

# Unknown Complicated Celiac Disease as an Unexpected Finding in Patients Investigated with Capsule Endoscopy for Crohn's Disease. A Case Series

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Received: 10.11.2012  
Accepted: 20.12.2012

## ABSTRACT

Atypical symptoms of celiac disease may cause a late diagnosis, revealed by the onset of complications, which may inaccurately be attributed to Crohn's disease, as manifestations frequently overlap. Assessing the entire small bowel mucosa, capsule endoscopy may be an accurate procedure in these challenging situations. We present four Crohn's disease patients diagnosed with ulcerative jejunoileitis complicating celiac disease after capsule endoscopy procedure. In three of these patients, the ulcerative jejunoileitis led in time to stricture formation, suggesting Crohn's disease. Administration of non-steroidal anti-inflammatory drugs made the diagnosis even more difficult in one case. In patients with Crohn's disease not responding to immunosuppressive or biological treatment, complicated celiac disease should be considered and capsule endoscopy should be performed for reassessing the diagnosis.

**Key words:** celiac disease – Crohn's disease – capsule endoscopy.

## INTRODUCTION

Celiac disease is more and more often diagnosed in patients with minor or atypical symptoms, such as dyspepsia, heartburn, bloating, constipation, osteopenia, polyneuropathy, stomatitis or infertility [1-3]. It is assumed that many of these patients remain undiagnosed until complications, such as jejunoileitis, enteropathy-associated T-cell lymphoma or adenocarcinoma develop. There are no literature data regarding the diagnostic rate of celiac disease in such patients. Other challenges for diagnosing celiac disease are the "patchy distribution" of mucosal atrophy in some cases, and the association with immunoglobulin A immunodeficiency or with autoimmune disorders such as inflammatory bowel diseases.

In recent years, the extensive use of capsule endoscopy has proved to be a useful, noninvasive procedure with a high diagnostic yield both in celiac disease and in Crohn's disease. The positive predictive value of typical mucosal atrophy findings, suggestive for celiac disease is very high, 96.5-100% [4-9]. For Crohn's disease lesions, the positive predictive value of capsule endoscopy investigation was reported to be only 77% in patients with a highly suspicious clinical background [10], as ulcers may also be found in jejunoileitis complicating celiac disease, infectious diseases or non-steroidal anti-inflammatory drugs (NSAIDs) - induced enteropathy. As most of the published studies have focused on the diagnostic yield of capsule endoscopy for specific small bowel pathology, there are no sufficient data regarding the frequency of unexpected pathology. To the best of our knowledge, only one case of ulcerative jejunoileitis complicating celiac disease was reported to be diagnosed with capsule endoscopy in a patient suspected with Crohn's disease [11].

In our experience, comprising 201 capsule endoscopies performed in the last 7 years, 47 patients were investigated for Crohn's disease. Four of them were diagnosed with complicated celiac disease by using this procedure.

## CASE 1

A 23 year-old female was diagnosed with Crohn's disease 8 months prior to capsule endoscopy procedure, based on clinical

symptoms (intense abdominal pain, fever chronic diarrhea for more than 6 weeks), inflammatory markers, ileoscopy with deep ulcers suggestive of Crohn's disease, biopsy with chronic inflammatory infiltrates, without specific granuloma. As she was regularly using NSAIDs, a differential diagnosis was suggested, but the Crohn's disease features were dominant: fever and inflammatory markers. NSAIDs were stopped and she was treated with corticotherapy and azathioprine. The symptoms improved in the first two months and then worsened, with abdominal pain as the main complaint. The capsule endoscopy (Given, Pillcam) revealed atrophic mucosa in the proximal jejunum with a mosaic pattern (Fig. 1), multiple ulcers and inflammatory areas causing strictures in the jejunum and ileum (Fig. 2). The capsule was eliminated after three days. Biopsies from the duodenum revealed Marsh III atrophic mucosa. The diagnosis was celiac disease with severe jejunoileitis. She refused an enteroscopy and after a gluten free diet was started, the symptoms improved. After 18 months, repeat capsule endoscopy revealed villi pattern in jejunum, improvement of previously ulcerated mucosa, although some congestive and ulcerative areas were still present (Fig. 3). She was lost from the follow up.

## CASE 2

A 35 year old male was treated with azathioprine for five years and with infliximab for two years for ileal Crohn's disease (suggestive ileoscopy). As the symptoms did not improve, the patient refused further treatment. At presentation in our department, a severe malabsorption syndrome was present, as well as ascites. Capsule endoscopy revealed a severely atrophic mucosa in the duodenum and jejunum, with nodular pattern and fissures (Fig. 4). Multiple and profound ulcers were present in the jejunum. The capsule went beyond one ulcerative stricture area on the jejunum (Fig. 5), but could not pass another ulcerated, strictured area, suggestive for malignancy. An oral route enteroscopy was performed for biopsy and capsule recovery. Air insufflation during enteroscopy pushed the capsule from stricture to stricture and it could not be recovered. Duodenal biopsy revealed Marsh II lesions; in jejunum villous atrophy, erosions, inflammatory cells infiltrates were present, but without malignancy in the ulcerated, stenotic areas. The patient refused surgery and the malabsorption syndrome improved on a gluten free diet. After eight weeks, an emergency operation was performed for intestinal occlusion, with resection of distal jejunum. No specific findings for Crohn's disease or malignant cells were found on the surgically removed specimen.

## CASE 3

A 22 year old male, diagnosed one year before with ileal Crohn's disease (ulcers on terminal ileum and ileocecal valve) was referred to our department for persisting diarrhea on corticotherapy. Capsule endoscopy revealed a typical aspect of atrophic mucosa in the duodenum and jejunum, and multiple erosions on the jejunum and ileum. Duodenal biopsies showed Marsh III changes. The gluten free diet improved the symptoms and at one year follow up, capsule endoscopy revealed a normal aspect of the duodenal and jejunal mucosa.



Fig. 1. Case 1. Capsule endoscopy: atrophic mucosa in the proximal jejunum with a mosaic pattern.

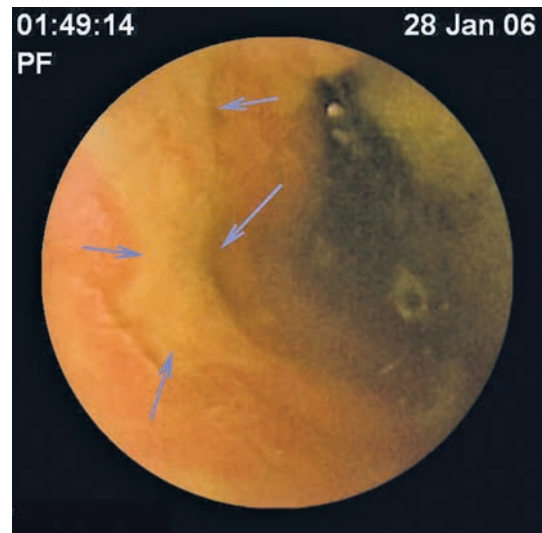


Fig. 2. Case 1. Capsule endoscopy: a large ulcer in the proximal jejunum.

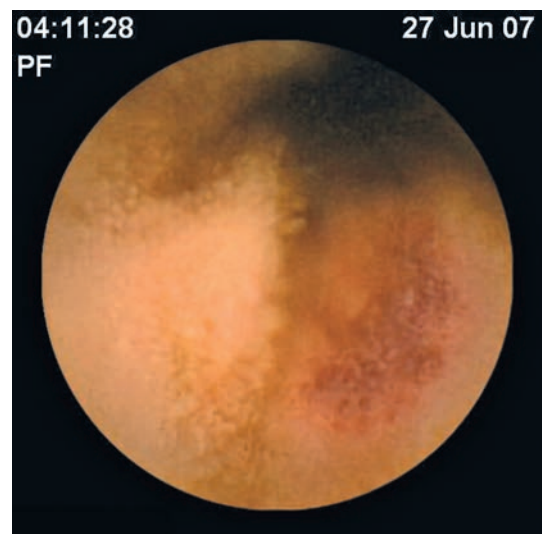


Fig. 3. Case 1 (after 18 months of gluten free diet). Capsule endoscopy: villi pattern in the jejunum with congestive area.

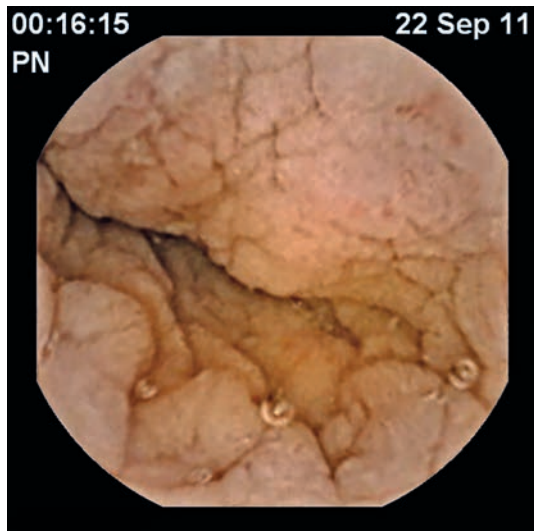


Fig. 4. Case 2. Capsule endoscopy: atrophic mucosa in the duodenum and jejunum, with nodular pattern and fissures.



Fig. 6. Case 4. Capsule endoscopy: ulcerated, bleeding area, with suspicion of malignancy, at the distal jejunum.



Fig. 5. Case 2. Capsule endoscopy: ulcerative stricture area on jejunum.

#### CASE 4

A 53 year-old male, with bronchial asthma, was referred for capsule endoscopy being suspected of small bowel Crohn's disease. He had colicative pain in left upper abdominal quadrant, weight loss, diarrhea and fever for two years, elevated inflammatory markers and anemia. Ileocolonoscopy did not find any lesions. CT enterography did not reveal parietal thickening or small bowel strictures. Capsule endoscopy found a typical aspect of jejunal mucosa atrophy, with a nodular pattern; an ulcerated, actively bleeding stenotic area, with suspicion of malignancy at the distal jejunum (Fig. 6). Capsule endoscopy did not pass over the stenotic area until the 5th day. Spiral enteroscopy was performed and multiple biopsies prelevated. Histological examinations revealed Marsh III features from the atrophic areas, chronic inflammatory infiltrates and erosions. The immunohistochemical staining did not identify malignant cells. After six months on a gluten free diet, the symptoms and the biological parameters improved.

#### DISCUSSION

In the last years, literature focused on the challenges in the diagnosis of celiac disease, as most of the patients have atypical forms, with few or even without gastrointestinal symptoms [3]. Delay in recognizing this disease may lead to severe complications, such as ulcerative jejunoileitis or gastrointestinal malignancy [12]. The clinical onset of these complications with abdominal pain, fever, weight loss, subocclusion, elevated inflammatory markers could also make the diagnosis difficult.

Ulcerative jejunoileitis is characterized by multiple chronic ulcers that could lead in time to stricture formation, simulating Crohn's disease [11, 12], as illustrated by our case series. The diagnosis is even more challenging as there are reports in the literature regarding the coexistence of these two disorders, on the background of genetic similarities [13].

Although most of the studies report the usefulness of capsule endoscopy for the diagnosis of ulcerative jejunoileitis in refractory celiac patients, there is only one report on the diagnosis of celiac disease by capsule endoscopy in a patient with suspected Crohn's disease [11].

Capsule endoscopy is presently a widely used procedure, with good diagnostic yield for both Crohn's disease and celiac disease as it is able to visualize the mucosa with 8 fold magnification. For the differential diagnosis of celiac disease and Crohn's disease on capsule endoscopy, ulcers, inflammatory areas, strictures and atrophy have to be considered. The sensitivity of capsule endoscopy is very high in detecting "mucosal breaks" of the small bowel, but the specificity is low, as erosions and ulcers are also found in infectious diseases, inflammatory diseases (Crohn's disease, vasculitis, celiac disease, eosinophilic enteritis), NSAIDs use, ischemia, after radiotherapy [14, 15] and even in 14% of the normal subjects [16]. In daily practice, in patients highly suspected of having small bowel Crohn's disease, capsule endoscopy findings such as ulcers, ulcerative stenosis and areas of villous atrophy could lead to a positive diagnosis in half of the patients [17]. The atrophic mucosa changes, highly specific for celiac disease, are

scalloping, mosaicism, micronodularity and reduction of folds [2], corresponding with Marsh III histological features. Mucosal changes are frequently continuous, duodenum being the most affected segment [7]. As already mentioned, the positive predictive value for these findings detected by capsule endoscopy is very high, 96.5-100% [4-9]. Based on these criteria, we also diagnosed a previously unknown celiac disease, and confirmation came by histology and improvement on gluten free-diet.

Narrowing ulcers of the intestinal lumen are frequently considered a feature of Crohn's disease. Recent evidence based on capsule endoscopy argues for similar findings among NSAIDs users [17]. The same pattern was reported in celiac disease [11], causing even intestinal obstruction [18]. However, some authors questioned this as being a separate entity, as most of the patients were eventually diagnosed with lymphoma [19]. In our case series, three patients presented ulcerated strictures, which caused capsule retention. The clinical outcome was good in two patients, but one patient required surgical removal. Histology, imunohistochemistry and follow up of our patients did not document malignancy in any of these cases. Whether NSAIDs triggered or worsened the ulcerative lesions in the first case, remains unclear.

The treatment of ulcerative jejunoileitis consists of a gluten free diet in association with immunosuppressive drugs, even biological therapy such as that used for Crohn's disease. The effect of immunosuppressive treatment without a gluten free diet has not been reported, since the published studies involved patients with known celiac disease. In our Case 1, prednisone and azathioprine did not influence the symptoms. The anti-TNF alpha drug used for two years had also no beneficial effect in Case 2.

The limitations of this case series report are the retrospective analysis of cases and the inclusion of patients with "typical" atrophic pattern visualized by capsule endoscopy. Patients with "suspected villous pattern" were not included. Despite these limitations, this report emphasizes the role of capsule endoscopy in the differential diagnosis between Crohn's disease and complicated unknown celiac disease.

## CONCLUSION

In patients with Crohn's disease not responding to immunosuppressive or biological treatment, complicated celiac disease should be considered and capsule endoscopy should be performed for reassessing the diagnosis.

**Conflicts of interest:** Nothing to declare.

**Acknowledgements:** This work was supported by a grant for young researchers (27020/15.11.2011) from the University of Medicine and Pharmacy, Cluj-Napoca, Romania.

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