Unusual presentation of more common disease/injury

Pneumatosis intestinalis in a patient with recurrent *Clostridium difficile* infectionDuc Ha,¹ Chung-Jyi Tsai²¹Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio, USA²Department of Gastroenterology and Hepatology, Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio, USA

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Summary

A 65-year-old man with long-standing diarrhoea, recurrent *Clostridium difficile* infection (CDI) in the previous 5 months presented to the gastroenterology clinic with recurrent diarrhoea and abdominal cramping. Physical examination was negative for signs of acute abdomen. Stool *C difficile* PCR was positive. Abdominal imaging demonstrated an extensive pneumatosis intestinalis involving the small bowel and a dilated small bowel loop. He was treated conservatively with oral vancomycin for recurrent CDI with resolution of diarrhoea and abdominal cramping on 1-month follow-up visit.

BACKGROUND

Pneumatosis intestinalis (PI) can be associated with intra-abdominal catastrophes including ischaemic/infarcted bowel in adults and necrotising enterocolitis in children and can require emergent surgical interventions. However, when not associated with life-threatening conditions, many cases of PI can be conservatively managed. Previous reports have described *Clostridium difficile* infection (CDI) leading to PI in immunocompromised patients. We describe the first case of PI associated with recurrent CDI in an immunocompetent patient without complicating pseudomembranous colitis.

CASE PRESENTATION

A 65-year-old man with long-standing history of diarrhoea presented to the gastroenterology (GI) clinic complaining of diarrhoea. He reported having diarrhoea 'as far back as (he could) remember', but more bothersome and worsening in the past 2 years (up to 10–15 watery stools per day). Approximately 5 months ago, he was tested for *C difficile* infection for the first time, the result of which was positive. He was started on a 7-day course of oral metronidazole during which period he felt 'like a new person'. Shortly after completing his metronidazole course, his diarrhoea recurred and he was given a 14-day course of oral vancomycin, again with resolution of diarrhoea during the treatment course but recurrence of diarrhoea shortly after completion of antibiotics. Since then, he had been given three courses of oral vancomycin in addition to one course of fidaxomicin, with relief during the treatment period but recurrence of diarrhoea after completing treatment. Every time he tested for *C difficile* by stool PCR, results came back positive. His latest regimen was an oral vancomycin taper over 7 weeks designed by his infectious disease specialist which he completed 5 days ago. He again presented to GI clinic with recurrent diarrhoea, 6–8 loose stools per day starting shortly after completion of his vancomycin taper. He reported abdominal cramping and periumbilical pain

similar to previous episodes of diarrhoea, but denied nausea, vomiting, fevers, chills or excessive weight loss.

His medical and surgical history was significant for hypertrophic obstructive cardiomyopathy, hiatal hernia requiring open repair approximately 25 years ago which since had been complicated by ventral hernia requiring three repairs and small bowel strangulation requiring resection of 18 inches of small bowel. His last abdominal surgery was 15 years ago, for ventral hernia repair. He had incidental findings of recurrent hiatal hernia on CT 1.5 years ago, which showed a 'large, type 4 hiatal hernia' involving stomach and meso-axial components including colon. There was no evidence of ventral hernia. No reflux was detected on upper GI series. He denied recent travels or illicit drug use.

In the office, he was found afebrile, blood pressure 132/89, HR 85. Abdominal examination revealed a soft, non-tender abdomen with no guarding or rebound tenderness. Bowel sounds were normal.

INVESTIGATIONS

His haematological profile was negative for leukocytosis or leukopenia/lymphopenia; basic metabolic panel was normal. Stool *C difficile* PCR was positive.

CT enterography showed small and large bowel herniating into a large hiatal hernia, multiple loops of small bowel that were involved in extensive pneumatosis, in addition to a markedly dilated small bowel loop in the left abdomen which measured 9 cm in diameter (figure 1). There was no active inflammation. The anastomosis site from previous bowel resection was without narrowing. There was no evidence of bowel obstruction. Within the colon, there was extensive sigmoid diverticulosis without findings of acute diverticulitis or colitis. Outpatient colonoscopy was done and random biopsies demonstrated colonic mucosa with mild chronic inflammation with the absence of pseudomembranous colitis features. CT abdomen 1.5 years ago also demonstrated extensive diverticulosis but no evidence of pneumatosis. A previous colonoscopy performed for

Figure 1 CT enterography demonstrating pneumatosis intestinalis involving the small bowel.

investigation of diarrhoea 6 months ago showed no significant findings except for mild diverticulosis. Random biopsies of the colon were taken at that time which was negative for dysplasia or colitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for PI includes associated conditions that are known to be catastrophic such as intestinal ischaemia, bowel obstruction, perforation and in the paediatric population, necrotising enterocolitis.^{1–3} Associated conditions of lower acuity can include infectious aetiologies such as viral gastroenteritis, *Mycobacterium tuberculosis* and *Candida albicans*.³ Pulmonary disorders such as chronic obstructive pulmonary disease and asthma should be considered.^{1–3} Diseases affecting GI motility such as adynamic ileus, scleroderma and Hirschsprung disease are known to be associated with PI.³ In the immunocompromised and transplant patients, HIV/AIDS causing enterocolitis, lymphoproliferative disorders, graft-versus-host disease are of important consideration.³

TREATMENT

The patient was managed conservatively with outpatient oral vancomycin to treat underlying CDI.

OUTCOME AND FOLLOW-UP

He was seen for follow-up 1 month later with resolved diarrhoea. Repeat *C difficile* PCR was negative. No abdominal imaging as deemed necessary as he was asymptomatic.

DISCUSSION

PI refers to the presence of gas within the bowel wall, which can include but not exclusive to the subserosal and submucosal regions of the small and large intestine.² Since its first description by Du Vernoi in 1730, it has had multiple synonyms, including pneumatosis cystoides intestinalis, pneumatosis coli and intestinal emphysema.^{4–5} Historically, PI has been associated with life-threatening conditions such as necrotising enterocolitis in children and ischaemic/infarcted bowel in adults, with death rates as high as 33% reported in small case series.^{2–6} In recent studies, the prevalence of PI has been reported to be in 0.37% patients undergoing abdominal CT. Approximately 50% of these patients were successfully managed without surgical interventions.^{2–6} Thus, rather than being a disease

per se, PI can be referred to as a radiographic finding which can be incidentally detected on routine imaging.¹

Several theories have been proposed for the pathogenesis of PI. The mechanical theory of mucosal disruption postulates that gas dissects into the wall of the bowel through a break in the integrity of a luminal surface and tracks along mesenteric blood vessels.¹ Similarly, the bacterial theory explains that gas formed by bacteria gains access to the submucosa through breaches in the mucosa.^{7–9} Proponents of the biochemical theory claim that intestinal bacteria produce an excessive amount of hydrogen which leads to increased pressure, causing gas to become trapped within the submucosa.^{10–12} Those favouring the immunosuppressive theory hypothesise that lymphoid depletion causes shrinkage of Peyer's patches, resulting in loss of structural integrity which in turn permits dissection of gas into the bowel wall.^{1–13} Lastly, the pulmonary theory proposes that alveolar rupture with air dissecting interstitially along the bronchopulmonary bundles to the mediastinum and then retroperitoneally along the vascular supply of the viscera.^{1–3}

Clinically, PI in adults typically present in the fifth to eighth of life.² Most patients with PI are asymptomatic and are probably never diagnosed. If symptomatic, patients with PI can complain of diarrhoea, abdominal pain, distension, flatulence and tenesmus.^{2–3} Complications associated with PI include portal venous gas, pneumoperitoneum, volvulus, intestinal obstruction, perforation and intussusception.^{2–3}

For diagnosis, CT abdomen is the most commonly used modality. PI can also be demonstrated on abdominal radiographs, barium enema studies, ultrasonography and MRI.¹ PI can be described on CT scan to have a 'bubble-like' or 'cystic' versus 'band-like' or 'linear' appearance.^{3–6} Traditionally, pneumatosis was thought to be a sign of transmural bowel wall infarction/necrosis and that a band-like/linear appearance was associated with more extensive disease. However, based on two different small studies, no direct correlation can be made between the appearance of pneumatosis on CT and the degree of transmural bowel wall infarction and clinical outcome.^{14–15} The appearance of portomesenteric gas with pneumatosis is associated with a higher incidence of transmural infarction/necrosis.^{14–15}

Management principals include timely identification of acute intra-abdominal processes such as bowel ischaemia/infarction. Physical exam findings suggestive of an acute abdomen, laboratory evidence of metabolic acidosis (ie, lactate acidosis) and imaging showing pneumatosis and portal venous gas may require prompt action for emergent and potentially life-saving exploratory laparotomy.^{6–16} In non-catastrophic, symptomatic patients, treatment can include antibiotics, elemental diet, inhaled or hyperbaric oxygen.^{9–17–20} In asymptomatic patients, no therapy is indicated as intramural gas usually resolves spontaneously over time.³

CDI is now by far the most common known cause of infectious diarrhoea in hospitalised patients in North America and Europe.²¹ Recurrent CDI is rarely ever a result of antimicrobial resistance to metronidazole or vancomycin.²¹ Instead, it is believed that treatment of CDI perpetuates the impairment of 'colonisation resistance' which underlies CDI.²¹ Approximately 20% patients affected with

a first episode of CDI will have symptomatic recurrence after treatment of the initial infection.^{18 21} Up to 45% who had one prior episode and 60% of those with two or more previous episodes will develop recurrence.^{18 21} Risk factors for the development of recurrent CDI include persistent disruption of the colonic flora, advanced age, long hospitalisations and administration of non-*C difficile* antimicrobial therapy.^{18 21} Treatment of the first CDI recurrence can include metronidazole or vancomycin. However, in patients with second CDI recurrence, a reasonable approach is a vancomycin taper over 6–10 weeks although this approach was devised from retrospective analysis.¹⁸ A recent randomised control trial (RCT) demonstrated fidaxomicin to be non-inferior to oral vancomycin in the treatment of CDI and is associated with a lower rate of recurrence.²² Fidaxomicin thus is a reasonable alternative for recurrent CDI however no reported RCT has studied fidaxomicin in the treatment of recurrent CDI. Other options include the addition of rifampin after a course of oral vancomycin, faecal transplantation and intravenous immunoglobulin although efficacy data to support routine use of these options are currently lacking.^{18 21}

PI associated with CDI is reported in the literature through case reports, more commonly in immunocompromised patients.^{8 23 24} Only one previous case report described CDI-associated PI in an immunocompetent adult, however, this case was complicated by pseudomembranous colitis.²⁵ To the best of our knowledge, our current case is the first to describe PI associated with CDI in an immunocompetent patient without features of complicating pseudomembranous colitis, and is also the first to describe PI associated with recurrent CDI. While difficulty to prove, we believe recurrent CDI most likely led to PI in our patient. He had no signs or symptom related to bowel obstruction or ischaemia. The dilated loop of small bowel detected on CT could have led to PI, however there was also PI in other bowel loops which were not dilated. A sliding hiatal hernia theoretically could have led to PI; however, given his long-standing history of hiatal hernia, recurrent disease after surgical repair, no previous history of PI and a 'fixed' hiatal hernia described on imaging, a sliding hiatal hernia was unlikely the aetiology. In addition, he had no evidence of colitis on biopsy samples obtained by colonoscopy, making inflammatory bowel disease and pseudomembranous colitis unlikely causes. It is interesting to propose that perhaps due to the long history of diarrhoea, this patient has developed CDI as the result of impairment of 'colonisation resistance', which in turn caused intestinal mucosal disruption which caused PI and a vicious cycle of recurrent CDI.

Learning points

- ▶ Pneumatosis intestinalis (PI) can be associated with chronic gastrointestinal tract infections and can be conservatively managed without surgical interventions.
- ▶ PI can be associated with recurrent *Clostridium difficile* infection (CDI), both in immunocompromised and immunocompetent patients.
- ▶ An effective treatment for patients with recurrent CDI associated with PI is oral vancomycin.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Pear BL.** Pneumatosis intestinalis: a review. *Radiology* 1998;**207**:13–19.
2. **Bailey J,** Shaffer EA. Pneumatosis coli associated with pseudomembranous colitis in a patient following colonic surgery. *Case Report Med* 2010;**2010**:138369.
3. **Khalil PN,** Huber-Wagner S, Ladurner R, *et al.* Natural history, clinical pattern, and surgical considerations of pneumatosis intestinalis. *Eur J Med Res* 2009;**14**:231–9.
4. **Olmsted WW,** Madewell JE. Pneumatosis cystoides intestinalis: a pathophysiologic explanation of the roentgenographic signs. *Gastrointest Radiol* 1976;**1**:177–81.
5. **Heng Y,** Schuffler MD, Haggitt RC, *et al.* Pneumatosis intestinalis: a review. *Am J Gastroenterol* 1995;**90**:1747–58.
6. **Morris MS,** Gee AC, Cho SD, *et al.* Management and outcome of pneumatosis intestinalis. *Am J Surg* 2008;**195**:679–82; discussion 682–3.
7. **Yale CE,** Balish E, Wu JP. The bacterial etiology of pneumatosis cystoides intestinalis. *Arch Surg* 1974;**109**:89–94.
8. **Schenk P,** Madl C, Kramer L, *et al.* Pneumatosis intestinalis with *Clostridium difficile* colitis as a cause of acute abdomen after lung transplantation. *Dig Dis Sci* 1998;**43**:2455–8.
9. **Ellis BW.** Symptomatic treatment of primary pneumatosis coli with metronidazole. *Br Med J* 1980;**280**:763–4.
10. **Hisamoto A,** Mizushima T, Sato K, *et al.* Pneumatosis cystoides intestinalis after alpha-glucosidase inhibitor treatment in a patient with interstitial pneumonitis. *Intern Med* 2006;**45**:73–6.
11. **Hayakawa T,** Yoneshima M, Abe T, *et al.* Pneumatosis cystoides intestinalis after treatment with an alpha-glucosidase inhibitor. *Diabetes Care* 1999;**22**:366–7.
12. **Kojima K,** Tsujimoto T, Fujii H, *et al.* Pneumatosis cystoides intestinalis induced by the alpha-glucosidase inhibitor miglitol. *Intern Med* 2010;**49**:1545–8.
13. **Wood BJ,** Kumar PN, Cooper C, *et al.* Pneumatosis intestinalis in adults with AIDS: clinical significance and imaging findings. *AJR Am J Roentgenol* 1995;**165**:1387–90.
14. **Kernagis LY,** Levine MS, Jacobs JE. Pneumatosis intestinalis in patients with ischemia: correlation of CT findings with viability of the bowel. *AJR Am J Roentgenol* 2003;**180**:733–6.
15. **Wiesner W,** Morteale KJ, Glickman JN, *et al.* Pneumatosis intestinalis and portomesenteric venous gas in intestinal ischemia: correlation of CT findings with severity of ischemia and clinical outcome. *AJR Am J Roentgenol* 2001;**177**:1319–23.
16. **Wayne E,** Ough M, Wu A, *et al.* Management algorithm for pneumatosis intestinalis and portal venous gas: treatment and outcome of 88 consecutive cases. *J Gastrointest Surg* 2010;**14**:437–48.
17. **Tak PP,** Van Duinen CM, Bun P, *et al.* Pneumatosis cystoides intestinalis in intestinal pseudoobstruction. Resolution after therapy with metronidazole. *Dig Dis Sci* 1992;**37**:949–54.
18. **Johnston BT,** McFarland RJ. Elemental diet in the treatment of pneumatosis coli. *Scand J Gastroenterol* 1995;**30**:1224–7.
19. **Masterson JS,** Fratkan LB, Osler TR, *et al.* Treatment of pneumatosis cystoides intestinalis with hyperbaric oxygen. *Ann Surg* 1978;**187**:245–7.
20. **Grieve DA,** Unsworth IP. Pneumatosis cystoides intestinalis: an experience with hyperbaric oxygen treatment. *Aust N Z J Surg* 1991;**61**:423–6.
21. **Kelly CP.** A 76-year-old man with recurrent *Clostridium difficile*-associated diarrhea: review of *C. difficile* infection. *JAMA* 2009;**301**:954–62.
22. **Louie TJ,** Miller MA, Mullane KM, *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011;**364**:422–31.
23. **Gillett PM,** Russell RK, Wilson DC, *et al.* *C difficile* induced pneumatosis intestinalis in a neutropenic child. *Arch Dis Child* 2002;**87**:85.
24. **Hochwald O,** Shaoul R. Pneumatosis intestinalis caused by *Clostridium difficile* in a neutropenic child. *Clin Gastroenterol Hepatol* 2007;**5**:A24.
25. **Kreiss C,** Forohar F, Smithline AE, *et al.* Pneumatosis intestinalis complicating *C. difficile* pseudomembranous colitis. *Am J Gastroenterol* 1999;**94**:2560–1.

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