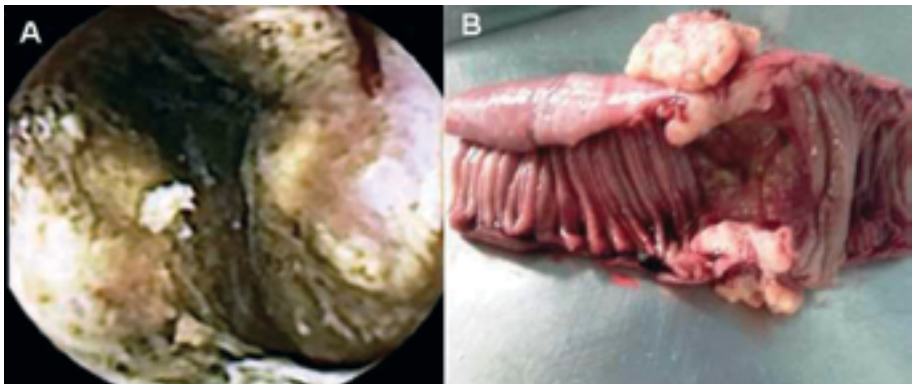

Fig. 1. (A) Videocapsule endoscopy: irregular and ulcerated mass with lumen narrowing. (B) The resected small bowel tract with the adenocarcinoma.

(hemoglobin 7.6 g/dL) with iron deficiency (ferritin 5 ng/mL; sideremia 23 μg/mL) and positive fecal occult blood test (FOBT). Therefore, the GP requested another colonoscopy, with the suspicion of a missed colon lesion at the previous colonoscopy. Nevertheless, the total colonoscopy, including visualization of terminal ileum mucosa, was unremarkable for macroscopic lesions, with the exception of hemorrhoids. Therefore, we proposed to the patient to perform an upper endoscopy in the same session to rule out potential blood loss from gastroduodenal lesions. The endoscopic examination documented absence of lesions in the oesophagus, stomach and duodenal bulb, revealing a mosaic pattern of mucosa with 'scalloping' of folds in the descending portion of duodenum, suggesting CD. Multiple biopsies were taken, and the histological examination documented sub-total villous atrophy, with increased villi-crypts ratio and intra-epithelial leucocytes count >25, confirming the diagnosis of CD. Both anti-endomysial antibodies (EMA +++) and anti-tissue transglutaminase antibodies (tTG 176 U/mL; normal values <10 U/mL) were positive. Iron supplementation was performed i.v. for 10 days and a gluten-free diet was started. Three months later, a laboratory control showed normalization of the iron deficiency anemia (Hgb 12.3 g/dL; ferritin 50 ng/mL), and negative serology for both EMA and tTG.

Despite the fact that she was totally adherent to a gluten-free diet, anemia recurrence (Hgb 10.1 g/dL; MCV 73.2 fL) was noted on April 2014, with positive FOBT result, whilst both EMA and tTG were still negative. Therefore, a refractory CD was ruled out, and a further ileocolonoscopy was performed without finding any macroscopic lesion, only hemorrhoids. At this point, a small bowel study was performed with videocapsule endoscopy (VCE). The examination revealed a circumferential and ulcerated narrowing in the small bowel at 13 minutes following the first duodenal image, suggesting a small bowel lymphoma in CD (Fig. 1A). The patient underwent laparoscopic resection of the duodenum-jejunum joint (Fig. 1B), and the final histological assessment disclosed a small bowel adenocarcinoma, with a small neuroendocrine component, and involvement of 1 out of 9 removed lymph nodes (pT3 pN1 pMx, G3; Stage III). Due to the advanced age (79 years) and the patient's preference, no oncologic therapy was performed, whilst she remained on an ongoing strict gluten-free diet. At the last visit (March 2017), the patient was in a good clinical condition and blood biochemistry values were normal.

SYSTEMATIC REVIEW OF THE LITERATURE

Review of the literature was performed by using PubMed. The search was limited to English and Italian language articles through April 2017, by using the exploded medical subject heading terms 'celiac disease' and 'intestinal adenocarcinoma'. Boolean operator (NOT, AND, OR) were also used in succession to narrow and widen the search. References of the retrieved articles were reviewed to searching for potentially missed

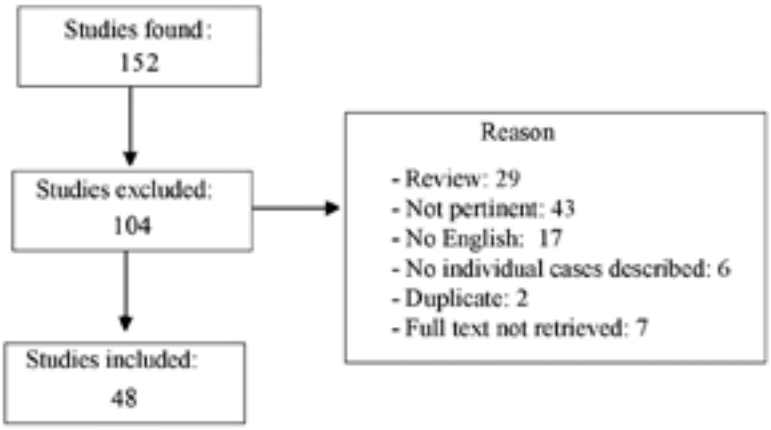

Fig. 2. Studies identified in the literature.

publications. Only those publications regarding adenocarcinoma of the small bowel were considered, whilst other neoplasia types (lymphoma, GIST, NET, etc.) and adenocarcinoma of other sites were excluded. A total of 152 studies were identified and, following evaluation of abstracts or full paper, 44 studies meeting the inclusion criteria were included in this pooled data analysis [5-49]. The reasons for the leading studies' exclusion are provided in Fig. 2. Overall, by considering also our case report, there were data of 136 patients from Italy (35 cases), USA (33), UK (32), The Netherlands (17), Austria (4), Australia (3), Morocco (3), Ireland (2), and 1 case from Czech Republic, Germany, Iran, Israel, Switzerland, Tunisia, and Turkey. There were 68 males and 63 females (not available: 5) with a mean age of 55.4 ± 13.2 years. The main symptom prompting clinical investigation was available for 70 patients, including vomiting (40 patients, 57%), anemia (10 patients, 14%), weight loss (9 patients, 13%), intestinal bleeding (5 patients, 7%), abdominal mass (4 patients, 6%), and perforation (2 patients, 3%). The cancer was simultaneously diagnosed with CD in 45 (38%) cases, whilst it developed in 73 (62%) patients within a median of 7 years (range: 1-50 yrs) from CD diagnosis (not available: 19). However, as many as 25 (34%) out of these 73 cancers were diagnosed within 2 years from CD diagnosis (1 year: 17; 2 years: 8), so that only the remaining 48 (66%) cancers may be considered true incident cases. By considering only these 48 cases, adenocarcinoma developed in 38 patients during a strict gluten-free diet and in 10 patients not performing (4 cases) or not compliant with (6 cases) the diet. The site of adenocarcinoma and the tumor staging are shown in Table I.

Table I. The site of neoplasia in the small bowel and tumor staging.

Tumor site (N = 131)	Number (%)
Duodenum	34 (26)
Jejunum	86 (66)
Ileum	11 (8)
Tumor staging (N = 78)	
I	8 (10)
II	30 (38)
III	25 (34)
IV	14 (18)

By comparing the tumor stage of the first 39 cases described (until 2004) with that of the 39 cases reported thereafter, the rate of cases diagnosed in stage I-II significantly increased in the last period (40% vs 59%; P = 0.044). Finally, multiple (synchronous or metachronous) small bowel adenocarcinomas occurred in 5 patients. In detail, a patient developed 2 synchronous tumours 1 year following gluten-free diet, 2 patients were diagnosed with two synchronous cancers following 1 and 9 years from the previous one, and another 2 patients developed a metachronous cancer 2 and 15 years from the previous surgical cancer removal.

DISCUSSION

The clinical history of our patient has some peculiarities. The presence of rectal bleeding and a family history for colorectal cancer prompted the colonoscopy. An adenoma was removed and the mild rectal bleeding episodes were attributed to hemorrhoids. Successively, the onset of anemia with positive FOBT in an elderly patient with a previous polypectomy was interpreted as a potential missing of a colorectal cancer. Only at this point was CD diagnosed in the 78-year-old patient. This was an unexpected diagnosis due to the presence of only vague abdominal symptoms in the previous clinical history. Moreover, when the upper endoscopy was performed and CD was diagnosed, the clinical work-up was deemed conclusive, particularly when a strict gluten-free diet was associated with a general improvement and recovery of anemia. Only when anemia recurred one year later and a further ileo-colonoscopy was negative, a videocapsule study was performed. Indeed, the onset of new symptoms in CD patients with a complete response to gluten free diet should alert physicians to the possibility of small bowel neoplasia [1, 2]. The VCE study revealed a duodeno-jejunal tumor, suggestive of lymphoma. The tumor was successfully removed by laparoscopy, and a stage III adenocarcinoma was evidenced.

It has been estimated that the risk of small bowel adenocarcinoma is 60-80 fold increased in CD patients as compared to controls, with an expected lifetime risk of approximately 1% [50]. Our systematic review of literature included a total of 136 patients with adenocarcinoma in CD. Unexpectedly, the vast majority of cases (overall 74%) were reported from Italy, UK and USA, that is countries where the incidence and prevalence of CD are grossly comparable with those of several other countries [51]. Therefore, a publication bias is the plausible explanation for such a finding. There was a similar prevalence of males and females in the collected series, the mean age at diagnosis was 55 years, the median between CD diagnosis and adenocarcinoma development was 7 years, and vomiting (with or without other symptoms) was the most prevalent symptom. The jejunum (mainly the proximal portion) was the most frequently involved intestinal site, with <10% of cases located in the ileum. Disappointingly, as many as 60% of adenocarcinoma cases were detected as a complication of undiagnosed CD or within 2 years from diagnosis, suggesting that more efforts are required to improve early diagnosis of CD in clinical practice. Indeed, it has been found that asymptomatic/subclinical presentation of CD has been significantly raised over the past 25 years [48], so that the CD diagnosis is increasingly evidenced in adult or even elderly subjects [52].

Of note, among the 48 true incident (i.e. diagnosed >2 year following CD diagnosis) adenocarcinoma cases, 38 patients were strictly adherent to the gluten-free diet and 10 patients were partially or not adherent to the diet. Generally, near 80% and 20% CD patients are adherent and not adherent to diet, respectively [48]. While a direct calculation is prevented, these data would suggest that the risk for intestinal adenocarcinoma in CD patients is not substantially reduced by the gluten-free diet. This could depend on the observation that mucosa remains flat and inflamed in a definite quote of CD patients even after an appropriate dietary treatment [53].

Regrettably, intestinal adenocarcinoma in CD patients is still diagnosed in an early stage only in a minority of cases (10%). Specific protocol for surveillance in CD patients could

be implemented, at least for patients considered at an increased risk of intestinal neoplasia, such as those diagnosed with CD in adulthood or even elderly [2, 54]. Different radiological and endoscopic tools, particularly VCE and double-balloon enteroscopy are now available to allow tailoring the follow-up in selected CD patients [36, 54-56].

CONCLUSION

Although improved, diagnosis of small bowel adenocarcinoma in CD patients is established in an advanced stage in the majority of cases, the two conditions being discovered at the same time or within two years of CD diagnosis in more than half of the patients. Tailored follow-up in a subgroup of CD patients at an increased risk could be implemented.

Conflicts of interest: None to declare.

Authors' contributions: A.Z. and R.L. conceived the study. V. D. F., R.M. and L.R. performed the systematic review of literature. A.Z. edited the manuscript.

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