

## Pneumatosis cystoides intestinalis following alpha-glucosidase inhibitor treatment: A case report and review of the literature

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### Abstract

A 69-year-old man was diagnosed as having myasthenia gravis (MG) in September 2004, and treated with thymectomy and prednisolone. He was then diagnosed as having steroid-induced diabetes mellitus, and received sulfonylurea (SU) therapy in May 2005. An alpha-glucosidase inhibitor ( $\alpha$ GI) was added in March 2006, resulting in good glycemic control. He experienced symptoms of abdominal distention, increased flatus, and constipation in October 2007, and was admitted into our hospital in late November with hematochezia. Plain abdominal radiography revealed small linear radiolucent clusters in the wall of the colon. Computed tomography (CT) showed intramural air in the sigmoid colon. Colonoscopy revealed multiple smooth surfaced hemispherical protrusions in the sigmoid colon. The diagnosis of pneumatosis cystoides intestinalis (PCI) was made on the basis of these findings. As the  $\alpha$ GI voglibose was suspected as the cause of this patient's PCI, treatment was conservative, ceasing voglibose, with fasting and fluid supplementation. The patient progressed well, and was discharged 2 wk later. Recently, several reports of PCI associated with  $\alpha$ GI therapy have been published, predominantly in Japan where

$\alpha$ GIs are commonly used. If the use of  $\alpha$ GIs becomes more widespread, we can expect more reports of this condition on a global scale. The possibility of PCI should be considered in diabetic patients complaining of gastrointestinal symptoms, and the gastrointestinal tract should be thoroughly investigated in these patients.

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**Key words:** Alpha-glucosidase inhibitor; Colonoscopy; Diabetes mellitus; Pneumatosis cystoides intestinalis; Voglibose

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### INTRODUCTION

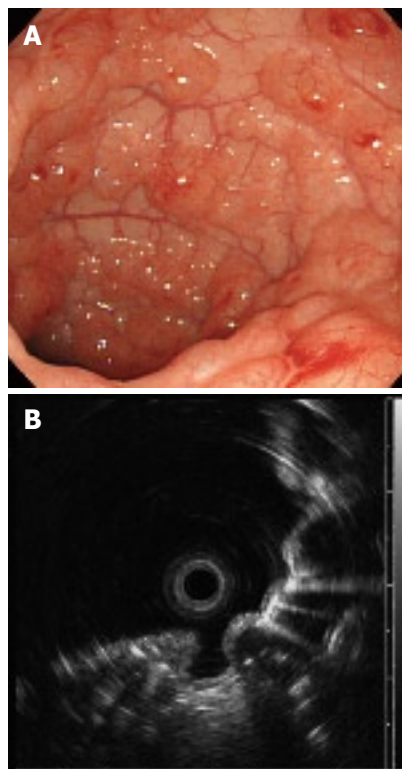
Pneumatosis cystoides intestinalis (PCI) is a rare condition in which multiple submucosal or subserosal pneumocystis develop in the submucosa or in subserosa of the colon<sup>[1,2]</sup>. The etiological mechanisms are unclear, although PCI has been reported to develop in association with raised intra-abdominal pressure due to ileus surgery<sup>[3-5]</sup>, colonoscopy<sup>[6]</sup>, pulmonary diseases such as chronic bronchitis and emphysema<sup>[7]</sup>, trichloroethylene exposure<sup>[8]</sup>, connective tissue disorders<sup>[9,10]</sup>, the use of immunosuppressants<sup>[11]</sup>, and ingestion of carbohydrates such as lactulose<sup>[12]</sup> and sorbitol<sup>[13]</sup>. Recently, the development of PCI during treatment with alpha-glucosidase inhibitors ( $\alpha$ GIs), a new class of anti-diabetic agents, has been reported<sup>[14,15]</sup>. Our literature search yielded only 13 cases of PCI associated with  $\alpha$ GI therapy<sup>[14-26]</sup>. Herein, we present a case depicting  $\alpha$ GI as the probable cause of PCI, along with a review of the literature.



**Figure 1** Plain radiography of the abdomen on admission revealing small linear and round radiolucent clusters in the wall of the colon (black arrows).



**Figure 2** Computed tomography (CT) scanning of the abdomen on admission revealing intramural gas in the sigmoid colon (white arrows).



**Figure 3** Colonoscopy on admission showing multiple round and smooth-surfaced elevated lesions like submucosal tumors in the sigmoid colon (A) and endoscopic ultrasonography (EUS) revealing hyperechoic lesions and acoustic shadows in the submucosal layer (B).

## CASE REPORT

A 69-year-old man was diagnosed as having severe myasthenia gravis (MG) in September 2004, and treated with prednisolone (5 mg/d) from October of that year. He underwent thymectomy in March 2005. Hyperglycemia was detected in May 2005, leading to the diagnosis of steroid-induced diabetes mellitus, and sulfonylurea (SU) therapy was commenced immediately. As his blood sugar could not be controlled,  $\alpha$ GI was prescribed in March 2006, resulting in good glycemic control. He claimed to have experienced abdominal distension, increased flatus and constipation, and noticed small amounts of bright rectal bleeding as early as mid-October 2007, but did nothing about it. The amount of rectal bleeding increased in late November that year, and he was referred to our hospital for investigation and treatment.

Laboratory investigations revealed no abnormalities in white blood cell (WBC) count, hemoglobin (Hb), or C-reactive protein, and HbA1c was slightly elevated to 6.0%. Plain abdominal radiography revealed small linear radiolucent gas collections along the wall of the colon (Figure 1). Unenhanced computed tomography (CT) of the abdomen showed intramural air in the sigmoid colon, and free gas in the peritoneal cavity around the sigmoid colon (Figure 2). Colonoscopy revealed multiple smooth surfaced small hemispherical protrusions in the sigmoid colon, and endoscopic ultrasonography (EUS) demonstrated highly echogenic submucosal lesions with

acoustic shadows (Figure 3). The diagnosis of PCI was made on the basis of these findings.

As voglibose was suspected to be the cause of this patient's PCI, conservative treatment was administered, including ceasing the voglibose, along with fasting and fluid supplementation. The patient progressed well and plain abdominal radiography 2 wk later showed that the linear collections of gas along the wall of the colon were disappeared, and consequently the patient was discharged. Colonoscopy 3 mo later showed complete resorption of the pneumocystis throughout the sigmoid colon, leaving white scars. EUS confirmed disappearance of the submucosal acoustic shadows, indicating the resolution of PCI.

## DISCUSSION

PCI, first reported by Du Vernoi<sup>[27]</sup> in 1730, is a rare condition in which multiple submucosal or subserosal pneumocystis develop in the submucosa or subserosa of the colon. It was previously thought to occur most frequently in the ileum, but with the recent increase in the number of barium enemas and colonoscopies performed, PCI now reportedly affects the colon more commonly.

There are some recent reports on PCI associated with  $\alpha$ GI therapy<sup>[14-26]</sup>. The mechanism is thought to involve intestinal gas production through fermentation by the intestinal flora of carbohydrates whose absorption is inhibited by  $\alpha$ GI. Along with peristaltic hypofunction

**Table 1** A summary of previously reported cases of pneumatosis cystoides intestinalis (PCI) after an alpha-glucosidase inhibitor ( $\alpha$ GI) treatment

Case No.	Author Reference number Yr	Age Sex	Chief complaint	The $\alpha$ GI agent Quantity of $\alpha$ GI Dosage period of $\alpha$ GI prior to PCI onset	Disease other than diabetes mellitus	Concomitant drug	Prescription of $\alpha$ GI after PCI onset	Treatment Outcome Duration to the outcome
1	Hayakawa <i>et al</i> 14 1999	64 F	Abdominal distention	Voglibose 0.6 mg/day 1 mo	Unknown	Insulin	Discontinuation	Conservative treatment Healing 4 d
2	Azami 15 2000	87 F	Abdominal distention Appetite loss	Acarbose 150 mg/day 1 yr	Hypothyroidism	SU	Discontinuation	Conservative treatment Healing 5 d
3	Maeda <i>et al</i> 16 2002	55 F	Abdominal distention	Acarbose 300 mg/day 42 d	Pemphigus vulgaris	Insuline steroid Immunosuppressant	Continuation	Conservative treatment Healing 141 d
4	Tachibana <i>et al</i> 17 2002	73 F	Abdominal distention	Acarbose 150 mg/day 8 yr	Henoch-Schonlein purpura nephritis	SU Steroid	Discontinuation	Conservative treatment Healing 28 d
5	Yanaru <i>et al</i> 18 2002	61 M	Abdominal distention Constipation Hematochezia	Voglibose 0.6 mg/day 5 yr	Unknown	SU	Discontinuation	Conservative treatment Healing 28 d
6	Matsuda <i>et al</i> 19 2004	62 M	Abdominal pain	Voglibose Unknown Unknown	Lung cancer	Morphine sulfate	Unknown	Operation Remission 16 d
7	Nagahara <i>et al</i> 20 2006	66 M	Left abdominal pain	Acarbose Unknown 11 yr	Unknown	Unknown	Discontinuation	Conservative treatment Healing 21 d
8	Hisamoto <i>et al</i> 21 2006	56 M	No abdominal symptoms	Voglibose 0.6 mg/day 7 d	Interstitial pneumonia	Steroid	Discontinuation	Conservative treatment Healing 7 d
9	Furio <i>et al</i> 22 2006	64 F	Abdominal pain Diarrhea Tenesmus Weight loss	Acarbose Unknown 3 yr	Unknown	Insulin	Discontinuation	Conservative treatment Healing 15 d
10	Miyagawa <i>et al</i> 23 2006	65 M	Abdominal pain Diarrhea	Voglibose 0.6 mg/day 6 years	Gastric cancer	SU	Continuation→ Discontinuation	Conservative treatment Healing 120 d
11	Yasuoka <i>et al</i> 24 2007	75 M	Abdominal distention	Voglibose 0.6 mg/day 10 yr	Lung cancer Rectal carcinoid	SU	Discontinuation	Conservative treatment Healing 20 d
12	Maeda <i>et al</i> 25 2007	72 F	Rt lower abdominal pain	Voglibose 0.9 mg/day 3 yr	Minimal change disease	Insulin Steroid Immunosuppressant	Discontinuation	Conservative treatment Healing 7 d
13	Saito <i>et al</i> 26 2007	53 F	Abdominal distention Nausea	Voglibose 0.6 mg/day 1 mo	Dermatomyositis	Steroid Immunosuppressant	Discontinuation	Conservative treatment Healing 21 d
14	Our case 2008	69 M	Abdominal distention Hematochezia	Voglibose 0.6 mg/day 1 yr 8 mo	Myasthenia gravis	SU Steroid	Discontinuation	Conservative treatment Healing 14 d

associated with diabetes mellitus, this leads to raised intraluminal pressure, allowing the gas-producing bacteria to invade the colonic mucosa through breaks in the mucosal integrity, forming pneumocysts<sup>[14,15]</sup>.

Our review of the medical literature between 1983 and 2008 yielded 7 cases of PCI associated with  $\alpha$ GI

therapy in PubMed [English language; 14, 15, 18, 21, 22, 25, 26], and 6 in Japana Centra Revuo Medicina [Japanese language; 16, 17, 19, 20, 23, 24]. The details of these cases, totaling 14 with the addition of our present case, are shown in Tables 1 and 2. All but 1 of the 14 cases was reported in Japan. About 30% of

Table 2 Imaging findings in previously reported cases of PCI after an  $\alpha$ GI treatment

Case No.	Author Reference number Year	Plain radiography of the abdomen	Computed tomography of the abdomen	Barium enema	Colonoscopy
1	Hayakawa <i>et al</i> 14 1999	Distention of the ascending and proximal transverse colon with cystic radiolucencies, indicating intramural gas	Subserosal cystic areas of gas and distention of the involved segments	Translucent areas of gas clustered along the distorted contours of the ascending and transverse colon	ND
2	Azami 15 2000	Noticeable gaseous distension of the small intestine	Noticeable gaseous distention of the small intestine with pockets of small gas bubbles in the submucosal space	No constriction in the sigmoid or lower descending colon	ND
3	Maeda <i>et al</i> 16 2002	Multiple cystic radiolucencies in the abdomen	Pneumatosis intestinalis around the bowel wall and gas within the retroperitoneum	ND	ND
4	Tachibana <i>et al</i> 17 2002	Free gas of the right peritoneal cavity and pneumatosis intestinalis throughout the ascending colon	Free gas below the right diaphragm, and pneumatosis intestinalis throughout the ascending colon	ND	Polypoid lesions in the ascending and transverse colon
5	Yanaru <i>et al</i> 18 2002	Small round radiolucent clusters in the middle abdomen	ND	Numerous submucosal protrusions of sessile of semipedunculated configurations	Numerous submucosal protrusions of sessile of semipedunculated configurations
6	Matsuda <i>et al</i> 19 2004	Noticeable gaseous distention of the colon, and curvilinear radiolucency within the bowel wall	Free gas in the peritoneal cavity, pneumatosis intestinalis throughout the bowel wall	ND	ND
7	Nagahara <i>et al</i> 20 2006	Free air below the diaphragm	Pneumatosis intestinalis throughout the ascending colon	ND	ND
8	Hisamoto <i>et al</i> 21 2006	Free air below the diaphragm, and noticeable gaseous distention of the ascending and transverse colon	Slight dilatation, mesenteric edema, and diffuse pneumatosis intestinalis throughout the ascending colon	Many cystic areas of the ascending colon	Multiple sessile polypoid lesions covered with normal-appearing mucosa in the area from the ascending colon
9	Furio <i>et al</i> 22 2006	ND	The presence of numerous intraparietal cysts, of varying size, diffuse in the varied colic segments, compatible with wall pneumatosis of the colon	ND	Multiple polypoid formations of varying sizes in the sigmoid, descending, ascending and cecum
10	Miyagawa <i>et al</i> 23 2006	Cystic radiolucencies in the colon	ND	Multiple numerous round polypoid lesions from the ascending colon to the sigmoid colon	Numerous round polypoid lesions from the ascending colon to the sigmoid colon
11	Yasuoka <i>et al</i> 24 2007	Noticeable gaseous distension of the small intestine	Free gas in the peritoneal cavity	ND	ND
12	Maeda <i>et al</i> 25 2007	Diffuse air shadows along the intestine suggesting gas accumulation in the bowel wall	Circumferential collections of air adjacent to the bowel lumen that ran parallel to the bowel wall	ND	ND
13	Saito <i>et al</i> 26 2007	Pneumoperitoneum with free air under the diaphragm and curvilinear radiolucency within the bowel wall	Intramural air in the ascending colon, and gas collection in the mesentery	ND	ND
14	Our case 2008	Small linear radiolucent gas collections along the wall of the colon	Intramural air in the sigmoid colon, and free gas in the peritoneal cavity around the sigmoid colon	ND	Multiple smooth surfaced small hemispherical protrusions in the sigmoid colon

ND: Not done.

the Japanese diabetics are prescribed  $\alpha$ GIs, which are rarely administered in Western countries where fats account for a larger proportion of the caloric intake than carbohydrates<sup>[28,29]</sup>. The preponderance of Japanese reports on  $\alpha$ GI-associated PCI is not surprising as the Japanese market accounts for 98% of the total sales of

voglibose, and 34% of those for acarbose.

The mean age of the 14 patients was 65.9 years, while 7 were male and 7 were female. The causative agent was voglibose in 9 cases and acarbose in 5, while none was caused by miglitol. The global market share in 2005 for voglibose and acarbose was in a ratio of

roughly 3:2. Miglitol was not released in Japan until 2006, and accordingly no reports are available on PCI associated with the newest agent. As future cases are reported, we expect that there will be no significant differences in the incidence of PCI between these agents. The mean prescribed dosages were 0.64 mg/d for voglibose and 200 mg/d for acarbose. The interval between commencement of  $\alpha$ GI therapy and the onset of PCI varied greatly, ranging from 7 d to 11 years. The most common symptoms were abdominal distention (57%) and abdominal pain (36%), while only 2 cases had hematochezia (14%) as in the case described herein (Table 1).

Different radiological and endoscopic modalities are useful in the diagnosis of PCI. To summarize the imaging findings in the 14 reported cases (Table 2), linear or round radiolucent gas collections were seen along the wall of the colon in plain abdominal radiographs in most cases, and pneumatosis was seen within or along the wall of the colon on abdominal CT scanning. Subserous pneumocystis in particular are liable to rupture, releasing free gas into the peritoneal cavity, making it important to distinguish this condition from bowel perforation<sup>[30]</sup>. Multiple rounded protrusions are a common finding in barium enema examinations of patients with PCI. The colonoscopic findings may be similar to multiple polyposis or collections of submucosal tumors, but subserous pneumatosis may go undetected.

With cessation of  $\alpha$ GI therapy, conservative treatment could lead to resolution of PCI within 28 d. In the 2 cases where  $\alpha$ GI therapy was continued, resolution took more than 120 d. Therefore, ceasing the  $\alpha$ GI therapy is the key to successful treatment of PCI. One case underwent emergency surgery due to the presence of free air in the peritoneal cavity, where bowel perforation could not be ruled out<sup>[19]</sup>. In our case, there were 2 possible causes, namely, the  $\alpha$ GI voglibose and prednisolone. Since our patient claimed to have experienced abdominal distention, increased flatus and constipation prior to the onset of PCI, we considered voglibose the causative agent. We therefore ceased  $\alpha$ GI and continued corticosteroid therapy, and kept our patient fasting with fluid supplementation, achieving resolution of PCI after 14 d (Table 1).

The symptoms of PCI include abdominal pain, diarrhea and abdominal distention, none of which is disease specific. Diabetic patients sometimes develop autonomic neuropathy, with gastrointestinal symptoms similar to those of PCI. As  $\alpha$ GI therapy is commonly used in Japan, it is difficult to determine whether diabetic patients complaining of gastrointestinal symptoms are suffering only from diabetes mellitus or from PCI. If the clinical picture of diabetes mellitus is consistent with that of PCI, diabetes mellitus can be detected by plain abdominal radiography. The possibility of PCI should be considered in diabetic patients complaining of gastrointestinal symptoms, and appropriate investigations should be performed with this potential diagnosis in mind.

In this report, we presented a case of PCI associated

with  $\alpha$ GI therapy, and a review of the literature. Our patient recovered rapidly after conservative treatment, including ceasing of the voglibose, fasting, and fluid supplementation. Recently, several reports on PCI associated with  $\alpha$ GI therapy have been published, predominantly from Japan where  $\alpha$ GIs are commonly used<sup>[14-21,23,24]</sup>. If the use of  $\alpha$ GIs becomes more widespread internationally, we can expect more reports of this condition globally. The possibility of PCI should be considered in diabetic patients complaining of gastrointestinal symptoms, and the gastrointestinal tract should be thoroughly investigated in these patients.

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