Pneumatosis Cystoides Intestinalis Induced by the Alpha-glucosidase Inhibitor Miglitol

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Abstract

Pneumatosis cystoides intestinalis (PCI) is a rare condition in which pneumocysts develop in the submucosa or subserosa of the colon. We report herein a case of PCI induced by the alpha-glucosidase inhibitor (α GI) miglitol. There have been 9 recorded cases of PCI induced by other α GIs, but this is the first report of miglitol causing PCI. The PCI lesions in our case were smaller than those induced by voglibose or acarbose. The possibility of PCI should be considered in diabetic patients on α GI therapy who complain of gastrointestinal symptoms, and the gastrointestinal tract should be thoroughly investigated in these patients.

Key words: pneumatosis cystoides intestinalis, alpha-glucosidase inhibitor, miglitol, colonoscopy, diabetes mellitus

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Introduction

Pneumatosis cystoides intestinalis (PCI) is a rare condition in which multiple pneumocysts develop in the submucosa or subserosa of the colon (1). The etiological mechanisms are unclear although a mechanical theory, a chemical theory, a bacterial theory, and a counter-perfusion supersaturation theory have been proposed. In recent years, cases of PCI induced by alpha-glucosidase inhibitors (α GIs), a new class of antidiabetic agents, have been reported. Our PubMed search yielded only 9 cases of PCI associated with α GI therapy (2-10). Of the different α GIs, reports of PCI induced by voglibose and acarbose have been published, but this is the first report of miglitol causing PCI. In this case report, we present a case of PCI probably induced by miglitol, along with a review of the literature.

Case Report

A 58-year-old man started receiving 150 mg per day of miglitol (an α GI) in June 2008 for the treatment of type 2 diabetes mellitus. He did not receive any medicine other than miglitol. Plain abdominal radiography before miglitol therapy did not reveal gas collection along the wall of the colon or free air. His subsequent glycemic control was good. There was nothing particular in his medical history except for diabetes mellitus. His family history was not remarkable. He was admitted into our hospital for investigation and treatment of lower abdominal pain, and rectal bleeding in February 2009.

Laboratory investigations revealed no abnormalities in the white blood cell count (WBC: 8,000/ μ L), red blood cell count (RBC: 410 $\times$ 10⁴/ μ L), hemoglobin (Hb: 14.9 g/dL), hemoglobinA1c (HbA1c: 5.4%), and carcinoembryonic antigen (CEA: 5.0 ng/mL), but the C-reactive protein (CRP) was slightly elevated (0.45 mg/dL). Abdominal computed to-

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Figure 1. Abdominal computed tomography (CT) scans on admission. A: Horizontal scan. Thickening of the walls is noticed in the ileocecal region and ascending colon, and cloudiness of the adjacent adipose tissue is seen. B: Vertical scan. Submucosal (black arrows) and subserosal (white arrows) gases are seen in the bowel wall. C: Horizontal scan. Extramural gases are seen in the mesenteries and retroperitoneal cavity. D: Vertical scan. Extramural gases are seen in the mesenteries and retroperitoneal cavity.

Figure 2. Colonoscopy on admission revealed multiple small projections associated with erythema and erosions in the ileocecal region and ascending colon.

coecal region and ascending colon, as well as submucosal and subserosal gas. Extramural gas also was seen in the mesenteries and retroperitoneal cavity (Fig. 1). Colonoscopic examination revealed multiple small projections associated with erythema and erosions in the ileocecal region and ascending colon (Fig. 2). The histopathological examination demonstrated multiple small pneumocysts within the submucosa (Fig. 3). Bowel perforation was considered unlikely on the basis of the patient's stable condition, the lack of signs of peritonism, and the weak evidence of inflammation, and the diagnosis of PCI was made on the basis of the aforementioned findings. Miglitol was suspected as the cause of this patient's PCI. Management was therefore conservative, comprising cessation of miglitol, fasting, and fluid supplementation. The patient progressed well, and was discharged 12 days after repeat colonoscopy confirmed the disappearance of pneumocysts in the ileocecal region and ascending colon (Fig. 4).

mography (CT) revealed thickening of the walls of the ileo-

Discussion

PCI is a rare condition in which submucosal or subserosal pneumocysts develop in the submucosa or subserosa of the colon. The etiological mechanisms are unclear, although PCI reportedly develops in association with raised intra-intestinal pressure due to ileus (11), surgery (12), colonoscopy (13), respiratory conditions such as chronic bronchitis and emphysema (14), trichloroethylene exposure (15), connective tissue diseases (16), immunosuppressant therapy (1), ingestion of carbohydrates such as lactulose (17) and sorbitol (18), and counter-perfusion super-saturation (19).

A few reports have been recently published on PCI associated with α GI therapy. The mechanism is thought to in-

volve intestinal gas production through fermentation by the intestinal flora of carbohydrates, of which absorption is inhibited by α GI. This factor, along with peristaltic hypofunction associated with diabetic autonomic neuropathy, leads to raised intraluminal pressure, allowing the gas-producing bacteria to invade the colonic mucosa through mucosal breaks, forming pneumocysts (3).

Our review of the medical literature in PubMed between 1983 and 2009 yielded 9 case reports of PCI associated with α GI therapy (2-10). We highlighted the details of these cases, totaling 10 in addition to the present case, in Table 1,

Figure 3. Histopathological examination of the colonic mucosa, using Hematoxylin and Eosin stain, revealed multiple pneumocysts within the submucosa of the colon (x100).

Figure 4. Colonoscopy on discharge revealed disappearance of the pneumocysts with erythema and erosion in the ileo-coecal region and ascending colon.

Table 1. A Summary of Previously Reported Cases of Pneumatosis Cystoides Intestinalis (PCI) after Alpha-Glucosidase Inhibitor (α GI) Treatment for Diabetes Mellitus

No.	Author	Age Sex	Chief complaint	The α GI agent Quantity of α GI Duration	Disease other than diabetes mellitus	Concomitant drug	Localization	Prescription of α GI after PCI onset	Treatment Outcome Duration to outcome
1	Hayakawa <i>et al.</i> (2)	64 F	Abdominal distention	Voglibose 0.6 mg/day 1 month	Unknown	Insulin	Ascending colon, Transverse colon	Discontinuation	Conservative treatment Healing 4 days
2	Azami (3)	87 F	Abdominal distention, Anorexia	Acarbose 150 mg/day 1 year	Hypothyroidism	SU	Small intestine	Discontinuation	Conservative treatment Healing 5 days
3	Yanaru <i>et al.</i> (4)	61 M	Abdominal distention, Constipation, Hematochezia	Voglibose 0.6 mg/day 5 years	Unknown	SU	Sigmoid colon	Discontinuation	Conservative treatment Healing 28 days
4	Hisamoto <i>et al.</i> (5)	56 F	No abdominal symptoms	Voglibose 0.6 mg/day 7 days	Interstitial pneumonia	Steroid	Ascending colon	Discontinuation	Conservative treatment Healing 7 days
5	Furio <i>et al.</i> (6)	64 F	Abdominal pain, Diarrhea, Tenesmus, Weight loss	Acarbose unknown 3 years	Unknown	Insulin	Caecum, Ascending colon, Transverse colon, Sigmoid colon	Discontinuation	Conservative treatment Healing 15 days
6	Maeda <i>et al.</i> (7)	72 F	Rt lower abdominal pain	Voglibose 0.9 mg/day 3 years	Minimal change disease	Insulin Steroid Immunosuppressant	Unknown	Discontinuation	Conservative treatment Healing 7 days
7	Saito <i>et al.</i> (8)	53 F	Abdominal distention, Nausea	Voglibose 0.6 mg/day 1 month	Dermatomyositis	Steroid Immunosuppressant	Ascending colon, Descending colon	Discontinuation	Conservative treatment Healing 21 days
8	Tsujimoto <i>et al.</i> (9)	69 M	Abdominal distention, Hematochezia	Voglibose 0.6 mg/day 1 year 8 months	Myasthenia gravis	SU Steroid	Sigmoid colon	Discontinuation	Conservative treatment Healing 14 days
9	Vogel <i>et al.</i> (10)	65 F	Lt abdominal pain	Acarbose 150 mg/day 12 years	Hypertention	Nothing	Ascending colon	Discontinuation	Conservative treatment Healing 7 days
10	Our case	58 M	Lower abdominal pain, Hematochezia	Miglitol 150 mg/day 8 months	Nothing	Nothing	Caecum, Ascending colon	Discontinuation	Conservative treatment Healing 12 days

and include a review of the literature. The patients' ages ranged from 53 to 87 (mean: 64.9) years. The male to female ratio was 3 to 7. The causative agent was voglibose in 6 cases, acarbose in 3, with the present case being the first to be caused by miglitol. The interval between commencement of α GI therapy and the onset of PCI varied greatly (from 7 days to 11 years). The presenting symptom was abdominal fullness in 4 cases (40%) and rectal bleeding in 3 (30%), neither of which is specific for PCI (Table 1). The most commonly affected site was the ascending colon in 6 cases (60%), followed by the sigmoid colon in 3 (30%).

Various radiological modalities are useful in the diagnosis of PCI. In an earlier case report and literature review, we analyzed the radiological findings of the previously reported cases (9). Plain abdominal radiography demonstrated linear radiolucent gas collections along the bowel wall in most cases, and abdominal CT scanning demonstrated pneumatosis within or along the bowel wall. Subserous pneumocysts in particular are liable to rupture, exhibiting intraperitoneal free gas, making it important to distinguish this condition from bowel perforation. The colonoscopic findings include multiple smooth-surfaced hemispherical submucosal tumor-like protrusions, similar in color to the mucosa and resembling cystic lesions. In the present case, however, the mucosal surfaces of the lesions were reddish, and the projec-

tions were smaller than those induced by voglibose or acarbose. The histopathological findings of the multiple small pneumocysts also differed from those in previous case reports.

Once the diagnosis of PCI is made, conservative management is the general rule. Stopping α GI therapy is important, with all reported cases resolving within 28 days of cessation. In our case, miglitol was suspected as the causative factor for PCI, and consequently miglitol was ceased and recovery was confirmed 12 days later with conservative measures comprising fasting and fluid supplementation.

Having experienced a case of PCI thought to be caused by miglitol, we conducted a search of the literature. Although few cases of α GI-associated PCI have been recently reported, this is the first report of miglitol causing PCI. The pneumocysts in this case were smaller than those caused by voglibose and acarbose. This may be characteristic for miglitol, as it is absorbed in the small intestine (20). Endoscopic findings of miglitol-induced PCI will become clear with the increase of the reports in the future. The possibility of PCI should be considered in diabetic patients on α GI therapy with gastrointestinal symptoms, and the gastrointestinal tract should be thoroughly investigated in these patients.

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