CASE REPORT

Wireless capsule endoscopy as a tool in diagnosing autoimmune enteropathy

Eva-Marie Gram-Kampmann,¹ Søren T Lillevang,² Sönke Detlefsen,³ Stig Borbjerg Laursen¹

¹Department of Medical Gastroenterology and Hepatology, Odense University Hospital, Odense C, Denmark

²Department of Clinical Immunology, Odense University Hospital, Odense C, Denmark

³Department of Pathology, Odense University Hospital, Odense C, Denmark

Correspondence to

Dr Eva-Marie Gram-Kampmann, Eva.Gram-Kampmann@rsyd.dk

Accepted 18 June 2015

SUMMARY

Autoimmune enteropathy (AE) is an immune mediated illness of the intestinal mucosa. The cause is unknown, and the diagnosis is based on typical characteristics displayed. There is no gold standard for treatment. We present two adult cases of AE and demonstrate the challenges in establishing the diagnosis. The extensive diagnostic work up excluded other more common causes of protracted diarrhoea. Wireless capsule endoscopy (WCE) displayed universal small intestinal mucosal damage with shortened villi that led to the suspicion of AE in both patients. The diagnosis was confirmed with microscopy, showing shortened villi, villous blunting and hyperplasia of crypts in both patients. In one patient, deep crypt lymphocytosis with minimal intraepithelial lymphocytosis was found as well. Both patients were successfully treated with high-dose immunosuppressant therapy to induce and maintain remission. Use of WCE as a diagnostic tool was invaluable in establishing the diagnosis of AE.

BACKGROUND

Autoimmune enteropathy (AE) is a rare disorder, caused by immune-mediated damage to the intestinal mucosa, leading to protracted severe diarrhoea and weight loss from malabsorption. The cause of AE is unknown.¹ Antibodies directed against the intestinal brush border or the cytoplasm of enterocytes have been identified in most patients with AE.² These antibodies were previously believed to play a central role in the pathogenesis.³ AE is mainly a rare infant disorder affecting less than 1/100 000.⁴ It is even less common in adults, where only a few cases have been reported. The treatment is challenging and based on immunosuppression, and long periods of treatment with parenteral nutrition are needed with severe impact on the quality of life. Immunosuppressive treatment in adults has been used in case reports and includes corticosteroids together with a wide range of immunosuppressants.^{5–9}

We report two adult cases of AE to demonstrate the difficulties in establishing the diagnosis, use of mycophenolate mofetil (MMF) as a treatment option and the beneficial use of Wire Capsule Endoscopy (WCE). The proposed criteria for diagnosis are listed in [table 1](#).

CASE PRESENTATION**Case 1**

The first patient was a 33-year-old man with a 5-week history of watery diarrhoea accompanied by mild lower abdominal pain. There was no family history of gastrointestinal disease or autoimmune disease. The patient smoked 10 cigarettes a day. The number of bowel movements attained 20/day and there was an unintended weight loss of 10–12 kg from his premonitory weight of 82 kg, height 1.84 m and body mass index (BMI) of 24.5 kg/m². He was completely healthy except for a presumed diagnosis of psoriatic arthritis 1½ years earlier. He had used non-steroidal anti-inflammatory drugs (NSAIDs), but discontinuation resulted in only minor improvement of bowel function. Short-course treatments with ciprofloxacin and loperamide had no effect on the diarrhoea. There was no history of allergies, no recent travelling and no family history of gastrointestinal disease, immunological diseases or amyloidosis. The physical examination was normal, except for paleness and signs of rapid weight loss. When attending for ileocolonoscopy 1 week later, he had developed a complete loss of appetite and a further 5 kg weight loss. The 24-h stool volume amounted to 5–7 L/day. The output was unchanged even though the patient was unable to eat due to nausea. He suffered from faecal incontinence, was confined to bed and immediately admitted to our department with a need for parenteral nutrition and intravenous fluids.

Case 2

For the second patient, a 28-year-old woman, the medical history was similar. There was no family

CrossMark

To cite: Gram-Kampmann E-M, Lillevang ST, Detlefsen S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207931

Table 1 Criteria for diagnosis and small bowel histology in autoimmune enteropathy¹⁰

Proposed criteria of AE diagnosis	Specific small bowel histology
Adult-onset chronic diarrhoea with malabsorption	Partial/complete villous blunting
Exclusion of other causes of small bowel villous atrophy	Deep crypt lymphocytosis
Specific small bowel histology (right column)	Increased crypt apoptotic bodies
If antienterocyte antibodies and/or antigoblet cell antibodies are present, they are supportive of the diagnosis	Minimal intraepithelial lymphocytosis
AE, autoimmune enteropathy.	

history of autoimmune disease, gastrointestinal disease or pancreatitis. She stopped smoking 6 years prior to development of the disease. She was admitted to a regional hospital about 1 year later than case 1. Premorbid weight was 91.8 kg, height 1.63 m and BMI 34.6 kg/m². She had a 10-week history of diarrhoea, multiple bowel movements and an unintended weight loss of 20 kg. One month prior to admission, she had given birth by caesarean section. Stool output varied between 5 and 7 L a day in spite of fasting, and the patient had severe hypokalaemia and hypophosphataemia. She had nausea and vomiting but no abdominal pain. In her medical history, there was only a short period of self-limiting diarrhoea 1 year earlier. At admission, she also required intravenous fluids and parenteral nourishment for survival.

INVESTIGATIONS

For case 1, all diagnostic investigations were performed in our department, while for case 2, almost all investigations were performed at the regional hospital where she was admitted. The time course stretched over several months for both patients.

Case 1

Blood tests showed signs of inflammation, hypokalaemia, slightly elevated serum orosomucoid (S-orosomucoid; 1.27 g/L) and elevated faecal calprotectin (750 µg/g). Thyroid-stimulating hormone (TSH), serum amylase and IgA, IgE and IgG, were all within normal ranges. Serologic tests for coeliac disease were negative, as were human leucocyte antigen (HLA) typing for HLA DQ2 and DQ8. A trial lactose-free diet and gluten-free diet supervised by a dietician had no effect on stool volume. No pathogens or parasites were found in stool culture or microscopy and there was no blood or pus in the stools. Combined antibody and antigen testing for HIV was negative. Plasma vasoactive intestinal peptide (P-VIP), serum-gastrin and a 24 h urine test for catecholamines were all normal. On abdominal CT scan and MRI, the only abnormality was discrete thickening of the duodenal wall. There were no signs of pancreatitis. An In-111 octreotide scan showed no signs of a neuroendocrine tumour. An upper endoscopy showed macroscopic villous atrophy and oedema in the second part of the duodenum. Microscopy showed villous blunting, villous atrophy and hyperplasia of the crypts (figure 1), together with mixed acute and chronic inflammation, and only focally and slightly increased intraepithelial lymphocytes. Culture and microscopy of the duodenal juice were negative for bacteria, giardia and other parasites. Ileocolonoscopy was performed on the suspicion of inflammatory bowel disease or microscopic colitis as the cause of diarrhoea. However, the mucosa in the ileum and right colon appeared macroscopically normal and there were only minor signs of inflammation from the left colonic flexure to rectum. Biopsies were normal, except for rectal biopsies, which showed acute and chronic inflammation, irregular crypts and cryptitis, but with no erosions or ulcerations.

In spite of intravenous fluids and nutrition, weight loss continued to lowest morbid weight of 64 kg corresponding to a BMI of 18.9 kg/m². Flow cytometry on duodenal biopsies and a F-18 fluorodeoxyglucose positron emission tomography/CT (F-18-FDG PET-CT) scan showed no signs of lymphoma. However, the small bowel needed to be examined further, starting with a WCE. This showed that the macroscopic changes of the mucosa included the entire small bowel (figure 2). Indirect immunofluorescence supported a suspected diagnosis of AE by confirming presence of antienterocyte and goblet cell antibodies. Briefly, sections of monkey intestinal tissue were incubated with

Figure 1 At microscopy, villous blunting, shortened villi and crypt hyperplasia are found (H&E stain).

patient's serum diluted 1:10 for 30 min, and washed and stained with fluorescein isothiocyanate-conjugated goat anti-human IgA and IgG. Sections were studied in a fluorescence microscope and scored on a semiquantitative scale from negative to strongly positive (+++). Typical enterocyte antibodies appear as a linear staining of the brush border (figure 3A), whereas goblet cell antibodies stain goblet cell mucus in a lumpy pattern (figure 3B).

Case 2

The diagnostic investigation programme for the female patient was very similar to case 1. Inflammatory markers were elevated with S-orosomucoid >4 g/L and faecal calprotectin elevated to 450 µg/g. TSH, amylase and IgA, IgG and IgM, were within normal ranges. Stool culture and microscopy, screening and

Figure 2 Wireless capsule endoscopy (WCE) findings in the male patient. WCE image of affected small bowel showing shortened villi.

Figure 3 (A) Image of enterocyte antibodies lining the small bowel mucosa and (B) goblet cell antibodies.

HLA typing for coeliac disease, screening for HIV, P-VIP and P-chromogranine A, and a 24 h urine screening for laxatives and catecholamines, were all normal. There was no detection of blood in the stools. However, antinuclear antibodies (ANA) and antimitochondrial antibodies (AMA) were positive, and a lactose tolerance test showed impaired absorption. A trial gluten-free diet and lactose-free diet had no effect on symptoms.

In medical imaging, abdominal ultrasound, CT of the thorax and abdomen and abdominal MRI, were all without pathological findings, including no signs of pancreatitis. An upper and a lower endoscopy were both macroscopically normal. However, biopsies

from the duodenum showed mixed inflammation, colonic biopsies were normal and biopsies from the terminal ileum showed atrophic villous mucosa with histiocytosis and increased crypt granulocytes, but no granulomas or increased intraepithelial lymphocytosis. A WCE was at first interpreted as being normal. Repeated serological screening and HLA-typing for coeliac disease were negative. Repeated upper endoscopy now revealed oedema, villous atrophy and aphthous ulcerations of the duodenal mucosa. Microscopy showed villous blunting and atrophy, and crypt hyperplasia (figure 4A). Of note, there was focal deep crypt lymphocytosis with minimal intraepithelial lymphocytosis (figure 4B, C). Culture and microscopy of duodenal juice were without abnormal microbiological findings. Flow cytometry on duodenal biopsies ruled out lymphoma. A FDG-PET-CT scan indicated inflammatory activity throughout the whole small intestine and colon, but no signs of lymphoma and no wall thickening.

Weight loss continued to lowest weight of 64 kg and BMI 24.1 kg/m². It was decided to re-evaluate the WCE recording, which was found to show shortened, blunted villi throughout the entire small bowel, compatible with an autoimmune villous disease (figure 5). The previously described immunological evaluation of possible presence of antienterocyte and goblet cell antibodies was negative.

DIFFERENTIAL DIAGNOSIS

The diagnosis of AE is challenging, as the disease is rare, and other more common causes of diarrhoea and villous atrophy (infectious enteritis, coeliac disease, inflammatory bowel disease, NSAID-induced enteritis, lymphoma, neuroendocrine tumour, HIV) should be excluded. However, in coeliac disease, there is a response to gluten-free diet therapy, which in both described cases had no effect on stool volume, texture of stool or further weight loss. Neither did a course of antibiotics or a lactose-free diet. As described above, the other differential diagnoses were excluded through an extensive investigation programme. The first patient was initially suspected of having NSAID-induced enteritis, but it soon became obvious that he lacked the typical small bowel lesions.¹¹

TREATMENT

Case 1

As the diagnosis was suspected, the patient started treatment with prednisone 60 mg/day orally. Stool frequency and volume now decreased rapidly, the appetite increased and the patient

Figure 4 (A) Duodenal mucosa with villous blunting, shortened villi and crypt hyperplasia. Note the focal infiltration of neutrophilic granulocytes (arrows) into the crypt epithelium (H&E stain). (B) Duodenal mucosa with deep crypt lymphocytosis (arrow) and minimal intraepithelial lymphocytosis (CD3 immunostaining). (C) Serial section of area shown in B (H&E stain).

Figure 5 Wireless capsule endoscopy findings from the small bowel in the female patient.

began to gain weight. Parenteral nutrition and intravenous fluids were discontinued. Ten days after starting treatment with prednisone, dosage was lowered to 40 mg/day and treatment with steroid-sparing azathioprine 150 mg/day was administered. A repeat upper endoscopy showed improved villous appearance and the patient was discharged a few days later.

Case 2

Corticosteroid treatment with high-dose prednisone 60 mg/day was instituted as soon as the similarity with case 1 became obvious. After a 2-week treatment with corticosteroids, there was clinical improvement with decrease in number of bowel movements, more solid output and a decrease in inflammatory markers. However, bowel output was still around 3 L a day. Intravenous corticosteroid treatment was, therefore, supplemented with azathioprine (150 mg/day). The bowel output decreased over the next 3 weeks, S-albumin and S-orosomucoid approached normal levels and the patient regained weight.

OUTCOME AND FOLLOW-UP

Case 1

Owing to side effects of azathioprine, the steroid-sparing treatment was changed to another purine-synthesis inhibitor, MMF 1 g two times per day. Clinical response has now been maintained for 2½ years with MMF and low-dose prednisolone. A rheumatologist re-evaluated the earlier diagnosis of psoriatic spondylitis and changed it to spondylitis associated with bowel inflammation. Several attempts to discontinue prednisone have been made, but every time this causes a flare in the rheumatological illness.

Case 2

Shortly after instituting azathioprine treatment, the patient developed side effects with elevation of liver function tests and relapse of diarrhoea, which required intensified parenteral nutrition and corticosteroid therapy. Azathioprine was, as for case 1, replaced with MMF, initially 1 g two times per day and later increased to 2 g two times per day for optimal effect. Some, but insufficient, recovery was seen and oral tacrolimus (2 mg two

times per day) was therefore added; the patient finally obtained full clinical improvement.

To date, the patient has regained all the lost weight and is in total clinical remission. Prednisone therapy is discontinued, but an attempt to reduce the dosage of MMF and tacrolimus failed, with relapse of diarrhoea.

DISCUSSION

AE in adults is a rare condition, although increasingly reported.⁹ The presented cases demonstrate the difficulties in establishing the diagnosis of AE. In both cases, the clinical picture was quite typical for AE,¹⁰ with exceedingly large volume diarrhoea, anorexia and weight loss. The excessive villous atrophy throughout the small bowel with ileum involvement caused the very large bowel output and dependence of intravenous fluids and nutrition for survival. In the second case, we benefitted from our recent experience with the first case, and acknowledged the diagnosis in shorter time.

The current diagnostic criteria are chronic diarrhoea with malabsorption and small bowel villous atrophy with deep crypt lymphocytosis, increased crypt apoptotic bodies and minimal intraepithelial lymphocytosis. It is important that other causes of villous atrophy are excluded.¹⁰ Existence of antienterocyte and/or antigoblet cell antibodies supports the diagnosis, but lack of antibodies does not exclude AE, if the typical clinical and histopathological findings are present. In a literature review by Bishu *et al*,² 15% of patients did not display antienterocyte antibodies, but had an associated autoimmune disease such as hypothyroidism. In our second patient, the detection of ANA and AMA indicated an autoimmune association.

In both described cases, the complete visualisation of the intestinal mucosa with WCE contributed to the diagnosis. WCE has not been a standard in the diagnostic work up, even though small bowel villous atrophy is one of the characteristics. In the study performed by Akram *et al*,¹⁰ 7 patients of 15 were examined with capsule endoscopy, and showed villous pathology restricted to the proximal small bowel in all patients but one, while we found shortened villi throughout the small bowel. WCE is a valuable diagnostic tool in a variety of diseases where mucosal damage is involved, such as coeliac disease and refractory coeliac disease.¹² However, in coeliac disease, capsule endoscopy does not contribute to diagnosis when compared with duodenal biopsies.¹³ In our cases, the capsule endoscopy raised suspicion of an enteropathy affecting the entire small bowel different from coeliac disease. The conspicuous findings were very short villi without the significant furrows and scalloping characteristic of coeliac disease. Hence, WCE can contribute to evaluate the extent of disease in the small bowel, particularly in areas that are difficult to biopsy. Together with microscopic examination of endoscopic biopsies, information about the extent as well as quality of pathological changes can be assessed.

There is no gold standard for treatment of AE. Standard dosage of azathioprine was successful, with both patients responding well, until they developed side effects, so it became necessary to choose an immunosuppressant with similar effects. MMF is generally well tolerated¹⁴ and is typically used after organ transplant or in autoimmune disorders.^{15 16} In one previous case report, MMF was used to induce remission of AE.¹⁷ Reports about tacrolimus treatment in AE are also found.^{7 8 18 19} The need for potent immune suppressants in addition to corticosteroids demonstrates the dependency of massive immunosuppression to treat and prevent relapse of this disease.

Learning points

- ▶ Autoimmune enteropathy (AE) should be considered in patients with large volume diarrhoea, anorexia, weight loss and excessive small bowel villous atrophy.
- ▶ Wireless capsule endoscopy can, particularly when combined with microscopy of endoscopic biopsies, be an important tool in establishing the diagnosis.
- ▶ Mycophenolate mofetil can be used for the treatment of AE.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Montalto M, D'Onofrio F, Santoro L, *et al.* Autoimmune enteropathy in children and adults. *Scand J Gastroenterol* 2009;44:1029–36.
- 2 Bishu S, Arsenescu V, Lee EY, *et al.* Autoimmune enteropathy with a CD8+ CD7-T-cell small bowel intraepithelial lymphocytosis: case report and literature review. *BMC Gastroenterol* 2011;11:131.
- 3 Blanco Quiros A, Arranz Sanz E, Bernardo Ordiz D, *et al.* From autoimmune enteropathy to the IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome. *Allergol Immunopathol (Madr)* 2009;37:208–15.
- 4 Catassi C, Fabiani E, Spagnuolo MI, *et al.* Severe and protracted diarrhea: results of the 3-year SIGEP multicenter survey. Working Group of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP). *J Pediatr Gastroenterol Nutr* 1999;29:63–8.
- 5 Carroccio A, Volta U, Di Prima L, *et al.* Autoimmune enteropathy and colitis in an adult patient. *Dig Dis Sci* 2003;48:1600–6.
- 6 Rolny P, Sigurjonsdottir HA, Remotti H, *et al.* Role of immunosuppressive therapy in refractory sprue-like disease. *Am J Gastroenterol* 1999;94:219–25.
- 7 von Hahn T, Stopik D, Koch M, *et al.* Management of severe refractory adult autoimmune enteropathy with infliximab and tacrolimus. *Digestion* 2005;71:141–4.
- 8 Daum S, Sahin E, Jansen A, *et al.* Adult autoimmune enteropathy treated successfully with tacrolimus. *Digestion* 2003;68:86–90.
- 9 Gentile NM, Murray JA, Pardi DS. Autoimmune enteropathy: a review and update of clinical management. *Curr Gastroenterol Rep* 2012;14:380–5.
- 10 Akram S, Murray JA, Pardi DS, *et al.* Adult autoimmune enteropathy: Mayo Clinic Rochester experience. *Clin Gastroenterol Hepatol* 2007;5:1282–90; quiz 45.
- 11 De Petris G, Lopez JL. Histopathology of diaphragm disease of the small intestine: a study of 10 cases from a single institution. *Am J Clin Pathol* 2008;130:518–25.
- 12 Akin E, Ersoy O. Capsule endoscopy in celiac disease. *Gastroenterol Res Pract* 2012;2012:676073.
- 13 Ersoy O, Akin E, Ugras S, *et al.* Capsule endoscopy findings in celiac disease. *Dig Dis Sci* 2009;54:825–9.
- 14 Zwerner J, Fiorentino D. Mycophenolate mofetil. *Dermatol Ther* 2007;20:229–38.
- 15 Czaja AJ. Autoimmune hepatitis: focusing on treatments other than steroids. *Can J Gastroenterol* 2012;26:615–20.
- 16 Tan T, Lawrance IC. Use of mycophenolate mofetil in inflammatory bowel disease. *World J Gastroenterol* 2009;15:1594–9.
- 17 Quiros-Tejeira RE, Ament ME, Vargas JH. Induction of remission in a child with autoimmune enteropathy using mycophenolate mofetil. *J Pediatr Gastroenterol Nutr* 2003;36:482–5.
- 18 Bousvaros A, Leichtner AM, Book L, *et al.* Treatment of pediatric autoimmune enteropathy with tacrolimus (FK506). *Gastroenterology* 1996;111:237–43.
- 19 Steffen R, Wyllie R, Kay M, *et al.* Autoimmune enteropathy in a pediatric patient: partial response to tacrolimus therapy. *Clin Pediatr (Phila)* 1997;36:295–9.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow