Intestinal pseudo-obstruction caused by *Giardia lamblia* infection

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SUMMARY
A woman in her 40s presented with malaise, nausea, reduced appetite, abdominal distention, loose stools and weight loss. Symptoms had started 6 months earlier and worsened in the last 2 weeks. CT enterography showed hypotonic diluted small bowel loops in absence of any mechanical obstruction. Endoscopic examinations including capsule endoscopy did not reveal any obstructing lesion, but a delayed small bowel transit time of the capsule. Duodenal histology revealed Marsh 3a villous atrophy. Secondary causes of intestinal pseudo-obstruction and villous atrophy were investigated. *Giardia lamblia* trophozoites were found in the stools and in the duodenal biopsies. The patient’s symptoms quickly resolved after metronidazole treatment with complete normalisation of duodenal histology.

BACKGROUND
Intestinal pseudo-obstruction (IPO) is characterised by signs and symptoms of mechanical obstruction of the small or large bowel in absence of obstructive anatomical lesions. The condition may be acute or chronic. In acute IPO, a transient and reversible imbalance of excitatory and inhibitory neural factors is responsible for motor impairment and small bowel or colonic dilatation. In chronic IPO, the motor impairment is caused by permanent alterations of the smooth muscle, enteric nerves or interstitial cells of Cajal. Signs and symptoms of IPO lasting more than 6 months define the chronic form, which is a rare disease with an estimated prevalence of <1/100 000.

Acute IPO may be secondary to severe trauma, drugs or infections. Chronic IPO may be idiopathic or secondary to such systemic diseases as scleroderma, amyloidosis, and neurological or infectious disorders. *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*) is the most common protozoal intestinal parasite isolated worldwide, with seroprevalence rates ranging from 2% to 7% in high-income countries to 20%–40% in resource-limited settings. In Northern and Central Italy, the estimated prevalence of giardiasis is around 2%. *G. lamblia* infection may present with acute symptoms including diarrhoea, malaise, abdominal cramps and weight loss or with chronic symptoms related to malabsorption. *G. lamblia* infection has shown to alter gastrointestinal (GI) motor function and to increase the risk of such functional bowel disorders as dyspepsia or irritable bowel syndrome (IBS). We have reported the case of a woman presenting with IPO caused by *G. lamblia* infection for whom the treatment of the infection led to the complete resolution of the condition.

CASE PRESENTATION
A female in her 40s was referred to our gastroenterology clinic because of malaise, nausea, reduced appetite, abdominal distention, loose stools (two evacuations per day without macroscopic blood) and weight loss (−Δ 5 kg, ie, 10% of body weight in the last 6 months). Symptoms had started 6 months earlier and significantly worsened in the last 2 weeks. Clinical evaluation revealed a cachectic woman with a body mass index of 18 kg/m² and with severe abdominal distention. Blood tests including glucose and thyroid function did not reveal any gross abnormality. Abdominal X-ray showed dilated small bowel and the presence of air–fluid levels. Abdominal ultrasound with intestinal assessment showed remarkable gastric dilatation with maximum gastric diameter of 6.5 cm and substantial residual food despite overnight fasting, distended ileal loops and an ‘onion bulb-shaped’ tract of small intestine compatible with intestinal intussusception (figure 1).

The patient reported a family history of ovarian cancer, coeliac disease and ulcerative colitis. She did not refer any foreign travel in the last year and any contact with either domestic or wild animals. Her profession was not at increased risk of infectious diseases. She also denied taking any medication or illicit drugs. The patient was hospitalised.

INVESTIGATIONS
CT enterography was performed (figure 2), showing dilated (diameter >3 cm) and bundling small bowel loops with diffuse air–fluid levels in absence of mechanical obstructing lesions and increased thickness or hyperenhancement of the small bowel wall.

Esophagogastroduodenoscopy showed a macroscopically normal mucosa. Multiple stomach biopsies showed mild gastritis; *Helicobacter pylori* was absent. Duodenal biopsies revealed intraepithelial lymphoplasmocytosis with increased number of CD3+ intraepithelial lymphocytes (40% in 100 enterocytes) and villous atrophy, consistent with modified Marsh 3a type (figure 3). Coeliac disease was ruled out by normal levels of IgA, antitissue transglutaminase (anti-tTG), antigliadin IgG and IgA and antidiemysium IgA, and negative genotyping of the human leucocyte antigens (HLAs) for HLA DQ-2 and HLA DQ-8.

Colonoscopy did not evidence any obstructing lesion. To further exclude a mechanical obstruction, capsule endoscopy was performed (after permissive patency capsule examination), revealing...
a diffusely normotrophic small bowel mucosa and a slowed (362 min) small bowel transit time (median small bowel transit time 157.0–240.5 min).19

Faecal calprotectin and blood count were normal as well as C reactive protein, procalcitonin plasma levels, vitamin B₁₂, electrolytes, iron levels and transferrin saturation. Folates were slightly reduced (3.1 ng/mL, normal levels >3.8 ng/mL).

The diagnosis of IPO was made on the basis of the presence of dilated small bowel loops with air–fluid levels and in absence of any mechanical obstruction assessed by cross-sectional imaging and endoscopy.

Secondary causes of IPO and of Marsh 3a villous atrophy were revised (see the Differential diagnosis section).

DIFFERENTIAL DIAGNOSIS

Our patient’s symptoms had begun 6 months earlier and worsened in the last 2 weeks. Therefore, the differential diagnosis of IPO considered both acute and chronic forms. Clinical history and physical examinations excluded the most frequent causes of acute pseudo-obstruction or Ogilvie’s syndrome including surgery, severe trauma or acute infections. The patient denied the use of drugs affecting GI motility such as opioids, anticholinergic, alpha-2-adrenergic agonists, antipsychotics, calcium channel blockers, and cytotoxic and dopaminergic drugs. Diabetes, hypothyroidism and hypoparathyroidism were ruled out by normal glycaemia, thyroid-stimulating hormone and serum calcium levels.

Clinical history and physical examination excluded progressive systemic sclerosis, Ehlers-Danlos syndrome and neurological disorders such as stroke, encephalitis, dermatomyositis and myotonic dystrophy. Amyloidosis was ruled out by normal gastric biopsies. Absence of anti-Hu antibodies and antigliutamic acid decarboxylase antibodies excluded any paraneoplastic or autoimmune form of pseudo-obstruction.20–22

 Infective causes of acute and chronic pseudo-obstruction were considered. Bacterial stool cultures for Shigella, Salmonella and Campylobacter were negative as well as interferon gamma release assay and serologies for HIV, Epstein-Barr virus, cytomegalovirus, Borrelia burgdorferi, Toxoplasma gondii, Toxocara and Strongyloides stercoralis.22

 Differential diagnosis of Marsh 3a villous atrophy considered coeliac disease, which was ruled out by negative serology and negative HLA DQ-2 and DQ-8 genotyping. Enteropathy-associated T-cell lymphoma was unlikely as strongly associated with coeliac disease. Drug-related villous atrophy was excluded as our patient did not take such medications as olmesartan, ipilimumab, colchicine, mycophenolate mofetil, methotrexate and azathioprine. Tropical sprue is an endemic condition in certain parts of the world such as South Asia, the Caribbean, and Central and South America, but it is unlikely in Italy. Crohn’s disease may cause villous atrophy but was excluded by cross-sectional imaging and normal faecal calprotectin. Collagenous sprue and Whipple disease were excluded by histological examination of duodenal biopsies. Common variable immunodeficiency was unlikely because of the normal levels of IgM and IgG and the reported normal response to vaccines. Small intestinal bacterial overgrowth was excluded by normal glucose breath test.23

 The diagnosis of giardiasis was considered among the causes of Marsh 3a villous atrophy.24 The research of ova and parasites in the stools revealed the presence of trophozoites and cysts of G. lamblia. The parasite was found in the duodenal biopsies at a second look after the finding on stool examination (figure 4). Autoimmune enteropathy, another rare cause of villous atrophy, was unlikely as it requires a diagnosis of exclusion.23
daughter also had abdominal distension and diarrhoea, successfully treated with bowel loops dilatation. After 3 days with rapid regression of symptoms.

OUTCOME AND FOLLOW-UP

Three month after treatment, upper GI endoscopy was repeated and multiple duodenal biopsies displayed normotrophic villi, with slight residual lymphoplasmocytic infiltration, and normal levels of CD3+ intra-epithelial lymphocytes (figure 5). G. lamblia trophozoites were absent in the duodenal biopsies and in the stools. Abdominal ultrasound showed no more signs of small bowel loops dilatation. After 3 months, the patient was asymptomatic with 3 kg body weight increase. Her 18-month-old daughter also had G. lamblia in the stools. She reported abdominal distension and diarrhoea, successfully treated with metronidazole.

DISCUSSION

We reported the case of a female patient with IPO caused by giardiasis. According to our search through the PubMed and Google Scholar databases, this is the first reported case of giardiasis presenting with a dilated small bowel mimicking IPO. The rapid and complete resolution of both symptoms and small bowel dilatation after Giardia eradication suggests that small bowel dilatation was due to an imbalance of reversible mechanisms controlling the intestinal tone. Gut tone is under the influence of cholinergic muscarinic excitatory and adrenergic, cholinergic nicotinic and nitric oxide (NO)-like inhibitory transmitters. An increased release of NO has been shown to play a pivotal role in the control of infections with numerous microbes including G. lamblia. In vitro studies showed that NO inhibits G. lamblia growth, and studies on NO synthase-deficient mice revealed a reduced clearance of the parasite in vivo. These findings raise the hypothesis that an enhanced release of NO might underlie the reduced small bowel tone in our patient. In line with this hypothesis, a significant increase in NO synthase-containing cells has been reported in the myenteric plexus of the small intestine of patients with chronic IPO, suggesting that NO overproduction may be related to the pathogenesis of ileal dilatation in these patients.

G. lamblia infection has been recognised as one of the causes of postinfectious IBS and functional dyspepsia (FD). The pathogenesis of these syndromes after bacterial or parasitic infection is probably multifactorial and is still insufficiently understood, but increased levels of inducible NO synthase associated with mast cell degranulation were found in the duodenal biopsies of subjects with IBS and FD, suggesting that NO dysregulation might be involved in the mechanism of postinfectious IBS and FD. G. lamblia infection caused a histopathological pattern in our patient which was almost indistinguishable from that of coeliac disease. In this condition, anti-tTG and negative HLA DQ-2 and DQ-8 genotyping maintained their diagnostic ability to discriminate between coeliac disease and giardiasis. This result is in line with the almost 100% negative post-test probability previously reported for negative HLA DQ-2 and DQ-8 genotyping in patients with a clinical suspicion of coeliac disease. The recognition of the parasite in the duodenal lumen of our patient occurred only after a second look, suggesting that diagnosis might be difficult for the pathologist. In line with this observation, 18% of false negatives were reported in a retrospective histological analysis of duodenal samples from 567 cases of giardiasis presenting with celiac-like duodenal histology. In this context, the microscopic analysis of duodenal aspirate might have represented another diagnostic option, although not superior to the analysis of duodenal biopsies when available.

Abdominal ultrasound with intestinal assessment showed the presence of transient small bowel intussusception that was not confirmed at CT enterography. The transient nature of small bowel intussusception was previously reported in an observational study of 25 paediatric patients, none of whom had persistent intussusception requiring surgery. In this study, four patients with persistent symptoms had an underlying disease requiring treatment, two of them with giardiasis, suggesting that G. infection may predispose to transient small bowel intussusception.

Contributors TP, LS and MF conceived of the presented idea. TP and GB developed the text. GB and MF supervised the findings of this work. All authors followed the clinical development of the case, discussed the results and contributed to the final manuscript.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.
Case report

Learning points

► *Giardia lamblia* infection could rarely present as intestinal pseudo-obstruction.
► The histological diagnosis of giardiasis via duodenal biopsies is possible but difficult should be considered, particularly for patients presenting with duodenal atrophy.
► Transient small bowel intussusception at abdominal ultrasound with intestinal assessment should raise suspicion of *G. lamblia* infection.

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REFERENCES

1 Coulie B, Camilleri M. Intestinal pseudo-obstruction. *Annu Rev Med* 1999;50:37–55.
2 Wells CI, O’Grady G, Bissett JF. Acute colonic pseudo-obstruction: a systematic review of aetiology and mechanisms. *World J Gastroenterol* 2017;23:5634–44.
3 Downes TJ, Cheruvu MS, Karunarathne TB, et al. Pathophysiology, diagnosis, and management of chronic intestinal pseudo-obstruction. *J Clin Gastroenterol* 2018;52:477–89.
4 Iida H, Dihkoo H, Imanori M, et al. Epidemiology and clinical experience of chronic intestinal pseudo-obstruction in Japan: a nationwide epidemiologic survey. *J Epidemiol* 2013;23:288–94.
5 Leung AK. Giardiasis. In: Leung AK, ed. Common problems in ambulatory pediatrics: specific clinical problems. New York: Nova Science Publishers, Inc, 2011: Volume 2 39–42.
6 Daly ER, Roy SJ, Blaney DD, et al. Outbreak of giardiasis associated with a community drinking-water source. *Epidemiol Infect* 2010;138:491–500.
7 Cama VA, Mathison BA. Infections by intestinal Coccidia and *Giardia duodenalis*. *Clin Lab Med* 2015;35:423–44.
8 Dixon BR. *Giardia duodenalis* in humans and animals - Transmission and disease. *Res Vet Sci* 2021;135:283–9.
9 Feng Y, Xiao L. Zoonotic potential and molecular epidemiology of *Giardia* species and giardiasis. *Clin Microbiol Rev* 2011;24:110–40.
10 Capelli G, Paolotti B, Iorio R, et al. Prevalence of *Giardia* spp. in dogs and humans in northern and central Italy. *Parasitol Res* 2003;90 Suppl 3:5154–5.
11 Hill DR, Nash TE. Intestinal flagellate and ciliate infections. In: Guerrant RL, Walker DA, Weller PF, eds. *Tropical infectious diseases: principles, pathogenesis and practice*. 3rd ed. Saunders Elsevier, Philadelphia, 2011: p623.
12 Li E, Zhou P, Singer SM. Neuronal nitric oxide synthase is necessary for elimination of *Giardia lamblia* infections in mice. *J Immunol* 2006;176:516–21.
13 Bistac V, Spiller R, Singh G, et al. Relative importance of abnormalities of CCK and 5-HT (serotonin) in *Giardia*-induced post-infectious irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther* 2010;31:883–91.
14 Li E, Zhao A, Shea-Donohue T, et al. Mast cell-mediated changes in smooth muscle contractility during mouse giardiasis. *Infect Immun* 2007;75:4514–8.
15 Abedi SH, Fazladeh A, Mollao A, et al. The neglected role of Blastocystis sp. and *Giardia lamblia* in development of irritable bowel syndrome: a systematic review and meta-analysis. *Microb Pathog* 2022;162:105215.
16 Hanefik V, Dizdar V, Langeland N, et al. Development of functional gastrointestinal disorders after *Giardia lamblia* infection. *BMJ Gastroenterol* 2009;9:27.
17 Haliez MCM, Motta J-P, Feener TD, et al. *Giardia* duodenalis induces paracellular bacterial translocation and causes postinfectious visceral hypersensitivity. *Am J Physiol Gastrointest Liver Physiol* 2016;310:E574–85.
18 Rami Reddy SR, Cappell MS. A systematic review of the clinical presentation, diagnosis, and treatment of small bowel obstruction. *Curr Gastroenterol Rep* 2017;19:28.
19 O’Grady J, Murphy CL, Barry L, et al. Defining gastrointestinal transit time using video capsule endoscopy: a study of healthy subjects. *Endosc Int Open* 2020;8:E396–400.
20 Darnell RB, DeAngelis LM. Regression of small-cell lung carcinoma in patients with paraneoplastic neuronal antibodies. *Lancet* 1993;341:21–2.
21 Maniani A, Camilleri M, Petersen IA, et al. Audit of suspected chronic intestinal pseudo-obstruction in patients with gynecologic cancer. *Eur J Gynaecol Oncol* 2008;29:578–82.
22 Antonucci A, Fronzoni L, Cogliandro L, et al. Chronic intestinal pseudo-obstruction. *World J Gastroenterol* 2008;14:2953–61.
23 Kamboj AK, Oxentenko AS. Clinical and histologic mimickers of celiac disease. *Clin Transl Gastroenterol* 2017;8:e114.
24 Edling L, Rathmsen S, Eriksos S, et al. Celiac disease and giardiasis: a case report. *Eur J Gastroenterol Hepatol* 2012;24:984–7.
25 Basilo G, Phillips SF. Ileal distension relaxes the canine colon: a model of megacolon? *Gastroenterology* 1994;106:606–14.
26 Brunet LR. Nitric oxide in parasitic infections. *Int Immunopharmacol* 2001;1:1457–67.
27 Wang ZQ, Watanabe Y, Toki A, et al. Involvement of endogenous nitric oxide and c-kit-expressing cells in chronic intestinal pseudo-obstruction. *J Pediatr Surg* 2000;35:539–44.
28 Barbara G, Grover M, Berzik P, et al. Rome Foundation working team report on Post-Infection irritable bowel syndrome. *Gastroenterology* 2019;156:46–58.
29 Yuan H-P, Li X-P, Yang W-R, et al. Inducible nitric oxide synthase in the duodenal mucosa is associated with mast cell degranulation in patients with functional dyspepsia. *Ann Clin Lab Sci* 2015;45:522–7.
30 An S, Zong G, Wang Z, et al. Expression of inducible nitric oxide synthase in mast cells contributes to the regulation of inflammatory cytokines in irritable bowel syndrome with diarrhea. *Neurogastroenterol Motil* 2016;28:1083–93.
31 Leung AKC, Leung AAM, Wong AHC, et al. Giardiasis: an overview. *Recent Pat Inflamm Allergy Drug Discov* 2019;13:134–43.
32 Sorell L, Garrote JA, Galvan JA, et al. Celiac disease diagnosis in patients with giardiasis: high value of antitransglutaminase antibodies. *Am J Gastroenterol* 2004;99:1330–2.
33 Hadithi M, von Blomberg MBE, Crusius JBA, et al. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. *Ann Intern Med* 2007;147:294–302.
34 Grillo F, Campora M, Canlin L, et al. “Stranger things” in the gut: uncommon items in gastrointestinal specimens. *Virchows Arch* 2022;480:231–45.
35 Oberhuber G, Kastner N, Stolle M. Giardiasis: a histologic analysis of 567 cases. *Scand J Gastroenterol* 1997;32:48–51.
36 Gupta SK, Croffie JM, Pfefferkorn MD, et al. Diagnostic yield of duodenal aspirate for *G. lamblia* and comparison to duodenal mucosal biopsies. *Dig Dis Sci* 2003;48:605–7.
37 Strouse PJ, DiPietro MA, Saez F. Transient small-bowel intussusception in children on CT. *Pediatr Radiol* 2003;33:316–20.