CASE REPORT

Combination therapy for systemic sclerosis-associated pneumatosis intestinalis

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SUMMARY

We present a case of a patient with pneumatosis intestinalis and pneumoperitoneum secondary to gastrointestinal systemic sclerosis, who presented following recurrent accident and emergency attendances with abdominal pain. Pneumatosis intestinalis is a rare complication of systemic sclerosis; management approaches focus largely on exclusion of life-threatening surgical pathologies and subsequent symptom control. To date, there are still no established gold-standard treatment strategy and no large-scale trial data to support a specific management strategy. We describe a case of successful medical management with a combination of antimicrobial, elemental diet and high-flow inhalation oxygen therapy, with supporting evidence of CT image confirming resolution. This case therefore contributes to the literature, being the first to report both symptomatic and radiological improvement following combination therapy without the need for surgical intervention.

BACKGROUND

Systemic sclerosis is a multiorgan connective tissue disorder characterised by early proliferative vascular changes of the skin and affected organ. Features of organ involvement include immune system activation and inflammatory changes in the early stages with subsequent progression to fibrosis with disease progression.^{1,2} Gastrointestinal (GI) involvement in systemic sclerosis occurs in 80%–90% of patients and is one of the leading causes of morbidity and mortality in patients with systemic sclerosis.¹ As any part of the GI tract can be affected, patients may therefore present with a plethora of different GI symptoms.³

Pneumatosis intestinalis (PI) is a recognised but rare complication of systemic sclerosis with only a few case reports published around the subject in the literature. First described in 1730 by Du Vernoy,⁴ PI is a rare radiological finding with an incidence rate of 0.03% worldwide,⁵ characterised by multiple gas-filled cysts in the intestinal submucosa and/or subserosa with or without the presence of pneumoperitoneum.⁶ There are many challenges clinicians face when managing patients with this rare entity; first, PI is a sign associated with a spectrum of conditions ranging from benign incidental finding to life-threatening surgical causes, and early recognition of these conditions are therefore imperative when making management decisions particularly if prompt surgical intervention is indicated.⁷

The pathogenesis of PI in systemic sclerosis is not fully understood. The evidence for treatment for GI scleroderma-related PI is also limited. Management approaches largely focus on exclusion of life-threatening acute surgical causes and subsequent symptom control. Here, we describe a case of PI secondary to GI scleroderma, our treatment approach and evaluation of the patient's objective and subjective response to treatment, averting the need for surgical intervention.

CASE PRESENTATION

A 74-year-old woman was admitted from the gastroenterology clinic with poorly controlled abdominal pain and vomiting. Over the 2 months prior to this appointment, she has had three emergency admissions to her local accident and emergency with the same symptoms, which had never fully resolved. Her medical history was remarkable for systemic sclerosis, which was diagnosed with histological confirmation in 2014 after a laparoscopic Toupet partial fundoplication for persistent symptoms of reflux and dysphagia secondary to oesophagitis and peptic stricturing. This was complicated by various GI manifestations including dysphagia, oesophagitis, small intestinal bacterial overgrowth (SIBO) and intermittent bowel obstruction. Other surgical history included endovascular aneurysm repair for infrarenal abdominal aortic aneurysm in 2016. Medication history included amitriptyline, gaviscon and coamoxiclav, which had been prescribed as long-term treatment for SIBO. She had previously trialled, but was intolerant of erythromycin, metronidazole, ciprofloxacin, rifaximin and cotrimoxazole. She also reported adverse reactions to proton pump inhibitors and prokinetics.

The patient gave a history of severe spasmodic abdominal pain associated with increasing distension, nausea and occasional vomiting. She had lost around 5 kg in weight which she attributed to anorexia. She reported opening her bowels daily. Physical examination revealed a tympanic, distended abdomen, which was tender across her central abdomen but no signs of guarding or peritonism. Auscultation revealed scanty bowel sounds. Her vital signs were within normal range, haemodynamically stable and afebrile. Admission bloods were: haemoglobin 12.4 g/dL, mean cell volume 78.3 fL, platelets $296 \times 10^9/L$, white cell count $6.2 \times 10^9/L$, sodium (Na) 136 mmol/L, potassium (K) 4.1 mmol/L, urea 3.2 mmol/L, creatinine 107 $\mu\text{mol/L}$ and C reactive protein 36.6 mg/L (normal range <5 mg/L). A venous lactate was

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Figure 1 Pretreatment axial CT reconstructed image, shown in a modified bone window, taken in the portal venous phase. There are multiple, pathologically dilated small bowel loops, with extensive gas in the bowel wall (blue arrow) and free intraperitoneal gas (red arrow). An aortic stent graft for an aneurysm repair is noted (yellow arrow).

1.4 mmol/L. An abdominal radiograph showed appearances consistent with extensive PI, and prominent loops of both small and large bowel. Subsequent CT of the abdomen and pelvis (CTAP) showed free gas within the abdomen and pelvis with PI, a small volume of free fluid and several distended loops of small and large bowel filled with air, fluid and more distally faeces, without a transition point. The axial and coronal views of the CTAP performed on admission are shown in [figures 1 and 2](#).

Urgent surgical review was arranged in light of the CTAP findings, and in the absence of clinical peritonism, normal observations and venous lactate, no acute surgical intervention was felt necessary.

TREATMENT

Following initial clinical, biochemical and radiological investigations, she was commenced on supportive therapy with the administration of intravenous fluid and insertion of a Ryles tube for aspiration of stomach contents. Regular coamoxiclav was continued, due to multiple antibiotic intolerances, and regular prokinetics—prucalopride and promethazine—were commenced. A dietetic review was organised with a view to starting elemental diet and the patient was counselled appropriately. The patient was also administered high-flow inhalation oxygen therapy (10 L/min) administered through a facemask for up to 20 hours a day. Elemental diet and high-flow oxygen therapy was continued empirically for 10 days.

OUTCOME AND FOLLOW-UP

The patient reported good clinical improvement in her symptoms following therapy: reporting complete resolution of pain, distension and vomiting. A repeat CTAP showed marked improvement

Figure 2 Pretreatment coronal CT reconstructed image showing multiple, pathologically dilated small bowel loops (blue arrow), with extensive gas in the bowel wall and free intraperitoneal gas (red arrow).

in the appearance of PI; the distended bowel loops had returned to their normal calibre with complete resolution of pneumoperitoneum as shown in [figures 3 and 4](#). The patient was discharged

Figure 3 Post-treatment axial CT reconstructed image taken in the portal venous phase showing resolution of the small bowel dilatation, pneumatosis intestinalis and pneumoperitoneum.

Figure 4 Post-treatment coronal CT reconstructed image taken in the portal venous phase showing resolution of the small bowel dilatation, pneumatosis intestinalis and pneumoperitoneum.

from hospital and remained well at clinical review in the outpatient department, having reintroduced a normal soft diet.

Three months following discharge, the patient represented with similar symptoms of abdominal pain and vomiting; she was recommenced on empirical treatment with high-flow oxygen and elemental diet. She responded well and was discharged after completing 10 days of combination therapy.

DISCUSSION

CT is the gold-standard diagnostic tool in establishing a diagnosis of PI. The appearances of pneumoperitoneum and PI as seen in this case mimic appearances of sinister pathologies including visceral perforation, bowel ischaemia and bowel infarction. Detailed clinical history, physical examination, laboratory investigations and review of radiological images are therefore imperative to patient's management.⁸ Laboratory markers including pH < 7.3, bicarbonate level < 20 mmol/L, lactate level > 2 mmol/L, amylase level > 200 U/L and portal venous gas on imaging are useful predictors of bowel necrosis and/or mortality in patients with PI.⁹ Certain radiological findings are also found to be useful in distinguishing the severity underlying the different causes of PI. The probability of life-threatening causes of PI increases in the presence of bowel wall thickening, dilated bowel calibre, arterial or venous occlusion, ascites and hepatic portal or portomesenteric venous gas. Hepatic portal venous gas must be differentiated from biliary gas which is benign based on the distribution of gas that extend to the periphery of the liver from those that are central, respectively.¹⁰

The evidence for the treatment for GI scleroderma-related PI is limited. Management approaches largely focus on exclusion of life-threatening acute surgical causes and subsequent symptom control. Following exclusion of life-threatening signs and symptoms, the management approach taken for this case

was largely supportive with a combination of elemental diet, high-flow inhalation oxygen therapy, prokinetics and empirical antibiotics treatment for SIBO thus averting the need for surgical intervention.

The rationale for the use of elemental diet in PI is to reduce nutrient transit in the large bowel. Elemental diet is theorised to be readily absorbed in the small intestine, in turn leading to reduced nutrient availability within the colon, reducing colonic flora gas production.¹¹ van der Linden and Marsell observed that patients with PI had extremely high end-expiratory hydrogen fasting value in the absence of lung pathology.¹² Hydrogen gas is not a product of mammalian cell metabolism and is usually a product of bacterial fermentation of unabsorbed colonic carbohydrate.¹³ Decreased hydrogen value and cyst regression observed following treatment with 2 weeks of elemental diet therefore support the postulation that excessive intestinal gas production contribute to the pathogenesis of cysts seen in PI. The use of elemental diet to reduce colonic carbohydrate load therefore should lead to reduction in hydrogen gas formation and subsequently cystic formation in PI.^{11 13} However, evidence around the use of elemental diet in PI is limited. A case report published by Johnston and McFarland described colonoscopically documented resolution of PI in two patients previously unresponsive to medical therapy 2 weeks after commencing elemental diet.¹⁴

Resolution of PI complicated by pneumoperitoneum has been reported following the use of metronidazole 500 mg three times a day in multiple case reports.^{15–17} The rationale for the use of antibiotics in PI is largely to target gas-producing anaerobic bacteria. The use of antibiotic agent is attractive, as this does not necessitate patient to be admitted as an inpatient in contrast to the use of high-flow inhalation oxygen therapy. As our patient has tried multiple antibiotic regimens in the past, our choices of antibiotics were limited. Unlike metronidazole used in previous case reports,^{15–17} the use of coamoxiclav in the context of SIBO in systemic sclerosis-related PI has never been reported.

Forgacs *et al* first described the use of high-flow oxygen in PI in 1973.¹⁸ The high oxygen tissue concentration achieved through the use of high-flow inhalation oxygen therapy is found to be toxic to gas-producing anaerobic bacteria. Achieving high tissue oxygen concentrations helps reduce the number of these gas-producing anaerobic bacteria and subsequent gas production and cysts formation. Second, high-flow inhalation oxygen creates a PaO₂ diffusion gradient that promotes exit of gas across the cystic wall. Increasing the blood oxygen concentration through high-flow inhalation oxygen therapy forces oxygen into the oxygen-poor cysts down the concentration gradient. The increased non-oxygen PaO₂ in the cysts causes the gas to diffuse out of the high-pressure cyst into the blood stream. Cyst resolution subsequently follows as oxygen reabsorption occurs for use in cellular metabolism.¹⁹ In addition to high-flow inhalation oxygen therapy, hyperbaric oxygen therapy has also been put forward as a management option for patients with PI, with a similar mechanism of action and is a subject of recent reviews and case reports,^{19 20} the obvious limitation being availability of hyperbaric facilities.

We present a case of successful management of systemic sclerosis-associated PI using a combination of prokinetics, antimicrobials, elemental diet and high-flow inhalation oxygen therapy. The striking clinical and radiological improvement support the use of this approach in subsequent cases, and adds to the evidence basis for therapeutic management in this rare presentation.

Learning points

- When managing patients presenting with pneumatosis intestinalis, detailed clinical history, physical examination, laboratory investigations and review of radiological images are imperative to patient's management as the presentation can mimic appearances of sinister pathologies including visceral perforation, bowel ischaemia and bowel infarction.
- Combination therapy with high-flow inhalation oxygen therapy, elemental diet and optimised medical therapy can offer therapeutic benefits in patients with pneumatosis intestinalis.
- Case reports can lend valuable support in the management of rare case presentations where limited higher level evidence is available to form standards of practice.
- Multidisciplinary approach is essential when managing complex cases.

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