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BRIEF ARTICLE

A systematic analysis of pneumatosis cystoids intestinalis

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Abstract

AIM: To increase the understanding, diagnosis and treatment of pneumatosis cystoides intestinalis (PCI) and to find the characteristics and potential cause of the disease in China.

METHODS: We report here one case of PCI in a 70-year-old male patient who received a variety of treatment methods. Then, we systematically searched the PCI eligible literature published from an available Chinese database from May 2002 to May 2012, including CBM, CBMDisc, CMCC, VIP, Wanfang, and CNKI. The key words were pneumatosis cystoides intestinalis, pneumatosis, pneumatosis intestinalis, pneumatosis coli and mucosal gas. The patients' information, histories, therapies, courses, and outcomes were reviewed.

RESULTS: The study group consisted of 239 PCI cases (male:female = 2.4:1) from 77 reported incidents. The mean age was 45.3 ± 15.6 years, and the median illness course was 6 mo. One hundred and sixty patients (66.9%) were in high altitude areas. In addition, 43.5% (104/239) of the patients had potential PCI-related disease, and 16.3% had complications with intestinal obstruction and perforation. The most common symptom was abdominal pain (53.9%), followed by diarrhea (53.0%), distention (42.4%), nausea and vomiting (14.3%), bloody stool (12.9%), mucous stool (12.0%) and constipation (7.8%). Most multiple pneumocysts developed in the submucosa of the colon (69.9%). The efficacy of the treatments by combined modalities, surgery, endoscopic treatment, conservative approach, oxygen, and antibiotics were 100%, 100%, 100%, 93.3%, 68.3% and 26.3%, respectively.

CONCLUSION: PCI can be safely managed by conservative treatments, presents more frequently in males, in the large bowel and submucosa, than in females, in the small intestine and subserosa. High altitude residence maybe associated with the PCI etiology.

Key words: Pneumatosis cystoides intestinalis; Pneumatosis; Cyst; Intestinal; Colon

Core tip: Pneumatosis cystoids intestinalis (PCI) is a rare disease characterized by the presence of multiple gas-filled cysts in the submucosa and/or subserosa of the intestinal wall. PCI is still a poorly understood entity, and nearly all of the studies for PCI are case reports. In this work, we systematically evaluated and demonstrated for the first time the characteristics of PCI patients in China.

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INTRODUCTION

Pneumatosis cystoids intestinalis (PCI) is an uncommon disease with an unknown etiology, characterized by the

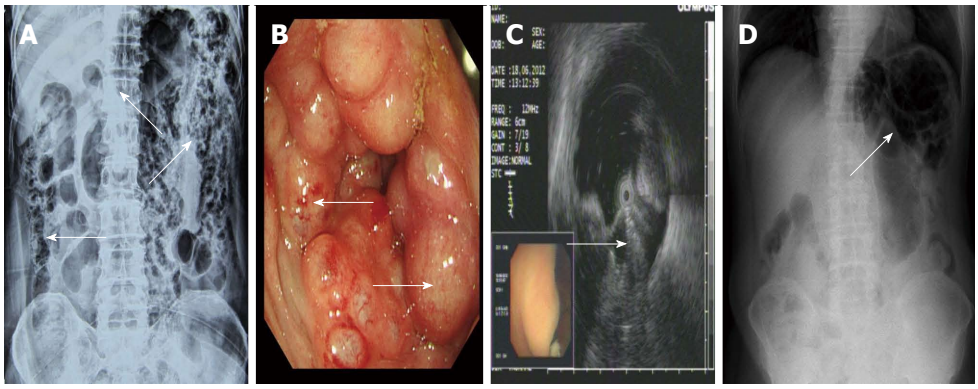

Figure 1 Imaging features of pneumatosis cystoides intestinalis. A: Barium enema study revealing multiple polypoid lesions with air shadows (arrow) and grape-like intramural gas in the whole colon; B: Colonoscopy revealing multiple round and smooth-surfaced elevated lesions (arrow) similar to submucosal tumors in the colon; C: Endoscopic ultrasonography revealing hyperechoic lesions and acoustic shadows in the submucosal layer (arrow); D: Plain radiography of the left upper quadrant abdomen revealing dilatation of the intestine and small linear, round radiolucent areas (arrow) on the clusters in the wall of the colon.

presence of gas within the submucosa or subserosa of the intestine[1,2]. Since it was first described by Du Vernoy[1] in autopsy specimens in 1730 and subsequently named by Mayer as PCI in 1825, it has been reported in various publications. However, after reviewing the literature, we found no epidemiologic studies, no randomized clinical trials, very few case series, and a large number of case reports. Many of the patients underwent misdiagnosis, mistreatment or even surgical exploration[3-5].

Our case report and systematic analysis are based on the Chinese publications to increase the understanding, diagnosis and treatment of PCI and to find the potential cause of the disease in China.

MATERIALS AND METHODS

Materials

A 70-year-old male was admitted for intermittent diarrhea accompanied by abdominal pain and bloody purulent stool for almost 2 years. The abdomen showed no relevant physical findings. Routine biochemical tests, inflammation indices and tumor markers were within normal values. He was diagnosed with hypertension and diabetes 10 years ago. Barium enema (Figure 1A) and colonoscopy (Figure 1B) disclosed multiple submucosal cysts protruding into the lumen of the whole colon. When a cyst was biopsied, it disappeared immediately. Endoscopic ultrasonography revealed gas in the cysts (Figure 1C). PCI was diagnosed. The patient received antibiotics and became asymptomatic with normal bowel movements. However, the diarrhea recurred after 4 mo. The patient then started hyperbaric oxygenation therapy. Unfortunately, he suffered from a hearing disorder and could not tolerate the hyperbaric therapy. Thus, the conservative approach was employed (observation only). Regular follow-up visits half a year later revealed improved clinical and radiological signs of PCI (Figure 1D).

Search strategy

The literature search used the available Chinese databases from May 2002 to May 2012, including CBM, CBMDisc, CMCC, VIP, Wanfang, and CNKI. The key words were pneumatosis cystoides intestinalis, pneumatosis, pneumatosis intestinalis, pneumatosis coli and mucosal gas. The patients' information, histories, therapies, courses, and outcomes were reviewed. Moreover, extended information was collected with regard to the nature and pathophysiology of PCI, and the incomplete reports were removed.

Statistical analysis

All data are presented as the mean ± SE. The demographic characteristics are presented as number (%).

RESULTS

The study group included 77 reports that contained an adequate amount of clinical information on 239 PCI cases (168 male:71 female = 2.4:1). The number of case reports was 62 (80.5%). The mean age was 45.3 ± 15.6 years (range: 2-81 years). The group was nationwide and particularly included high altitude areas and poor areas, including Qinghai, Sinkiang and Gansu (Table 1).

One hundred and four cases (43.5%) had comorbidities that may be related to PCI, with peptic ulcer being the most common concomitant disorder. In addition, 16.3% of the patients had complications including intestinal obstruction and perforation (Table 2).

The illness course from onset to identification ranged from 0 to 20 years, with a median of 6 mo. Overall, 217 cases (90.8%) had symptoms, and the most common symptom was abdominal pain (n = 117, 53.9%), followed by diarrhea (n = 115, 53.0%), distention (n = 92, 42.4%), nausea and vomiting (n = 31, 14.3%), bloody stool (n = 28, 12.9%), mucous stool (n = 26, 12.0%) and constipation (n = 17, 7.8%) (Figure 2A). PCI was most frequently diagnosed by colonoscopy (51.9%, 124/239), followed by surgery (40.6%, 97/239) and X-ray (10.9%, 26/239) (Figure 2B). The primary involved site was the colon, followed by the small intestine, especially the descending

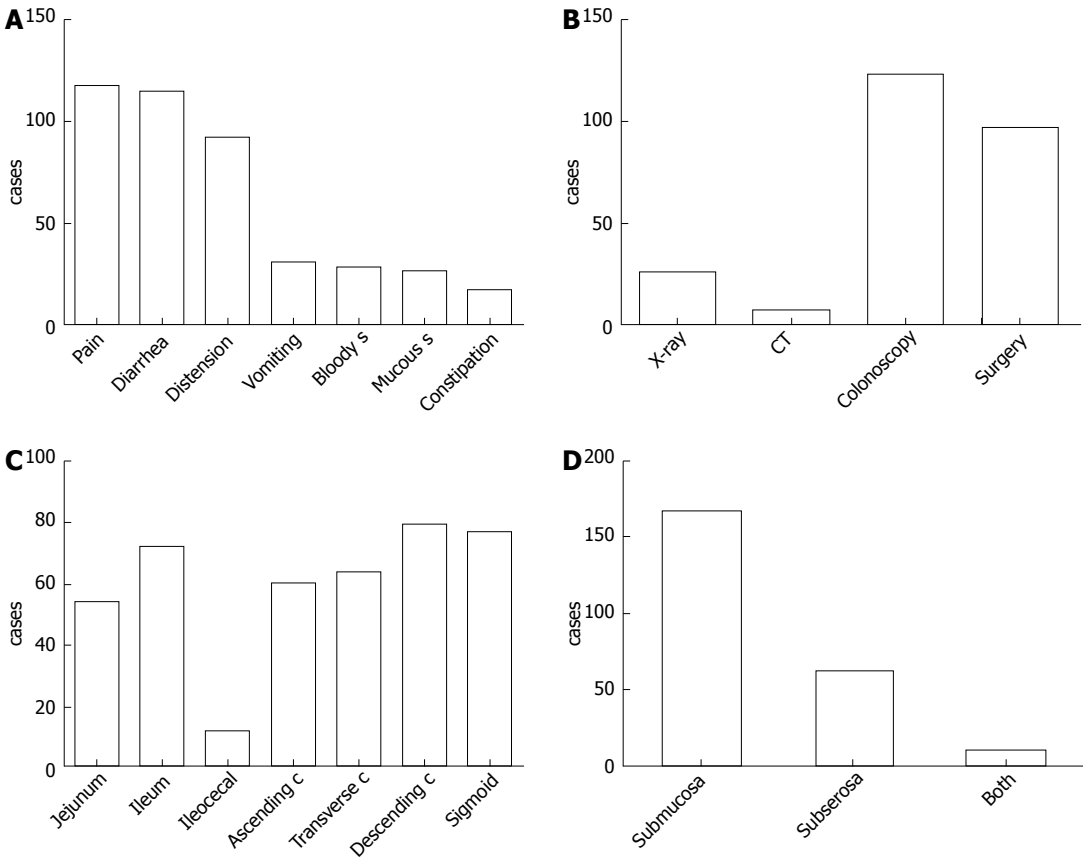

Figure 2 Clinical information of all 217 cases. A: The chief complaints; B: The methods of diagnosis; C: The primary involved site; D: The localization of gas in the intestinal wall. S: Stool; C: Colon; CT: Computed tomography.

colon (*n* = 79, 33.1%), sigmoid (*n* = 77, 32.2%) and ileum (*n* = 72, 30.1%) (Figure 2C). The majority of the cysts were found in the submucosa (69.9%, 167/239). Only 11 (4.6%) patients had both submucosa and subserosa involvement (Figure 2D).

The management of PCI included antibiotics, oxygen therapy, endoscopic therapy, surgery and the conservative approach. The efficiency of the conservative treatment reached up to 93.3% (Table 3). During the follow-up, which ranged from 1 mo to 20 years (median, 1 year), no symptoms recurred.

DISCUSSION

PCI is a rare disease and is still poorly understood. In a retrospective review of PCI, Koss[6] found a 3.5:1 male-to-female ratio of the occurrence of PCI in an age group of 30-50 years, and Jamart[7] found a 3:1 male-to-female ratio (aged from 41-50 years old) of the occurrence of PCI. However, both of these old reports contained few patients. A prospective study by Knechtle *et al*[8] showed equal incidence among males and females. PCI was previously thought to occur most frequently in the small intestine, but in recent barium enemas and colonoscopies studies, PCI has been reported to more commonly affect the colon. Most older studies showed PCI to occur more commonly in the small intestine. However, Horiuchi *et al*[9] showed that PCI appeared more commonly in the colon (61.8%) of females (mean age 55.4 years), followed by the small intestine (15.4%). Recently, Morris *et al*[10] showed the incidence of PCI was 46% in the colon; 27% in the small intestine, only 7% in the colon and small intestine combined. In contrast to previous reports using different ethnic cohorts, PCI in the patients in this study (Chinese cohort) showed a male-to-female ratio of 2.4:1 and a mean age of 45.3 ± 15.6 years. The most frequent location of PCI was the colon instead of the small bowel (rate of 1.3:1), with only 2.9% (7/239) of the cases being combined colon and small intestine. The most common localization of gas was in the submucosa (69.9%) (Figure 1).

PCI has been associated with a wide variety of underlining etiologies to explain the abnormal accumulation of gas[11-23]. There are five major theories: (1) The mechanical theory: Intestinal obstruction, inflammatory bowel disease, ischemic bowel disease, gastroenteric tumor, anorectal surgery, bowel preparation or colonoscopy resulting in intestinal wall injury or increased intraluminal pressure serve as the driving force in PCI that causes the intramural gas[14,15]. However, this theory cannot explain how the cysts are maintained once they have formed; (2) The pulmonary theory: Pulmonary diseases, such as chronic obstructive pulmonary disease, asthma, and interstitial pneumonia, may result in pulmonary alveolar rupture

Table 1 Geographical distribution of pneumatosis cystoides intestinalis in China *n* (%)

Province	Mean altitude (m)	Cases
Qinghai	4000	92 (38.5)
Sinkiang	2000	28 (11.7)
Beijing	50	21 (8.8)
Gansu	3000	17 (7.1)
Shanghai	4	10 (4.2)
Yunnan	1500	8 (3.3)
Shanxi	1000	8 (3.3)
Henan	1500	7 (2.9)
Tianjin	5	7 (2.9)
Sichuan	500	7 (2.9)
Tibet	4000	7 (2.9)
Shandong	1500	4 (1.7)
Shaanxi	1000	4 (1.7)
Zhejiang	50	3 (1.3)
Jiangxi	50	2 (0.8)
Guangdong	100	2 (0.8)
Kiangsu	50	2 (0.8)
Hainan	200	2 (0.8)
Heilongjiang	200	2 (0.8)
Jilin	800	2 (0.8)
Liaoning	500	2 (0.8)
Inner mongolia	1000	1 (0.4)
Hebei	400	1 (0.4)

Table 2 Pneumatosis cystoids intestinalis concomitant diseases and pneumatosis cystoids intestinalis complications *n* (%)

Total	*n* = 239
PCI concomitant diseases	104 (43.5)
Pyloric obstruction	31 (29.8)
Duodenal ulcer	18 (17.3)
Gastric ulcer	17 (16.3)
Pulmonary diseases	15 (14.4)
Intestinal diseases	17 (16.3)
Abdominal external injury or surgery	10 (9.6)
Malnutrition	27 (26.0)
Connective tissue disease	3 (2.9)
Diabetes mellitus	5 (4.8)
Hypertension	3 (2.9)
PCI complications	39 (16.3)
Intestinal obstruction	20 (51.3)
Intestinal perforation	14 (35.9)
Atypical hyperplasia and canceration	4 (10.2)
Intussusception and intestinal necrosis	1 (2.6)

PCI: Pneumatosis cystoids intestinalis.

and then produce a pneumomediastinum that dissects along the aorta and then along the mesenteric vessels to the bowel wall. However, this theory alone also fails to account for the finding that hydrogen, a gas never produced by mammalian cells, may comprise up to 50% of the gas content of the cysts[16]; (3) The bacterial theory: The gas is produced by gas-forming bacteria that enter the mucosal barrier through mucosal rents or increased mucosal permeability and produce the gas within the bowel wall. Indirect support for this theory was obtained by the successful treatment of PCI with antibiotics. However, the presence of aerogenic bacteria in the cysts has not yet been proven. Although Yale *et al*[17] reported that pneumatosis has been produced in germ-free rats by the injection of Clostridium species into the wall of the intestine, the isolation and cultivation of these organisms is rarely possible. Conversely, many of the patients who have pneumoperitoneum resulting from the rupture of cysts show no signs of peritonitis, prompting the theory that in this population, the gas is not caused by bacteria; (4) The chemical theory or nutritional deficiency theory: Malnutrition can prevent the digestion of carbohydrates and increased bacterial fermentation in the intestine, producing large volumes of gas leading to distention and ischemia and subsequently the submucosal dissection of gas. Recently, the development of PCI during the treatment with α-glucosidase inhibitors (α-GI) has been reported. The cessation of α-GI therapy is the key to the successful treatment of PCI[18,19], which supports the fourth theory; and (5) There have been some recent reports on PCI associated with chemotherapy, hormonal therapy and connective tissue disease that are not generally accepted[20-23].

Although many theories exist to explain the etiology and pathogenesis of PCI, no theory can explain the entire pathologic processes. Our experiments showed that many patients accompanied with pyloric obstruction, peptic ulcer, malnutrition and pulmonary diseases may support the theories of mechanical, pulmonary and nutritional deficiency (Table 2). Moreover, we also found that many of the patients came from highland areas, such as Qinghai, Sinkiang and Gansu (Table 1). The passage of intraluminal gas into the submucosa requires damage to the mucosa, which might be possible in these geographic areas. Further studies should be performed in the highland areas.

Although there are many symptoms of PCI, including abdominal pain, abdominal distention, diarrhea, mucous stool and bloody stool, none is disease specific (Figure 2A). The cysts may cause obstruction by internal or external compression of the bowel lumen when the cysts become larger. Complications associated with PCI occur in approximately 16.3% of cases and include intestinal obstruction or intestinal perforation (Table 2).

Approximately 85% of cases fall under secondary PCI[6], which results from other diseases. In these cases, the main symptoms and also the main treatments are related to the primary disease. Thus, some scholars do not think PCI is a disease by itself but rather a secondary manifestation of the reaction of the body to a variety of conditions; therefore, they believe that it does not have a single etiology[24].

In general, the diagnosis of PCI is based on endoscopy or plain radiography of the abdomen and is usually not difficult because the typical radiolucency appears as grape-like clusters or honeycomb-shaped shadows along the wall of the intestine. After the identification of PCI, a prompt further evaluation, including concomitant radiographic findings, of the patient should be conducted. Although only a few patients were diagnosed through an abdominal CT scan in our study, CT is a useful method for diagnosing PCI and is important because it provides

Table 3 Pneumatosis cystoids intestinalis therapies and their efficiency *n* (%)

Methods	*n*	Efficiency
Antibiotics	19	5 (26.3)
Oxygen	41	28 (68.3)
Endoscopy	12	12 (100)
Surgery	97	97 (100)
Conservative	15	14 (93.3)
Antibiotics + Oxygen	1	1 (100)
Oxygen + Endoscopic	53	53 (100)
Oxygen + Surgery	6	6 (100)

data on other abdominal pathologies[25-27]. Radiographic signs of bowel perforation or peritonitis and endoscopic signs of a tumor often indicate the need for emergency surgery[28]. Using two different preoperative imaging modalities to make a precise diagnosis is necessary.

The appropriate therapy is related to the underlying cause of PCI. The majority of patients (93.3%, Table 3) without pronounced symptoms were cured without any treatments. If the symptoms are pronounced, a conservative approach to treatment is allowed, such as gastrointestinal decompression, intestinal "rest", parenteral nutrition, and fluid and electrolyte supplementation. However, in contrast to the case reports, we found the efficiency of treatment by antibiotics was only 26.3%. The most efficient treatment was therapeutic alliance. Although oxygen was first used by Forgacs *et al*[16] in 1973, the optimal concentration, duration and effect of oxygen have not been established. The application of 200-300 mmHg PO_2 pressure for 1.5-2.5 h/d for 2-14 d or 55%-75% oxygen inhalation for 1-3 h/d for 2-5 d was suggested to lead to gas absorption within the cysts. Surgery is reserved either for cases of suspected inconvertible intestinal obstruction or perforation or cases with precancerous conditions[29]. The extremely high rate of surgical resection in China (40.6%) is associated with the lack of realization and the misdiagnosis of PCI as many cases can recover with non-operative management. Therefore, diagnosing PCI as early as possible and providing fast and adequate therapy to treat PCI are extremely important[30,31].

In conclusion, after recognizing the disease for almost three centuries, PCI is still a poorly understood phenomenon. Several theories explaining PCI and the variety of treatments reflect the lack of knowledge regarding the underlying pathophysiology. A long-term follow-up study is suggested to evaluate the long-term outcome of these therapies.

COMMENTS

Background

Pneumatosis cystoides intestinalis (PCI) is a rare disease characterized by the presence of multiple gas-filled cysts in the submucosa and/or subserosa of the intestinal wall. PCI is still a poorly understood entity, and nearly all of the studies for PCI are case reports.

Research frontiers

PCI is a rare disease that has not been unequivocally addressed. In this study, the authors systematically evaluated and demonstrated for the first time the characteristics of PCI patients in China.

Innovations and breakthroughs

For the first time, the authors determined the prevalence and the characteristics of PCI in Chinese people.

Applications

The study results suggest that PCI in Chinese patients presents in the large bowel more often than in the small intestine and more frequently in middle-aged males than in females. The majority of the cysts are found in the submucosa rather than the subserosa. High altitude residence may be associated with the PCI etiology. The majority of PCI can be safely managed by conservative treatment.

Peer review

The authors review PCI in the published literature from China and report on 239 cases. Stats on geography and altitude is hare to interpret - as population density may be more important - would incidence per 100000 population at high or low altitude be more helpful.

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