

## Jejunitis and brown bowel syndrome with multifocal carcinogenesis of the small bowel

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### Abstract

This is the first report describing a case where prolonged, severe malabsorption from brown bowel syndrome progressed to multifocally spread small bowel adenocarcinoma. This case involves a female patient who was initially diagnosed with chronic jejunitis associated with primary diffuse lymphangiectasia at the age of 26 years. The course of the disease was clinically, endoscopically, and histologically followed for 21 years until her death at the age 47 due to multifocal, metastasizing adenocarcinoma of the small bowel. Multiple lipofuscin deposits (so-called brown bowel syndrome) and severe jejunitis were observed microscopically, and sections of the small bowel showed dense lymphoplasmacytic infiltration of the lamina propria as well as blocked lymphatic vessels. After several decades, multifocal nests of adenocarcinoma cells and extensive, flat, neoplastic mucosal proliferations were found only in the small bowel, along with a loss of the mismatch repair protein MLH1 as a long-term consequence of chronic jejunitis with malabsorption. No evidence was found for hereditary nonpolyposis colon carcinoma syndrome. This article demonstrates for the first time multifocal carcinogenesis in the small bowel in a malabsorption

syndrome in an enteritis-dysplasia-carcinoma sequence.

**Key words:** Brown bowel syndrome; Carcinogenesis of the small bowel; Enteritis-dysplasia-carcinoma sequence; Malabsorption

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**Core tip:** Severe malabsorption associated with brown bowel syndrome can progress to multifocally spread small bowel adenocarcinoma. This report describes the clinical course of a woman suffering from a long-lasting malabsorption syndrome who developed small bowel adenocarcinoma in an enteritis-dysplasia-carcinoma sequence. After several decades of chronic jejunitis with malabsorption, multifocal nests of adenocarcinoma cells were found only in the small bowel without evidence of hereditary nonpolyposis colon carcinoma syndrome.

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## INTRODUCTION

Brown bowel syndrome is caused by a lipofuscinosis, primarily in the small bowel, which is characterized macroscopically by an orange-brown appearance. The brown coloring occurs from increased lipofuscin aggregates, particularly in the apical enterocytes, which are thought to result from vitamin E deficiency caused by longtime chronic malabsorption<sup>[1-3]</sup>. This report describes the case of a woman with brown bowel syndrome that progressed over several decades into multifocally spread small bowel adenocarcinoma. To the best of our knowledge, this is the first presentation of a small bowel adenocarcinoma caused by long-term malabsorption and brown bowel syndrome.

## CASE REPORT

### **Clinical presentation at diagnosis**

The patient initially complained of watery diarrhea, recurrent attacks of vomiting bile, stomach cramps, recurrent edemas, and tympanites at the age of 26 years. Although both of her sisters were healthy, her father suffered from Menière's disease and her mother had hypertension and hypercholesterolemia. Otherwise, her family history was unremarkable and contained no reports of malignancies, including colorectal cancer. The patient was allergic to pork and to several medications, but was otherwise healthy. A clinical examination at this time showed that she was

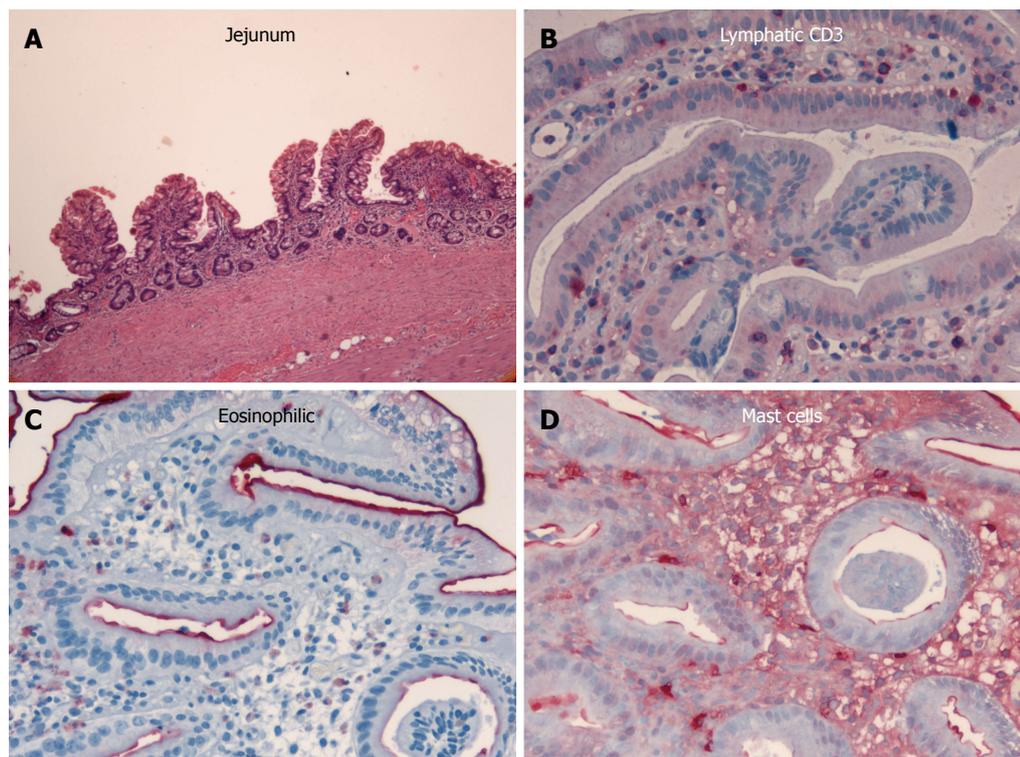
considerably underweight (body mass index, 17.7 kg/m<sup>2</sup>) and short (158 cm). She had increased kyphosis of the thoracic spine associated with funnel chest, a clubfoot position with pronounced edema in the ankle and lower leg, ascites, and periodontitis with heavy gum bleeding. Laboratory results indicated low-grade, normocytic anemia (hemoglobin, 11.8 g/dL; normal range: 12-16 g/dL), pronounced hypoproteinemia (4.5 g/dL; normal range: 6.6-8.3 g/dL), decreased erythrocyte sedimentation rate (1/3 mm/h), and hypogammaglobulinemia (IgG 509 mg/dL; normal range: 700-1600 mg/dL). The Gordon test (*iv* administration of 40  $\mu$ Ci <sup>51</sup>Cr-labelled albumin) showed abnormal (> 9%) excretion of the test substance in stool samples collected over 96 h (normal: < 1.5%), and confirmed a high-grade enteral loss of protein. These findings remained unchanged throughout the course of her disease, namely prominent intestinal protein loss (persistent hypoproteinemia, hypogammaglobulinemia) and vitamin (folate, vitamin B12, and D), electrolyte and zinc deficiencies, but without remarkable signs of systemic inflammatory reactivity (C-reactive protein < 10 mg/dL), and frequently with increased stool weights up to 780 g.

Transabdominal ultrasonography revealed normal parenchymatous organs, but with accentuated sonomorphology of the small bowel observed as increased wall thickness (4-6 mm), pronounced submucosa, and strict layer widening, which later progressed to a more hypoechoic small bowel appearance with layer loosening. Small bowel double-contrast imaging initially revealed hyperperistalsis and lymphonodular hyperplasia without any stenosis. Evaluations 12 years later revealed moderately dilated intestinal jejunal segments with flattened mucosa, diffuse edema, increased distance between loops, with some tubular, smooth narrowed loops.

The colonoscopic findings were normal at the initial presentation and throughout the course of disease. However, diffuse lymphangiectasia in the small bowel and chronic jejunitis were detected initially with esophagogastroduodenoscopy, and later with push enteroscopy. Differential diagnoses of malignant lymphoma, celiac disease, mesenteric lymph node metastases, Crohn's disease, rare intestinal manifestations of sarcoidosis or tuberculosis, Whipple's disease, retroperitoneal fibrosis, and cardiovascular disease (right ventricular insufficiency, vena cava or portal vein thrombosis) were excluded as possible causes. Endoscopic and histologic examinations subsequently confirmed a diagnosis of chronic malabsorption syndrome associated with exudative enteropathy as a result of prolonged intestinal primary lymphangiectasia and chronic jejunitis of undefined etiology (Figure 1).

### **Disease progression**

Over the 21-year course of her disease, the patient had > 30 hospital admissions at two university centers



**Figure 1** Histopathologic diagnosis of chronic malabsorption syndrome associated with exudative enteropathy as a result of prolonged intestinal primary lymphangectasia and chronic jejunitis of undefined etiology. A: The jejunum showed slight architectural deviations with flat mucosa due to partial villous atrophy; B: T cell lymphatic infiltrates were normal as seen in CD3 staining, which ruled out celiac disease and lymphoma; The amounts of C: Eosinophilic granulocytes; and D: Mast cells were normal, thus excluding mastocytosis and eosinophilic gastroenteritis. The histological sections were prepared with hematoxylin-eosin staining (magnification  $\times 40$ ) and additional immunohistochemistry was performed.

and two local hospitals. Her food tolerance declined and she failed to gain any weight, remaining at a body mass index of 16-18 kg/m<sup>2</sup> and requiring parenteral nourishment. Multiple drug treatment attempts (including loperamide, cholestyramine, and pancreatic enzymes) failed, and despite continued nutrition by percutaneous endoscopic gastrostomy (to avoid complications such as venous thrombosis), the diarrhea and intestinal protein loss persisted.

#### **Development of jejunal stenosis**

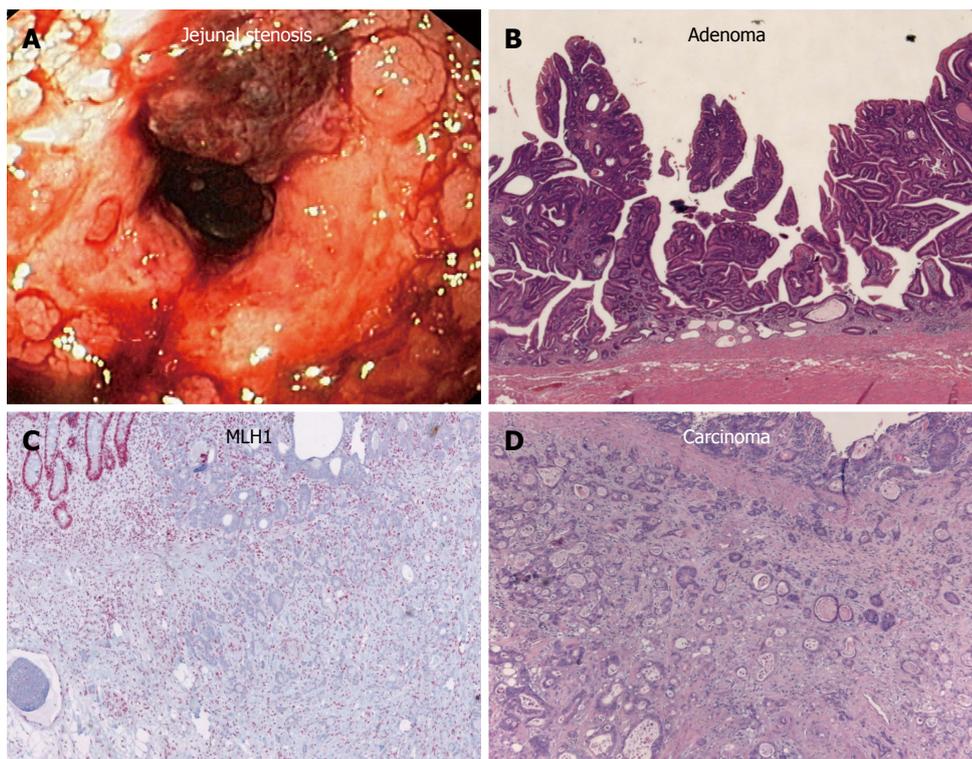
Twenty years after the initial diagnosis, the patient was again admitted to the hospital because of increasing abdominal colic, nausea, vomiting, and melena. An ultrasound revealed fluid-filled small bowel loops indicative of subileus, but without ascites. A short stenosis (about 25 mm long) was visualized in the middle part of the jejunum upon double-contrast small bowel (Sellink) imaging. Abdominal magnetic resonance imaging showed an abrupt transition from substantially dilated small bowel loops to non-dilated loops in the middle-right abdomen, but did not indicate a solid tumor mass. Thus, push enteroscopy and high-pressure balloon dilatation of the stenosis were performed (Figure 2A). Histology of the biopsy samples taken during enteroscopy showed the same features of chronic jejunitis associated with lymphangectasia that were observed 20 years before,

but no indication of malignant disease. Afterwards, a hemoglobin-effective (10.5 g/dL) hematemesis and hematochezia developed, which required emergency push enteroscopy. A Forrest IIB lesion in the area of the dilated stenosis was observed and treated with injections of suprarenin (1:100.000) and fibrin glue. However, the patient aspirated intestinal fluid and blood during the endoscopic procedure, developed asystole, and required cardiopulmonary resuscitation. She was then transferred to the intensive care unit for further treatment.

#### **Multifocal carcinogenesis**

The patient subsequently underwent segment resection of the jejunum. Histopathologic examination revealed a multicentric, poorly differentiated adenocarcinoma (Figure 2B-D). The tumor had infiltrated the blocked lymphatic vessel system (lymphangiosis carcinomatosa), and peritoneal carcinomatosis was detected at an incurable stage (pT4 [m] pN0 [0/1] L1 V0 R1). Other portions of the resected tissue exhibited foci of extensive, flat, neoplastic mucosal proliferation transitioning to adenocarcinoma, with signs of an enteritis-dysplasia-adenocarcinoma sequence, which is unusual in the small bowel. In addition, multiple lipofuscin deposits were discovered in the small bowel tissue, indicating brown bowel syndrome.

Eight months following the surgical resection, the



**Figure 2 Disease progression.** A: Push enteroscopy and high-pressure balloon dilatation of the stenosis were performed; Histology indicated the development of an B: Adenoma; and D: Carcinoma. Thus, 20 years of persistent inflammation led to malignancy according to an enteritis-dysplasia-adenocarcinoma sequence; C: Unaffected crypts showed strong nuclear MLH1 expression, while neoplastic tissue failed to express MLH1. Histological sections A-D were prepared with hematoxylin-eosin staining (magnification  $\times 40$ ) and additional immunohistochemistry was performed.

patient's general condition markedly deteriorated with colicky stomach pain, dyspnea, and additional weight loss (5 kg in 3 wk). In addition to ascites, bilateral pleural effusion, and pressure pain throughout the abdomen, bilateral pneumonic infiltrates were detected upon radiologic examination, and laboratory testing showed hypokalemia, hypocalcemia, hypoalbuminemia, and hypoproteinemia. Antibiotics and human albumin substitution therapy were administered and pleural and ascites puncture and drainage procedures were initiated. As a result, her general condition stabilized. However, she developed clinical symptoms of small bowel obstruction, which were confirmed radiologically and sonographically as mechanical ileus. An exploratory laparotomy was then performed, though further treatment was prohibited by the pronounced peritoneal carcinomatosis and obstructed ileus. The patient died 3 d later.

A postmortem examination demonstrated that, in addition to the known peritoneal carcinomatosis of the multifocal small bowel carcinomas and brown bowel syndrome (Figure 3), pleural carcinomatosis, lymphangiosis carcinomatosa, and pulmonary artery emboli had extended to the lungs. Further scientific evaluation of this disease was undertaken, including microsatellite instability diagnosis. Immunohistochemistry for MLH1 showed a considerable deficiency of the mismatch repair protein in the small bowel tissue (Figure 2D). In contrast, tumor specimens were

immunopositive for DNA repair proteins MSH2 and MSH6. Unfortunately, degradation of the DNA in the tumor specimen prohibited any further DNA analyses. However, the loss of the MLH1 repair protein was likely a consequence of the long-term chronic jejunitis and malabsorption, as there was no clinical evidence for hereditary nonpolyposis colon carcinoma syndrome.

## DISCUSSION

The adenoma-dysplasia-carcinoma sequence constitutes an important underlying cause of malignant tumor development in the lower gastrointestinal tract<sup>[4,5]</sup>. Moreover, diseases associated with chronic inflammation are risk factors for pancreatic carcinoma (chronic pancreatitis), cholangiocellular carcinoma, and colitis-associated colorectal carcinoma<sup>[4,5]</sup>. In the small bowel, celiac disease or polyposis syndromes (*e.g.*, familial adenomatous polyposis and Peutz-Jeghers syndrome) are risk factors for developing malignancy or primary extranodal lymphoma<sup>[5,6]</sup>. However, progression from enteritis to dysplasia and/or flat neoplasia and then to small bowel carcinoma as a consequence of a chronic inflammation has only been postulated in a few conditions, such as celiac and Crohn's diseases, and has not yet been systematically investigated or observed in individual patients<sup>[4,5,7]</sup>. Indeed, small bowel adenocarcinomas rarely develop beyond the ligament of Treitz, and tumor incidence further decreases distal to



**Figure 3** Postmortem confirmation of brown bowel syndrome associated with multifocal MLH1-positive small bowel adenocarcinoma.

this point<sup>[5,7,8]</sup>. The patient described in the present case did not have celiac disease (there was no response to a gluten-free diet and tests for celiac-specific antibodies [anti-TG2 and anti-endomysium IgA] were negative), Crohn's disease, or any of the polyposis syndromes. Rather, her chronic jejunitis and long-standing malabsorption syndrome were associated with primary diffuse lymphangiectasia. The clinical characterization of symptoms remained consistent throughout the > 20-year course of her disease, including the loss of intestinal proteins, electrolytes, nutrients and vitamins, subsequent vitamin E deficiency, and ultimately brown bowel syndrome. We postulate that the transformation to malignancy was caused by molecular and genetic changes in the small bowel that occurred during the longstanding period of malabsorption, similar to what has been described for colorectal carcinogenesis<sup>[9]</sup>. To our knowledge, this is the first report of multifocal carcinogenesis within the small bowel associated with severe malabsorption and brown bowel syndrome.

Histopathologic examinations from this patient over more than 20 years consistently indicated local, persistent inflammation, which induced neoplastic mucosal changes, and finally led to multifocal nests of adenocarcinoma cells. Thus, an enteritis-dysplasia-carcinoma sequence played a carcinogenic role in conjunction with a loss of the mismatch repair protein MLH1. Similar mechanisms are known to be involved in the carcinogenesis of colon carcinomas associated with chronically active ulcerative colitis<sup>[4,9]</sup>. Additionally, the loss of mismatch repair mechanisms

involving MLH1 or MSH2 have also been described in patients with celiac disease<sup>[10,11]</sup>. Thus, it is likely that the chronic, long-standing enteritis with continuous intestinal repair in the patient presented here resulted in inactivation of mismatch repair mechanisms. Loss of *MLH1* in hereditary nonpolyposis colon carcinoma syndrome has been reported to contribute to additional DNA replication errors and/or apoptosis failure<sup>[12,13]</sup>, which can cause multifocal spread of adenocarcinoma. However, the family history of the patient in the present case was negative for malignancy and no inflammatory or neoplastic lesions of the colon were found.

The severity of the malabsorptive state in this patient was reflected in the appearance of the brown bowel syndrome. The syndrome is thought to be the result of chronic malabsorption and vitamin E deficiency caused by intestinal lymphangiectasia associated with chronic jejunitis<sup>[14-16]</sup> or small bowel inflammation associated with intestinal malabsorption syndromes, such as celiac disease<sup>[3]</sup>. The characteristic lipofuscin deposits are typically found in the smooth muscle cells of the tunica muscularis, but can also occur in the lamina muscularis mucosae<sup>[1,2,16]</sup>. It is possible that the vitamin E deficiency or lipofuscinosis alters neuronal function in the small bowel and thus affects motility<sup>[1-3,17-19]</sup>. As conventional histologic staining methods often fail to reveal the lipofuscin deposits, specialized examinations, such as UV or electron microscopy, are required when this disease is suspected<sup>[1,14,16]</sup>. The deposits are thought to be products of mitochondria degeneration, and are rarely detected in other organs, *e.g.*, thyroid or intestinal lymph nodes, in brown bowel syndrome<sup>[1,2,15,16]</sup>.

The combined presence of brown bowel syndrome and small bowel adenocarcinoma has only been described previously in two reports<sup>[20,21]</sup>, though the connection between the two has not been clearly established. However, the role of vitamin E deficiency in small bowel carcinogenesis cannot be excluded and requires further study<sup>[21,22]</sup>. The appearance of brown bowel syndrome may also indicate clinical deficiencies in other nutrients involved in the regulation of intestinal epithelial proliferation, such as folate and vitamin D. Despite the continuous supplementation with essential nutrients that our patient received, reduced levels of folate occurred intermittently, which could have contributed to the inactivation of mismatch repair mechanisms, as has been reported in ulcerative colitis<sup>[12]</sup>.

In conclusion, this article provides the clinical observations from a greater than 20-year disease course of primary diffuse lymphangiectasia with persistent chronic jejunitis. Moreover, this report demonstrates for the first time multifocal carcinogenesis within the small bowel in association with loss of a DNA mismatch repair mechanism in a malabsorption syndrome. The evidence suggests that local enteritis activity caused the

dysplasia and neoplastic transformation and resulted in multifocal nests of small bowel adenocarcinomas, resembling the transformation process in chronic colitis<sup>[4,5]</sup>. The accompanying brown bowel syndrome and severe malabsorption may have further influenced the malignant transformation.

## COMMENTS

### Case characteristics

The patient initially complained of watery diarrhea, recurrent attacks of vomiting bile, stomach cramps, recurrent edemas, and tympanites.

### Clinical diagnosis

Severe malabsorption with a brown bowel syndrome progressed to multifocally spread small bowel adenocarcinoma.

### Differential diagnosis

Incidental small bowel adenocarcinoma.

### Laboratory diagnosis

Low-grade, normocytic anemia (hemoglobin, 11.8 g/dL); pronounced hypoproteinemia (4.5 g/dL); decreased erythrocyte sedimentation rate (1/3 mm/h); hypogammaglobulinemia (IgG 509 mg/dL); > 9% excretion in the Gordon test; C-reactive protein < 10 mg/dL; and increased stool weights, often up to 780 g.

### Imaging diagnosis

Small bowel obstruction that was confirmed as mechanical ileus by radiography, sonography, and endoscopy.

### Pathological diagnosis

Repeated histopathologic examinations consistently demonstrated local, chronic (20 years), persistent inflammation resulting in multifocal nests of adenocarcinoma cells.

### Treatment

The patient received supplementary nutritional treatment and was later fed by percutaneous endoscopic gastrostomy. Multiple drug treatment attempts (including loperamide, cholestyramine, and pancreatic enzymes) failed to reduce malabsorption.

### Related reports

This is the first known report of a small bowel adenocarcinoma caused by long-term malabsorption and brown bowel syndrome.

### Term explanation

Brown bowel syndrome is caused by long-term chronic malabsorption, which finally leads to formation of lipofuscin aggregates/lipofuscinosis of the small bowel. Small bowel adenocarcinoma is a rare malignant tumor of the small intestine.

### Experiences and lessons

This article provides observations from a greater than 20-year disease course of primary diffuse lymphangiectasia with persistent chronic jejunitis, and demonstrates for the first time multifocal carcinogenesis within the small bowel in association with loss of a DNA mismatch repair mechanism in a malabsorption syndrome.

### Peer-review

The authors conclude that long-term malabsorption associated with brown bowel syndrome may cause dysplasia and neoplastic transformation, ultimately leading to the formation of multifocal nests of small bowel adenocarcinoma,

resembling the transformation process in chronic colitis. The article highlights the clinical characteristics of this tumor and provides information about its development over course of the disease.

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