

BRIEF REPORT

Case of pneumatosis cystoides intestinalis with intra-abdominal free air developed during treatment with voglibose

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Introduction

Pneumatosis cystoides intestinalis (PCI) is a relatively rare disease in which air-containing cysts form in the submucosa and serosa of the intestinal wall of the small and large intestines.¹ There are several theories regarding the cause of PCI, including (i) increased intestinal pressure due to intestinal obstruction, constipation, or increased intestinal peristalsis, which causes intestinal gas to enter the intestinal wall through the damaged area of the mucosa, (ii) production of gas by gas-producing bacteria, such as *Clostridium* spp., (iii) pulmonary disease theory, in which chronic lung disease damages alveoli and the leaked air reaches the intestinal wall via the mediastinum and retroperitoneum, (iv) trichloroethylene exposure, etc.^{1–3} Plain abdominal X-rays show translucent images of grape cluster and unequally sized honeycomb shapes along the intestinal wall and sometimes free air. Abdominal CT reveals multiple low-absorption areas consistent with the intestinal wall and serosa, with intraportal gas in the fulminant form.^{4,5} The known risk factors include a history of gastrointestinal disease and corticosteroid administration.⁵

Recently, PCI has been reported in some diabetic patients receiving α -glucosidase inhibitors (α GI).^{6–10} We report a case of PCI with intra-abdominal free air in a 76-year-old woman who was receiving α GI, voglibose, and prednisolone.

Case report

A 76-year-old woman was visiting the doctor on a regular basis for diabetes mellitus, and she had been receiving α GI, voglibose at a

dose of 0.6 mg/day for 2 years and 4 months. She had undergone endoscopic submucosal dissection (ESD) for early gastric cancer 11 months ago. The resection specimen was 38 × 33 mm in size, the tumor size was 12 × 10 mm, and the pathological diagnosis was pT1a (M), Ly0, V0, pHM0, pVM0, and complete resection. The patient started receiving prednisolone 1 year and 4 months ago for polymyalgia rheumatica; initially started at 15 mg/day, the dose was gradually reduced and is now maintained at 1 mg/day. She had no history of respiratory disease. At this time, she had nausea and vomiting for 10 days, and her abdomen was tender on palpation. The recoil pain was not obvious. Four months ago, upper gastrointestinal endoscopy was performed as a follow-up after ESD for gastric cancer, which did not reveal any obvious abnormalities. The abdomen was immediately scanned using contrast-enhanced computed tomography (CT), and emphysematous changes in the ileal wall and free air in the abdominal cavity and under the right diaphragm were observed, indicating ileal perforation (Fig. 1).

The patient was rushed to the surgery department of the general hospital and admitted on the same day. In the hospital, she was diagnosed with α GI-induced PCI and concomitant intra-abdominal free air. On the same day, she discontinued the α GI and was treated with fasting and conservative therapy. Three days after onset, a CT scan was performed, which revealed residual PCI but no increase in free air levels (Fig. 2a,c), and the patient recommenced eating. Her symptoms did not worsen anymore, and she was discharged from the hospital. Two weeks later, an abdominal CT scan was performed (Fig. 2b,d), which

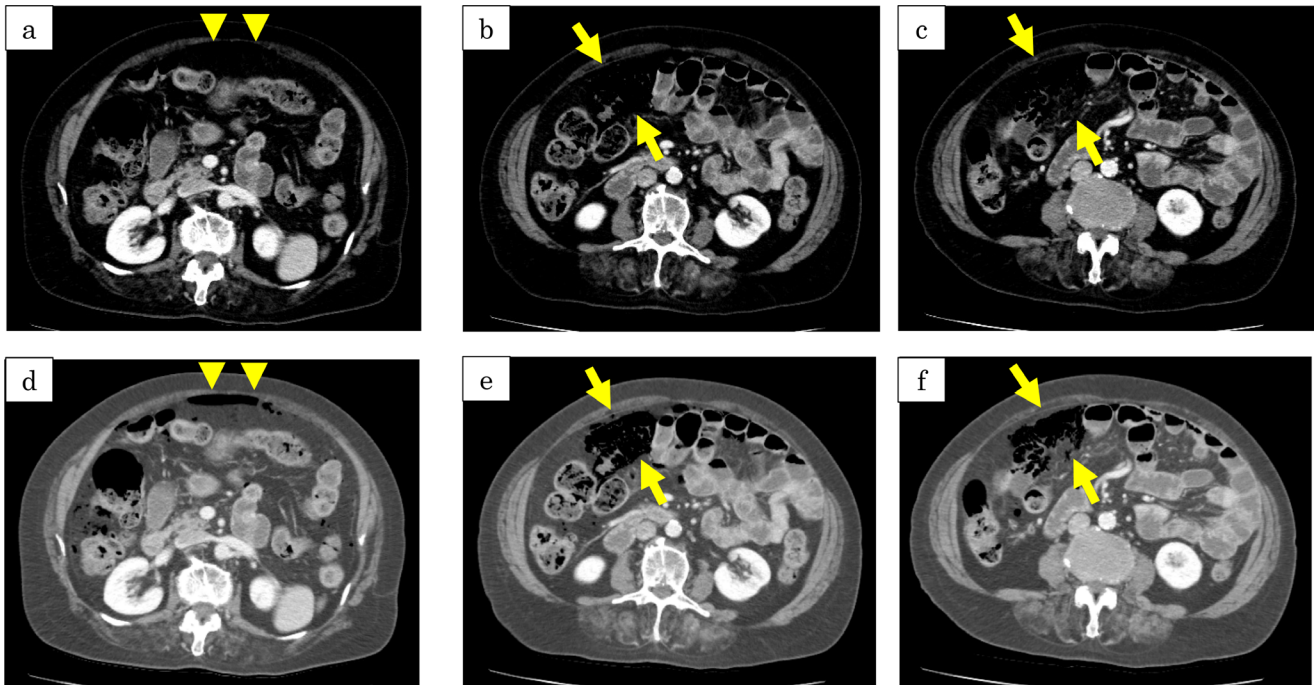


Figure 1 Contrast-enhanced computed tomography (CT) scan (portal phase) at the onset. Emphysema is detected in the ileal wall (b, c: Arrows) and free air is detected in the abdominal cavity (a: Arrowhead). CT scan imaging settings: (a-c) window level (WL) 60 and window width (WW) 300. (d-f) WL 0 and WW 433. By changing the imaging settings, intestinal emphysema and free air can be more easily identified.

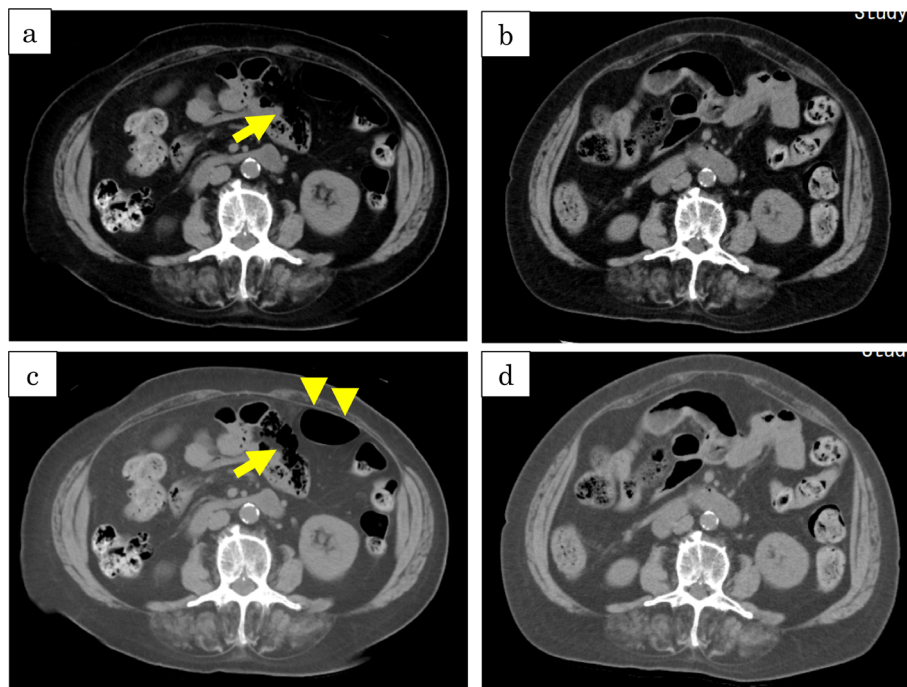


Figure 2 Computed tomography (CT) scan on the third day of onset: (a, c): Both intestinal emphysema (arrows) and free air (arrowheads) remain, but there is no increase in free air. CT scan 2 weeks after onset: (b, d): Intestinal emphysema and free air have resolved. Imaging settings: (a, b) Window level (WL) 30 and window width (WW) 300. (c, d) WL 0 and WW 433.

revealed that the free air and emphysematous changes in the ileal wall had resolved.

This study has been approved by the research ethics committee of Kusunoki Hospital.

Discussion

Recently, there have been multiple reports of the incidence of PCI in patients receiving α GI.^{6–10} α GI is an oral anti-diabetic drug that selectively inhibits α -glucosidase enzymes in the small intestine that degrade disaccharides to monosaccharides, slowing carbohydrate digestion and absorption and lowering postprandial hyperglycemia. The presence of undigested carbohydrates in the small and large intestines of patients taking α GI promotes the intestinal overgrowth of bacteria that ferments carbohydrates and produces nitrogen, hydrogen, oxygen, carbon dioxide, nitrous oxide, n-butane, isobutane, propane, and methane,¹¹ resulting in side effects, such as abdominal bloating and flatulence. This excessive gas production is believed to increase intestinal pressure, allowing gas to pass through the intestinal wall and cause PCI.¹²

Although there was intra-abdominal free air in this case, the patient recovered after only a few days of fasting and rehydration, indicating that there was no gastrointestinal perforation. Intra-abdominal free air is relatively common in PCI and is not always indicative of intestinal perforation. Peritoneal irritation symptoms, such as tenderness, recoil pain, and muscular defense, can be observed in the presence of intestinal perforation. The most common cause of intra-abdominal free air images is gastrointestinal perforation, which requires surgical treatment for peritonitis. However, many cases of intra-abdominal free air have been reported in PCI despite the absence of perforation or intestinal necrosis. The mechanism is thought to be as follows: nitrogen gas is normally physiologically inert in the body and dissolves in the blood; however, when intestinal pressure rises, it bubbles and causes gas retention within the intestinal wall. Then, as the intestinal pressure rises, air leaks into the abdominal cavity from the fragile intestinal mucosa and wall.¹³ However, cases of suspected intestinal perforation necessitating laparotomy have been reported.¹⁴

Once α GI-induced PCI has been diagnosed, the patient is often treated conservatively by discontinuing α GI, fasting, and fluids. Additionally, antimicrobial agents, oxygen inhalation therapy, and hyperbaric oxygen therapy may be required.¹⁴ Both normobaric and hyperbaric oxygen therapies have been used to treat patients with PCI who did not respond to conservative measures. The mechanism is that the oxygen concentration in arterial blood is increased by inhalation of high oxygen concentrations, which replaces nitrogen in the gas-filled cysts, and subsequently is absorbed into the tissues and capillaries, resulting in the disappearance of the cysts.¹⁵ In this case, the patient was considered to have a mild disease because the disease resolved after only fasting and discontinuing α GI.

Although this was a case of postoperative ESD for gastric cancer, it is unclear whether ESD itself is a risk factor for PCI. Since ESD was less invasive, 11 months had passed, and there was no recurrence of gastric cancer at the time of PCI, gastric cancer and ESD are unlikely to have been the triggers for this PCI. Here, the patient had been taking prednisolone at a low dose of 1 mg/day for approximately 1 year at the time of PCI. Peptic ulcer, gastrointestinal perforation, gastrointestinal bleeding, and pancreatitis are common side effects of long-term corticosteroid use.

Several cases of α GI-related PCI have been reported in cases of steroid use. Corticosteroid administration is believed to cause mucosal tissue damage due to a decrease in intestinal submucosal lymph nodes, weakening of mucosal resistance, and a delay in mucosal repair.¹⁴ It is speculated that intestinal gases enter the intestinal wall from the site of mucosal damage, resulting in the development of PCI. Hisamoto *et al.*¹⁶ reported that PCI occurred on the seventh day after starting voglibose for steroid diabetes in a patient with interstitial pneumonia receiving prednisolone at 50–40 mg/day for 1 month. Ezuka *et al.* also reported a case of PCI in a patient with asthma who developed PCI while receiving 30 mg prednisolone, but the PCI significantly improved when the prednisolone was tapered off, implying that the onset of α GI-related PCI may depend on the dosage of steroid.¹⁷ Although PCI can occur even in a short time (day 7) at high prednisolone doses, as demonstrated by Hisamoto *et al.*, it is unclear whether low-dose steroidal use increases PCI risk. According to Saito *et al.*, even a single factor that does not cause PCI development can result in PCI development if many of these factors overlap.¹⁸ It is possible that long-term use of even low doses of prednisolone, as in this case, may increase PCI risk.

Package inserts for α GIs, such as voglibose, acarbose, and miglitol, contain reports of adverse reactions to PCI and are, therefore, contraindicated for administration before and after surgery. However, the package inserts include cautionary statements regarding the concomitant use of steroids in terms of decreasing the hypoglycemic effect but exclude a caution or warning regarding PCI occurrence with steroids. Therefore, when risk factors, such as concomitant use of steroids and postoperative state for gastric ESD, are combined, as in this case, extreme caution may be necessary to prevent PCI development.

Internists and emergency physicians should have basic knowledge of the development of PCI in association with α GI. Furthermore, the threshold for suspicion of PCI should be lower in patients taking α GI and have other risk factors for PCI development (e.g. taking steroids, postoperative gastrointestinal surgery, and more) when they develop abdominal distention or other symptoms.

Patient consent. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Data availability statement. Data sharing is not applicable.

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