Introduction
Pneumatosis cystoides intestinalis (PCI) is a rare complication of mixed connective tissue disease and scleroderma.\(^1\,2\,3\,4\,5\,6\) PCI is defined as the presence of intramural accumulation of gas filled thin-walled multi-locular cysts in the submucosal or subserosal layers of the gastrointestinal tract.\(^1\,2\,3\,4\,5\,6\,7\,8\) Typically, PCI develops during scleroderma flare-ups associated with mechanical insult or bacterial overgrowth.\(^1\) Imaging studies are used for diagnosis with CT or plain film radiography showing gaseous cysts in the bowel walls.\(^2\,3\,5\) Conservative treatment is usually all that is required for PCI, however with signs and symptoms of bowel ischemia or perforation, immediate surgical intervention is needed.\(^2\,5\) In addition, the appearance of apparently unexplained free air under the diaphragm suggests surgery is needed for the working diagnosis of perforated viscus, peptic ulcer disease, or diverticulum.\(^1\,2\,3\,4\,5\,6\,7\,8\,9\) In this case series we describe two patients, both presenting with PCI as a complication of scleroderma.

Case Presentation

Case 1
A 41-year-old woman was transferred to our hospital from another facility due to unresolved abdominal pain, nausea, emesis worsened by oral intake for the past month. Her history was significant for a long standing mixed connective tissue disease, systemic scleroderma, with severe gastrointestinal involvement diagnosed 7 years ago, and reliance on total parenteral nutrition (TPN). In addition, she had been diagnosed with systemic lupus erythematosus (SLE), Raynaud’s phenomenon, autoimmune hepatitis, Sjogren’s syndrome, and polymyositis. She had chronic abdominal pain with intermittent nausea and vomiting since 2013. Those symptoms were controlled with domperidone, a prokinetic, and antiemetic until about a month ago. In order to relieve her abdominal pain, she required fentanyl patch 100 mg every 3 days and hydromorphone 2 mg three times a day as needed. Prior to her current admission, she had stopped outpatient TPN for approximately 1 month. She resumed oral intake on her own, noting that her overall intake was poor since it would trigger nausea, vomiting and abdominal pain that gradually worsened. Her transfer records included abdominal computed tomography (CT) images which revealed extensive pneumatosis intestinalis in the distal ileum, and colonic and pneumoperitoneum with free air under the diaphragm (Figure 1). Ruptured viscus was suspected. She underwent immediate diagnostic laparotomy revealing intact bowel with no evidence of perforation. No resection or intervention took place at that time. It was her second diagnostic laparotomy, with the first one being performed 6 months prior in the same clinical setting of free air under the diaphragm resulting in similar negative findings. On admission to our hospital she complained of diffuse abdominal pain, 8 out of 10 in intensity, associated with nausea and occasional vomiting of solid food contents 3 hours post meal intake. During physical examination, the patient was afebrile, blood pressure 148/98 mmHg, and heart rate 87 beats per minute. She appeared cachectic and weighed 44.3 kg. On physical examination she had facial and digital skin tightening typical of systemic scleroderma, epigastric tenderness, her abdomen was soft and nondistended without rebound or guarding. The laboratory investigations revealed normal white blood cell count, hemoglobin 8.3, hematocrit 25.6, mean corpuscular volume 91.4, platelets 212, sodium 141, potassium 3.3, chloride 110, bicarbonate 21, blood urea nitrogen 6, creatinine 0.68, albumin 1.4, total protein 8.7, glucose 66, calcium 7.3, total bilirubin 0.3, AST 30, ALP 56. Patient was placed on in-

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Figure 1. Coronal and axial CT of the abdomen. Extensive pneumatosis intestinalis (arrows) and pneumoperitoneum.
travenous fluids (IV) and bowel rest (NPO). An abdominal ultrasound with Doppler flow showed no evidence of celiac artery compression. A glucose breath test for small intestinal bacterial overgrowth (SIBO) was also positive. A gastric emptying scintigraphy study was limited secondary to less than 75% consumption of the radiotracer tagged meal, with retention of the tracer within dilated distal esophagus. Upper gastrointestinal endoscopy revealed atonic esophagus, chronic gastritis, dilated first and second portions of duodenum. Pathological specimen was positive for \textit{H.pylori}. The patient was restarted on TPN while being treated with antibiotics for SIBO and \textit{H.pylori}, in addition to metoclopramide IV for gastrointestinal dysmotility. In order to overcome dependence on TPN with all its complication and costs, the patient underwent laparoscopic J-tube placement with antral smooth muscle biopsy revealing a few inclusion bodies, mild to moderate fibrosis in between the muscle bundles, and 15 interstitial cells of Cajal per high power field, which is within normal limits. Patient tolerated J-tube feeding very well during her remaining hospital stay. Nutrition formula (1.5 cal/cc Jevity, Abbott) feedings were administered over 8-10 hours at night at a rate of 60-80 cc per hour. The patient would try oral feeding during the day when there was no J-tube feeding. TPN was discontinued prior to discharge. She was discharged home on antibiotics, azathioprine (for her scleroderma) and medication to manage pain. As an outpatient, she continued with nocturnal J-tube feeding and soft mechanical diet during the day as tolerated. During her follow-up appointments with a gastrointestinal motility expert one month later, the patient’s condition remained stable. Her appetite improved, but she had not gained weight since discharge. Since her tolerance for oral food intake improved, the goal for the following visit was to gradually increase caloric intake.

Case 2
A 59-year-old female with history of scleroderma and gastroparesis, presented to the emergency room with nausea, vomiting, abdominal pain, decreased food intake, constipation for the past four days and sharp left-sided chest pain of one day duration. She had three previous admissions with similar symptoms at a different facility. Her past medical history was significant for breast cancer, status post bilateral mastectomy in 2005 and 2006 followed by chemoradiation treatment. She was diagnosed with scleroderma in 2012. She was seen by a gastrointestinal motility expert at our institution a few months prior to the current admission. At that time, she reported significant weight loss during the past 6 months. Treatment with the prokinetic/antiemetic agent, domperidone was initiated by way of FDA IND protocol. On admission to our medical center, the patient had a temperature of 36.6 degrees Celsius, heart rate 103 beats per minute, blood pressure 91/56 mm Hg (mean arterial pressure 68 mm Hg). On physical exam she was cachectic, with facial skin tightening characteristic of systemic scleroderma. Her abdomen was distented and tender with hypoactive bowel sounds. Laboratory work-up revealed hemoglobin 6.2, hematocrit 18, mean corpuscular volume 88.2, platelets 287, sodium of 124, potassium 3.7, chloride 86, bicarbonate 21, blood urea nitrogen 29, creatinine 0.92, glucose 153, calcium 7.3. Computed tomography (CT) of the chest showed cavitated necrotizing pneumonia in the left lung base, likely due to aspiration, with no evidence of significant pulmonary fibrosis (Figure 2). Her abdominal CT revealed a diffuse dilated small bowel with pneumatosis intestinalis and...
pseudo-obstruction (the gas pattern associated with small bowel overgrowth common in scleroderma) with no evidence of free air under the diaphragm (Figure 3). The patient was transferred to the Intensive Care Unit and treated with antibiotics. A nasogastric tube was placed to decompress her gastrointestinal tract and prevent aspiration. Blood cultures grew gram-positive cocci in clusters. Her mean arterial pressure started to drop with increase in white blood cell count. She became hypotensive. She was intubated for respiratory support, and was given pressors to maintain her mean arterial pressure above 65. She also received blood transfusions and platelets due to drop in hemoglobin and thrombocytopenia. She deteriorated rapidly within 24 hours and required more pressors, likely in the background of disseminated intravascular coagulopathy. The patient’s oxygen saturation was rapidly decreasing. Subsequent chest X-ray revealed pulmonary edema. In light of the patient’s comorbidities and her clinical state, patient’s family revised their intentions for medical interventions from “modified comfort measures only” to “do not resuscitate”. After discontinuing fluid resuscitation and pressors, comfort was provided with morphine. The patient died shortly thereafter.

**Discussion**

Pneumatosis cystoides intestinalis (PCI) was described during autopsy by DuVernoi in the 18th century. PCI is an extremely rare occurrence in scleroderma and mixed connective tissue disease. PCI is defined as the presence of intramural accumulation of gas filled thin-walled multi-locular cysts in the submucosal or subserosal layers of the gastrointestinal tract, sometimes resulting in pneumoperitoneum. The signs and symptoms of PCI can range from nonspecific abdominal discomfort, pain, nausea, vomiting, weight loss, diarrhea, to radiological signs consistent with abdominal perforation. These manifestations were well represented in both patients in this case series.

Scleroderma results in a multitude of pathologies including microangiopathic changes, atrophy of the intestinal layers, fibrosis, intestinal dysmotility, bacterial overgrowth, increased intraluminal pressure, and degradation of the intestinal wall. The small intestine is the part of the gastrointestinal tract most commonly involved. Cysts measuring 0.5-10 cm are most commonly found in the terminal ileum, less commonly the large intestine and rarely the stomach. Multiple theories exist for the pathogenesis of PCI, with two predominant mechanisms being a mechanical disruption versus bacterial overgrowth. The mechanical theory states that PCI development in scleroderma results from a pseudo-obstruction or compression state resulting in gas passing through the submucosal or subserosal layers of the intestines and small cysts forming subserosally. The bacterial overgrowth theory of PCI development in scleroderma results from bacterial hypomotility which creates bacterial overgrowth in the intestines and subsequent bowel distention and intraluminal pressure caused by increased bacterial fermentation production of hydrogen and methane being forced into submucosal or subserosal tissues, and breakdown of mucosal integrity.

Less common theories for development of PCI include chronic long term use of corticosteroids used in the course of treating scleroderma, which results in atrophy of the intestinal mucosa and relocation of bowel gas to the submucosal/subserosal area. However, it should be noted that neither of our patients had received corticosteroid treatment for any extended periods. A less supported theory of PCI development is pulmonary gas from ruptured alveoli result in air traveling down the mediastinum and tracking into the retroperitoneum eventually leading into the bowel mesentery, or in the setting of emphysema, intra-abdominal pressure, or pulmonary obstruction. Pre-existing pulmonary disease (i.e. pulmonary fibrosis, emphysema) was not evident in our patients.

Imaging studies are important for the diagnosis of PCI. The advent of CT has decreased the incidence of late stage disease complications such as intestinal perforation or pneumoperitoneum, such that most PCI in scleroderma is detected earlier while relatively asymptomatic. CT is sensitive for detecting PCI, but cannot distinguish between benign and life threatening causes. Although PCI is usually a late stage disease presentation, CT can indicate the presence of PCI with pneumatosis intestinalis. In this setting, a laparoscopy for “perforation of the bowel” is not indicated. This finding could be explained by diffusion of gas from the cysts rather than “true perforation.” As illustrated in our first case, two laparoscopies were performed for presumed perforation. However, bowel wall gas seen submucosally or in muscle is also observed in other conditions. Differential causes include gas-forming organisms (e.g. Clostridium), necrosis, ischemia or perforation can complicate toxic megacolon in inflammatory bowel disease, ischemic bowel. Conservative treatments include bowel rest, oxygen therapy, supportive care (fluids and electrolytes), total parenteral nutrition, bowel decompression, octreotide infusion and antibiotics. Increased oxygen can reduce submucosal/subserosal gas cysts due to the decreased partial pressure of nitrogen which decreases fermentation of intestinal bacteria.

Complications of PCI are rare, but can include pneumoperitoneum, volvulus, true complete obstruction, or bowel ischemia leading to hemorhage. Ischemia leading to gangrene should be suspected when elevation of lactate is detected, in which case immediate surgical intervention is necessary. Although usually benign, patients need to be watched carefully for bowel ischemia or perforation. PCI is usually a late stage disease presentation in scleroderma.

PCI as a radiographic finding may be present in patients with a wide spectrum of disease processes in addition to systemic sclerosis such as pulmonary causes (emphysema, pulmonary fibrosis, cystic fibrosis), intestinal causes (pseudo-obstruction, peptic ulcer disease, IBD, diverticulitis), and mesenteric vascular disease, colitis, and trauma. Although PCI can resolve with watchful waiting as in our first patient, clinicians should be aware of other complications of scleroderma where PCI can be a secondary finding, as illustrated in our second case, where we presume that gastroparesis due to scleroderma led to aspiration, pulmonary abscess, respiratory and circulatory failure, and death.

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REFERENCES


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