CASE REPORT

All that glitters is not always gold

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SUMMARY

Biopsies from the second part of the duodenum are routinely performed in patients with unintentional weight loss. When villous atrophy and an increased intraepithelial lymphocytosis are detected, the commonest cause of it is coeliac disease. Severe villous atrophy with increased intraepithelial lymphocytosis (Marsh IIIc) is highly specific for coeliac disease. However, coeliac disease with this presentation is very rare. Milder abnormalities such as Marsh I-II (microscopic enteritis) and Marsh IIIa are not specific for coeliac disease and could occur in other conditions like those listed in the discussion. We present the case of a 74-year-old woman who, after being diagnosed with seronegative coeliac disease, failed to improve on a gluten-free diet. We discuss the differential diagnosis of coeliac disease and the possible alternative causes for villous blunting, paying particular attention to the diagnosis of small intestinal bacterial overgrowth.

BACKGROUND

Unintentional weight loss, with or without any associated gastrointestinal (GI) symptoms, is a common indication for referral to a specialist. Small bowel biopsies are commonly performed as part of the diagnostic process. When villous atrophy is detected, the commonest cause is coeliac disease.¹ However, alternative diagnoses must also be considered, as failure to do this may result in a missed diagnosis and ongoing malabsorption, leading to further morbidity. This case highlights the importance of detailed clinicopathological correlation; there is a necessity to consider alternative diagnoses when a patient, initially thought to have coeliac disease based on histological findings, fails to improve following the adoption of a gluten-free diet.

CASE PRESENTATION

A 74-year-old, non-smoking, woman was referred for a second gastroenterology opinion to ascertain the cause of her ongoing weight loss and GI symptoms.

Ten months prior to this referral, she had presented to another gastroenterologist with an 11-month history of unintentional weight loss (6 kg), reduced appetite and increasing nausea. She had no other GI symptoms or other significant medical history. At that time, antiendomysial antibodies (EMA) were negative. A CT scan of her thorax, abdomen and pelvis was normal. Gastroscopy was unremarkable, although duodenal biopsies showed evidence of villous atrophy with an increased intraepithelial lymphocytosis (figure 1). Based on these investigations, seronegative coeliac

Figure 1 Light microscopy image of duodenal biopsy (H&E stain) showing an increase of inflammatory cells in lamina propria and partial villous atrophy.

disease was diagnosed. A gluten-free diet was started. One month later, the patient reported stools compatible with steatorrhoea. Her father had died of pancreatic cancer, aged 53. An MRI of her pancreas was normal, but her faecal elastase was low (<32 µg). Pancreatic replacement enzyme (Creon) therapy was initiated, but later stopped as it proved unhelpful.

Over the subsequent 3 months, despite adherence to the gluten-free diet, she lost a further 6 kg in weight. At this stage, a repeat duodenal biopsy showed persistent villous atrophy, an increased chronic inflammatory cell infiltrate within the lamina propria and an intraepithelial lymphocytosis. During the following 2 months, she lost a further 3 kg (weight 46.4 kg, body mass index (BMI) 19.9).

INVESTIGATIONS

At this point, she was referred to our hospital for a second gastroenterology opinion. After a detailed consultation, this second team arranged a series of further tests. These showed that she had a mild normocytic anaemia (haemoglobin 111 g/L (range 115–165)). Her bone, liver enzyme and thyroid function tests were normal. Antitissue transglutaminase antibody (anti-tTG) was normal (0.8 U/mL (range 0.0–3.0)), with normal serum IgA levels (3.91 g/L (normal 0.89–4.46)). Other serum immunoglobulins were not significantly depressed. Biochemical nutritional investigations showed slightly low vitamin D (47.3 nmol/L (range 50–125)), zinc (8.1 µmol/L (range 10–21)), serum folate (2.65 µg/L (range 4.6–18.7)) and vitamin B₁₂

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(100 ng/L (range 191–663)). Serum ferritin, copper and magnesium were normal. Faecal calprotectin was elevated (375 µg/g (normal <60)), but faecal elastase was normal (234 µg/g (normal >200)). Stool cultures for ova, cysts and parasites were negative.

Specialist review of the previous CT scan excluded mesenteric vascular disease and any other significant pathology. A barium follow-through showed slight prominence of the small intestine's folds, but this was not considered pathological. A dual-energy X-ray absorptiometry showed osteoporosis. Colonoscopy showed diverticular disease; random colonic biopsies excluded microscopic colitis.

Repeat duodenal biopsies again showed a blunted villous architecture with an associated intraepithelial lymphocytosis. Specialist review found no histological evidence of lymphoma.

A glucose/hydrogen breath test was conducted. The hydrogen level rose above the maximum detectable level (>150 ppm). The glycocholate part of the test was negative (0.5% at 6 h (normal <3%)). Overall, these results were diagnostic for small bowel bacterial overgrowth (SIBO).

DIFFERENTIAL DIAGNOSIS

Following these investigations the differential diagnosis was between seronegative coeliac disease and SIBO. It was evident that the patient had nutritional deficiencies, related to her ongoing small bowel involvement. Further investigations were conducted in an attempt to clarify the underlying diagnosis. Human leucocyte antigens (HLAs) typing showed both DQ2 and DQ8 to be absent. A capsule endoscopy was requested, but the patient failed to pass the patency capsule.

TREATMENT

Given the diagnostic uncertainty between SIBO and seronegative coeliac disease, the patient was treated for both. She started antibiotics (rifaximin) and continued the gluten-free diet. Nutritional supplements were started and vitamin and micronutrient deficiencies corrected with appropriate supplementation.

OUTCOME AND FOLLOW-UP

Following a single course of antibiotic therapy, the patient reported a dramatic resolution of her symptoms. Furthermore, her weight stabilised and then increased. Thirteen months after being diagnosed with SIBO, her weight had risen to 57 kg (BMI 24.3). At this stage, she remained on the gluten-free diet and was advised to take antibiotics only if symptomatic. To date, she has not required further courses.

Figure 2 Light microscopy image of repeat duodenal biopsy (H&E stain) taken after resolution of symptoms.

In order to clarify her diagnosis, when she was asymptomatic, despite admitting non-compliance with the gluten-free diet, her duodenal biopsy and breath test were repeated. Her duodenal architecture was significantly improved. The biopsy showed a significantly improved villous architecture with no obvious increased intraepithelial lymphocytosis (figure 2). Both a combined glucose hydrogen/methane and a glycocholate breath test were negative. The next step in her management will be to reinstate her normal gluten-containing diet and rebiopsy in the future.

DISCUSSION

This patient presented with significant weight loss accompanied by non-specific GI symptoms. As duodenal biopsies showed evidence of villous atrophy and intraepithelial lymphocytosis, the initial diagnosis given was coeliac disease. This is a common autoimmune disease affecting approximately 1% of the UK population.^{2 3} Its presentation may include symptoms of weight loss, anorexia, abdominal pain, altered bowel habit (diarrhoea, steatorrhoea or constipation); alternatively, it may be asymptomatic.^{4 5} At diagnosis, biochemical nutritional deficiencies, such as folate and zinc, may be present.^{5 6}

The diagnosis of coeliac disease depends on the presence of key histological findings, supported by compatible symptoms and serology (eg, EMA and anti-tTG). Different commercially available assay methods have differing sensitivities and specificities. A 16-study meta-analysis reported that EMA's sensitivity is >90% and specificity is 98%, while anti-tTG's sensitivity and specificity are both >90%.⁷ Both EMA and anti-tTG are IgA antibodies and thus both may show false negativity in selective IgA deficiency. The prevalence of IgA deficiency in the general European population is 0.24–0.61%.^{8 9} In coeliac disease, the prevalence of IgA deficiency is 2%.¹⁰ Although positive serology supports a diagnosis of coeliac disease, its absence does not exclude it. Seronegative coeliac disease is characterised by supportive clinical features and histology, and negative serology.

The small intestine is often biopsied when investigating GI symptoms and weight loss. Pathological features noted in coeliac disease, when exposed to gluten, include villous atrophy, increased intraepithelial T lymphocytes, decreased enterocyte height and crypt hyperplasia. Although these changes support coeliac disease's diagnosis, they are not pathognomonic for it, but are instead non-specific features. Current guidelines recommend the taking of multiple duodenal biopsies (one or two from the bulb and at least four from the distal duodenum) to diagnose or exclude coeliac disease.¹¹ The inclusion of biopsies from the bulb increases the detection of histological abnormalities, as more than 8% of patients with coeliac disease only have histological abnormalities in the bulb, which would otherwise be missed.^{12–14} Histological samples can be described using the Marsh classification scheme.¹⁵ The severity of histological involvement may correlate with the serum levels of coeliac disease antibodies. In the presence of partial, as opposed to total, villous atrophy the sensitivity of serum EMA is reduced.^{16 17}

In one study, 95% of patients with duodenal villous atrophy were diagnosed with coeliac disease, meaning that 5% had an alternative diagnosis.¹ Thus, in order to confidently diagnose coeliac disease, histological findings must be considered in conjunction with other supportive features, such as symptoms and antibody testing. Following the starting of a gluten-free diet, histological improvement may take several months, and complete resolution several years.¹⁸

In this case, the patient had supportive symptoms and histology, but negative EMA and anti-tTG, with a normal serum IgA concentration. Thus, she was thought to have seronegative coeliac disease. However, when she failed to improve despite adhering to a gluten-free diet, alternative diagnoses, including refractory seronegative coeliac disease, enteropathy-type intestinal T-cell lymphoma and SIBO were considered by the second gastroenterologist.

Coeliac disease has an underlying genetic predisposition. It is linked to certain major class II histocompatibility complexes, namely HLA-DQ2 and HLA-DQ8. These are not diagnostic as they are not confined to coeliac disease. They have a low positive predictive value, but a high negative predictive value (98–100%).^{19–20} This means they are not suitable for screening, but are useful to exclude coeliac disease. In an European study, only 6% of patients with coeliac disease had neither the HLA-DQ2 nor HLA-DQ8 heterodimer.²¹ However, almost all of these HLA-DQ2 and HLA-DQ8-negative patients with coeliac disease carried one of the HLA-DQ2 haplotype alleles. Thus, in our case, the absence of either HLA complex made coeliac disease unlikely.

As coeliac disease was an unlikely unifying diagnosis, viable alternatives were considered. However, while doing so the patient was continued on a gluten-free diet due to the severity of her presenting condition. A series of 30 patients, with villous atrophy, but in whom coeliac disease had been excluded, reported 10 different aetiologies, though more exist.²² These included peptic duodenitis (n=3), peptic duodenitis with *Helicobacter pylori* infection (n=2), collagenous sprue (n=3), eosinophilic gastroenteritis (n=2), acute viral gastroenteritis (n=2), SIBO (n=3), Crohn's disease (n=2), tropical sprue (n=1), food allergy (n=1), common variable immunodeficiency syndrome (n=1) and undefined immune mediated enteropathy (n=10). Other reported causes of villous atrophy, with or without increased intraepithelial lymphocytosis, include graft-versus-host disease, chronic intestinal ischaemia, chemoradiation, selected medications and nutritional deficiencies.^{23–24}

In one study, SIBO affected 11% of patients with biopsy-proven, non-responsive coeliac disease.²⁵ Proximal small bowel colonisation by colonic bacteria causes malabsorption through altered bile salt degradation. SIBO becomes more common with advancing age and is often predisposed to by an underlying abnormality affecting the small intestine or defensive mechanisms. In one study, a risk factor was found in 66% of cases.²⁶ Small intestinal abnormalities include those which affect the small intestine's structure (eg, surgical blind-loops, adhesions, fistulae and ileocaecal resections) or motility (eg, diabetes mellitus and systemic sclerosis).²⁶ Other predisposing factors include the prolonged use of acid-lowering medications, such as proton-pump inhibitors and chronic renal failure.^{26–27} None of these predisposing conditions were present in the presented case. In particular, prior to developing symptoms, the patient was not taking regular medications and her only medical history was of diverticular disease. The gold-standard test is jejunal aspirate culture. However, as in our case, patients are usually diagnosed by the more convenient radiolabelled breath testing, which measures exhaled bacterial fermentation products.

SIBO may cause microscopic changes to the duodenal mucosa, as in this case. However, histological changes are not present in most patients with SIBO. A study, involving aspirate proven cases of SIBO, found villous blunting in 24% and increased intraepithelial lymphocytosis in 26%.²⁶ However, 52% of the patients studied had no histological abnormality. Pathological changes resolve following eradication of the

luminal bacteria.²⁸ Thus, in our case, the mucosal improvement was likely to be a result of bacterial eradication. This was supported by the subsequent normal breath test. The patient's partial gluten-free diet was unlikely to be the cause of the improvement because, even when she had previously been fully compliant, this had failed to resolve her duodenal histological abnormalities, let alone her symptoms.

Other potentially confounding results in this case include the low faecal elastase, which later corrected, and raised calprotectin. Faecal elastase has a low sensitivity for mild pancreatic insufficiency.²⁹ Faecal elastase is low in non-specific diarrhoeal states, including untreated coeliac disease and acute infections, presumably due to mucosal damage, as it corrects on mucosal healing.^{30–31} This may explain the low faecal elastase in our case.

Faecal calprotectin is a marker of subclinical intestinal inflammation. Incidental intestinal diseases including SIBO and coeliac, have been found to be associated with raised faecal calprotectin.³² However, comparison studies have not demonstrated a difference between participants with and without SIBO or coeliac disease.^{33–35}

In summary, this case highlights the need to fully investigate patients who fail to respond as anticipated. Failure to do this may result in ongoing symptoms and nutritional decline.

Learning points

- ▶ Duodenal villous blunting and an intraepithelial lymphocytosis are non-specific findings and the differential diagnosis includes coeliac disease.
- ▶ If a patient thought to have coeliac disease fails to improve, then adherence to a gluten-free diet should be checked by a specialist dietitian.
- ▶ If a patient thought to have coeliac disease fails to improve as predicted when adhering to a gluten-free diet, alternative diagnoses, including bacterial overgrowth, should be considered.
- ▶ In the cases of suspected coeliac disease with discordant histology–serology findings, human leucocyte antigen determination must be performed.

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REFERENCES

- 1 Ludvigsson JF, Brandt L, Montgomery SM, *et al.* Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. *BMC Gastroenterol* 2009;9:19.
- 2 Sanders DS, Patel D, Stephenson TJ, *et al.* A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol* 2003;15:407–13.
- 3 West J, Logan RF, Hill PG, *et al.* Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. *Gut* 2003;52:960–5.
- 4 McElvaney NG, Duignan R, Fielding JF. Coeliac disease: clinical presentations, correlations of dietary compliance, symptomatic response and repeat biopsy findings. *Ulster Med J* 1992;61:134–8.
- 5 Fernandez A, Gonzalez L, de-la-Fuente J. Coeliac disease: clinical features in adult populations. *Rev Esp Enferm Dig* 2010;102:466–71.
- 6 Hogberg L, Danielsson L, Jarleman S, *et al.* Serum zinc in small children with coeliac disease. *Acta Paediatr* 2009;98:343–5.

- 7 Giersiepen K, Lelgemann M, Stuhldreher N, *et al.* Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report. *J Pediatr Gastroenterol Nutr* 2012;54:229–41.
- 8 Litzman J, Sevcikova I, Stikarovska D, *et al.* IgA deficiency in Czech healthy individuals and selected patient groups. *Int Arch Allergy Immunol* 2000;123:177–80.
- 9 Pereira LF, Sapina AM, Arroyo J, *et al.* Prevalence of selective IgA deficiency in Spain: more than we thought. *Blood* 1997;90:893.
- 10 Chow MA, Lebwohl B, Reilly NR, *et al.* Immunoglobulin a deficiency in celiac disease. *J Clin Gastroenterol* 2012;46:850–4.
- 11 Rubio-Tapia A, Hill ID, Kelly CP, *et al.* American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656–76. quiz 77.
- 12 Evans KE, Aziz I, Cross SS, *et al.* A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. *Am J Gastroenterol* 2011;106:1837–42.
- 13 Gonzalez S, Gupta A, Cheng J, *et al.* Prospective study of the role of duodenal bulb biopsies in the diagnosis of celiac disease. *Gastrointest Endosc* 2010;72:758–65.
- 14 Bonamico M, Thanasi E, Mariani P, *et al.* Duodenal bulb biopsies in celiac disease: a multicenter study. *J Pediatr Gastroenterol Nutr* 2008;47:618–22.
- 15 Marsh MN. Grains of truth: evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. *Gut* 1990;31:111–14.
- 16 Rostami K, Kerckhaert J, Tiemessen R, *et al.* Sensitivity of antiendomysium and anti gliadin antibodies in untreated celiac disease: disappointing in clinical practice. *Am J Gastroenterol* 1999;94:888–94.
- 17 Carroccio A, Iacono G, D'Amico D, *et al.* Production of anti-endomysial antibodies in cultured duodenal mucosa: usefulness in coeliac disease diagnosis. *Scand J Gastroenterol* 2002;37:32–8.
- 18 Hutchinson JM, West NP, Robins GG, *et al.* Long-term histological follow-up of people with coeliac disease in a UK teaching hospital. *QJM* 2010;103:511–17.
- 19 Hadithi M, von Blomberg BM, Crusius JB, *et al.* Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. *Ann Intern Med* 2007;147:294–302.
- 20 Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. *Am J Med* 2010;123:691–3.
- 21 Karel KLA, Moodie SJ, Ascher H, *et al.* European Genetics Cluster on Celiac Disease. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. *Hum Immunol* 2003;64:469–77.
- 22 Pallav K, Leffler DA, Tariq S, *et al.* Noncoeliac enteropathy: the differential diagnosis of villous atrophy in contemporary clinical practice. *Aliment Pharmacol Ther* 2012;35:380–90.
- 23 Bao F, Green PH, Bhagat G. An update on celiac disease histopathology and the road ahead. *Arch Pathol Lab Med* 2012;136:735–45.
- 24 Morini S, Elias G, Brown M, *et al.* Chronic morpho-functional damage as a consequence of transient ischemia/reperfusion injury of the small bowel. *Histol Histopathol* 2010;25:277–86.
- 25 Rubio-Tapia A, Barton SH, Rosenblatt JE, *et al.* Prevalence of small intestine bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. *J Clin Gastroenterol* 2009;43:157–61.
- 26 Lappinga PJ, Abraham SC, Murray JA, *et al.* Small intestinal bacterial overgrowth: histopathologic features and clinical correlates in an underrecognized entity. *Arch Pathol Lab Med* 2010;134:264–70.
- 27 Compare D, Pica L, Rocco A, *et al.* Effects of long-term PPI treatment on producing bowel symptoms and SIBO. *Eur J Clin Invest* 2011;41:380–6.
- 28 Haboubi NY, Lee GS, Montgomery RD. Duodenal mucosal morphometry of elderly patients with small intestinal bacterial overgrowth: response to antibiotic treatment. *Age Ageing* 1991;20:29–32.
- 29 Naruse S, Ishiguro H, Ko SB, *et al.* Fecal pancreatic elastase: a reproducible marker for severe exocrine pancreatic insufficiency. *J Gastroenterol* 2006;41:901–8.
- 30 Carroccio A, Iacono G, Ippolito S, *et al.* Usefulness of faecal elastase-1 assay in monitoring pancreatic function in childhood coeliac disease. *Ital J Gastroenterol Hepatol* 1998;30:500–4.
- 31 Salvatore S, Finazzi S, Barassi A, *et al.* Low fecal elastase: potentially related to transient small bowel damage resulting from enteric pathogens. *J Pediatr Gastroenterol Nutr* 2003;36:392–6.
- 32 Turvill J. High negative predictive value of a normal faecal calprotectin in patients with symptomatic intestinal disease. *Frontline Gastroenterol* 2012;3:21–8.
- 33 Montalto M, Santoro L, Dalvai S, *et al.* Fecal calprotectin concentrations in patients with small intestinal bacterial overgrowth. *Dig Dis* 2008;26:183–6.
- 34 Fundaro C, Fantacci C, Ansuini V, *et al.* Fecal calprotectin concentration in children affected by SIBO. *Eur Rev Med Pharmacol Sci* 2011;15:1328–35.
- 35 Montalto M, Santoro L, Curigliano V, *et al.* Faecal calprotectin concentrations in untreated coeliac patients. *Scand J Gastroenterol* 2007;42:957–61.

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