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Pneumatosis cystoides intestinalis as a complication of celiac disease

The role of diagnostic laparoscopy

A. Terzic, F. Holzinger, and Ch. Klaiber

Department of Surgery, Spital Aarberg, CH-3270 Aarberg, Switzerland

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Abstract

Pneumatosis cystoides intestinalis (PCI) is an uncommon but important condition characterized by the presence of gas-filled cysts in the submucosa and subserosa of the gastrointestinal tract. PCI has been associated with several clinical settings. We report a case where PCI developed in a patient with known celiac disease. To our knowledge, this type of coincidence has been described in seven prior cases. Since PCI often results in pneumoperitoneum through rupture of the cysts, it is important to differentiate the benign form of pneumoperitoneum, in which no intervention is indicated, from the life-threatening form with intestinal infarction and/or perforation, in which immediate surgery is mandatory. Differentiating between them can be difficult; this explains the high rate of negative laparotomy, which, in the past, occurred in 27% of cases. By performing diagnostic laparoscopy, we were able to establish the diagnosis of PCI and exclude intestinal perforation or infarction, thus permitting the patient to avoid an unnecessary laparotomy. Although diagnostic laparoscopy is not routinely indicated as a diagnostic tool for the detection of PCI, it proved to be a safe and accurate method to differentiate between the benign form of PCI and the life-threatening form. Whenever this differentiation has to be made, we recommend that diagnostic laparoscopy be performed first rather than primary laparotomy. Herein, the laparoscopic features of PCI are described and the coincidence of PCI with celiac disease is reviewed.

Keywords: Pneumatosis cystoides intestinalis, Celiac disease, Pneumoperitoneum, Laparoscopic features

Correspondence to: Ch. Klaiber — Email: aarchir@hitline.ch

Pneumatosis cystoides intestinalis (PCI) is an uncommon but important condition in abdominal pathology. PCI is characterized by the presence of multiple gas-filled cysts and clusters in the submucosa or subserosa of the gastrointestinal tract. PCI has been associated with several clinical settings, including necrotizing enterocolitis in infants, obstructive pulmonary disease in adults, and a wide variety of gastrointestinal conditions, such as pyloric stenosis, ischemic bowel disease, progressive systemic sclerosis. It is also seen in association with drug therapy, particularly when steroids, chemotherapy, and immunosuppression are involved [11].

The pathogenetic mechanisms of PCI are still uncertain, but it appears that there are two main sources for the gas, one mechanical and one bacterial. The mechanical theory proposes that gas enters the bowel wall from either an obstructed intestinal tract or the lung [4, 6]. The bacterial theory proposes that gas-forming bacilli (especially *Clostridia perfringens*) enter the submucosa through mucosal rents and produce gas within the intestinal wall [26]. Since cultures of the cysts are consistently sterile, it is assumed that intraluminal rather than intracystic bacteria produce an

excessive amount of gas, which under pressure enters the intestinal wall [11].

With the exception of a statistical study of 919 cases by Jamart [12], only small series of PCI have been reported. In contrast, celiac disease is a much more common pathological entity. To our knowledge, there have been only seven case reports describing the simultaneous appearance of both pathologies, PCI and celiac disease, in a patient.

PCI may therefore be encountered as a rare complication or concomitant disease of celiac disease. It may mimic intestinal perforation by showing free intraabdominal air on conventional radiographs. In patients with PCI of the small bowel, the subserosal cysts rupture in ~15% of cases, resulting in pneumoperitoneum [12]. In most of these patients, the cyst rupture does not produce bacterial peritonitis. This self-limiting and in most cases asymptomatic pneumoperitoneum has therefore been termed "benign pneumoperitoneum."

However, in a previous study, one of 12 such patients had documented bowel infarction [1]. Therefore, careful stationary observation of these patients seems to be mandatory. At the other extreme, PCI may be associated with a life-threatening intestinal infarction and/or perforation that requires immediate surgical intervention without permitting any diagnostic delay. Since PCI may mimic gastrointestinal perforation and differentiation between the benign pneumoperitoneum and the life-threatening form may be difficult to assess, some patients with the self-limiting form of PCI have erroneously undergone laparotomy.

We report herein on a patient with known celiac disease where the clinical course and radiological follow-up mimicked a gastrointestinal perforation. By performing diagnostic laparoscopy, we were able to diagnose the coincidence of PCI and exclude perforation or infarction of the intestinal tract. We will describe the laparoscopic features of PCI and review the literature on the coincidence of PCI in patients with celiac disease.

Case report

Three months before admission of the 66-year-old male patient to our department, a history of frequent foul-smelling stools, weight loss, and abdominal pain was noted in the patient. The ensuing endoscopic investigation of the upper gastrointestinal tract, including biopsy contributed to the diagnosis of celiac disease. After a gluten-free diet was established, there was some improvement of the intestinal discomfort during the following weeks. The medical history of the patient included a mild chronic obstructive lung disease (COPD), grand mal epilepsy with long-term medical treatment over 50 years, and paranoid schizophrenia, both of the latter conditions without actual activity. The patient's daily medication consisted of 500 mg clozapinum, 10 mg haloperidole, and 400 mg carbamazepine.

At admission, the patient showed all the clinical signs of mechanically induced intestinal subileus. The abdominal examination revealed a distended nontender abdomen with diffuse pain, high-frequency bowel sounds, and shifting dullness. The blood samples revealed a leukocytosis of 12,100 mg/L, a C-reactive protein of 140 mg/L, anisocytosis, and hypochromasia. An abdominal radiograph revealed dilated, air-filled small bowel loops with few fluid levels. After 24 h of conservative treatment, the patient developed the clinical sign of peritonitis in the upper abdomen, and radiographic control of the chest and abdomen revealed free air under both diaphragms, mimicking intestinal perforation (Figs. 1 and 2).

The patient was urgently brought into the operative theater, where a diagnostic laparoscopy was performed. By laparoscopy, multiple gas-filled cysts and clusters in the subserosa of the small bowel wall and its mesentery could be appreciated, and a diagnosis of PCI was established (Fig. 3). The insertion of two additional working trocars allowed the entire intraabdominal intestinal

tract to be mobilized. Intestinal perforation or infarction and mechanical obstruction were thereby excluded. As a consequence, laparotomy could be omitted.

The postoperative course was uneventful except for the onset of pneumonia, which was treated with a broad-spectrum antibiotic and respiratory treatment. One week after surgery, the patient was discharged home free of symptoms.

Review of PCI in celiac disease

In this section, we will summarize the clinical features of the eight patients, including ours, who presented with coincidental PCI and celiac disease. The different treatment modalities and outcomes are summarized in Table 1.

Clinical findings

The ages of the patients ranged from 46 to 83 years, with a peak incidence in the 5th and 6th decades. The female-to-male ratio was 1.7:1. At admission, the following clinical findings were noted: abdominal pain or distension (six cases), weight loss (six cases), increased bowel sounds (six cases), steatorrhea or an increased number of stools up to eight times a day (five cases), and peripheral edema (four cases). One patient developed peritonitis in the upper abdomen. None of the patients had a palpable abdominal mass or presented with fever.

Laboratory findings

The white blood cell count was normal in all patients, except in two patients who exhibited mild leukocytosis of 12,000 mg/L and 12,100 mg/L, respectively. Levels of C-reactive protein were not available for earlier seven cases, but in our patient the level of C-reactive protein was highly elevated, measuring 140 mg/L. The red blood counts revealed more disturbances, such as polychromasia (one case), poikilocytosis (one case), and anisocytosis (one case). Macrocytic or microcytic anemia was seen in four patients, whereas red blood count was normal in only one patient. The albumin level was decreased in four patients, and the iron level was decreased in two cases. Calcium or potassium levels were disturbed in three patients. Except for one case with elevated alkaline phosphatase (AP) and γ-glutamic transaminase (γ-gT) levels due to long-term carbamazepine medication, no other biochemical abnormalities were found.

Radiographic findings

The plain chest radiograph revealed pneumoperitoneum with free air under the diaphragm in seven patients, or 87.5% of all cases. The plain abdominal radiograph revealed intramural circular collections of gas in the anatomic position of the bowel in 62.5% of cases. Air-dilated intestinal loops were found in 50% of patients. In one patient, the radiological signs of an ileocolic intussusception were noted. Our patient presented initially with the radiological signs of a mechanically induced small bowel subileus.

History of celiac disease

PCI was described as the first clinical manifestation of celiac disease in two patients. In the remaining patients, celiac disease preceded the diagnosis of PCI for 3, 7, and 40 months. In two cases, PCI was diagnosed 5 years after the onset of celiac disease. In one patient, the duration of celiac disease has not been described. For seven patients, the diagnosis of celiac disease was based on histological verification of biopsy specimens, whereas in one patient celiac disease was described as an "established diagnosis." Celiac disease was treated in two patients with a systemic

steroid medication of 5 and 10 mg cortisol per day, respectively. All patients received a gluten-free diet after the diagnosis of celiac disease was established.

Localization of PCI

In five of eight cases, multiple gas-filled cysts were localized in the subserosa of the small bowel wall. Two of these patients had additional gas-filled clusters on their mesentery. Other reported localizations of PCI were the colon (one case), the mesentery alone (one case), and the retroperitoneum (one case). Two of the reports did not document the exact localization of PCI in their cases.

Diagnosis, treatment, and outcome of PCI in celiac disease (Table 1)

Four of eight patients, or 50% of all cases, underwent laparotomy. In three of them, the reason was a radiologically diagnosed pneumoperitoneum mimicking gastrointestinal perforation. In one patient, the reason for laparotomy was an ileocolic intussusception after the diagnosis of PCI had been established. In all patients undergoing laparotomy, the diagnosis of PCI was established or confirmed intraoperatively. Two patients were treated postoperatively with a strict gluten-flee diet and showed no evidence of residual PCI on a radiological control 2 weeks after the surgical procedure. A third patient was treated with the antibiotic metronidazole and had an uneventful further course. Two years later, a radiological control revealed an asymptomatic relapse into PCI. The fourth patient developed postoperative pneumonia, which was treated with prolonged oxygen therapy and antibiotics. There were no PCI findings on the plain abdominal radiographs 7 days after laparotomy. Following the gluten-free diet, the patient remained symptom-free over an 18-month control period.

In our patient with known celiac disease, diagnostic laparoscopy was performed because of the clinical and radiological suspicion of gastrointestinal perforation with proven pneumoperitoneum and clinical signs of epigastric peritonitis. Diagnostic laparoscopy proved to be useful to establish the diagnosis of PCI and to exclude intestinal perforation and infarction, thus preventing laparotomy. The postoperative course was complicated by the onset of pneumonia, which was treated with respiratory and antibiotic therapy while continuing a gluten-free diet. Our patient was discharged 1 week postoperatively without any complaints, but he had persistent radiological signs of PCI.

The remaining three patients were all treated conservatively with a gluten-free diet and/or oxygen therapy. No complications were reported in the further course of these patients.

Laparascopic features of PCI

To date, the laparoscopic features of PCI have only been described by Metha et al. [20] in a patient with marked ascites and radiographic evidence of PCI of the ileum. The presence of multiple glistening, translucent, gas-filled blebs and clusters in the subserosal plane of the bowel wall and/or mesentery is characteristic of PCI and cannot be mistaken for other conditions (Fig. 3). However, in some cases of Veress needle trauma to the omentum, mesentery, or bowel wall, the blind insufflation with carbon dioxide may result in gas-filled bubbles that could be misdiagnosed as PCI.

Discussion

PCI is a very rare complication of celiac disease. It seems to occur in celiac disease patients who fail to respond to a gluten-free diet and in patients who do not follow the diet strictly [16]. The pathogenesis of PCI is still unknown, but two theories have been proposed based on experimental

work and known clinical associations of PCI. The mechanical theory proposes that gas from either the intestinal lumen or the lung dissects into the bowel wall and mesentery. It has been suggested that obstruction of the upper intestinal tract (e.g., pyloric stenosis) allows gas under pressure to be forced into the submucosal tissues through a mucosal breach [4, 9, 18]. In patients with obstructive pulmonary disease, severe coughing may rupture the alveoli, allowing air to dissect into the mediastinum, tracking to the mesenteric root and following mesenteric branches to the intestinal wall [6, 15].

The bacterial theory proposes that gas-forming bacilli enter the submucosa through mucosal rents and produce gas within the intestinal wall. The fact that Yale et al. [29] were able to produce PCI by injecting *Clostridium perfringens* into the bowel wall of germ-free rats, in whom PCI does not occur in vivo, lends credence to the bacterial theory of PCI. However, since the cysts are consistently sterile, it is possible that intraluminal rather then intramural bacteria produce the excessive amount of gas that dissects into the intestinal wall [11]. The bacterial theory for the etiology of PCI is supported by the fact that various antibiotics, such as metronidazole, ampicillin, and vancomycin, have been used with some success to eradicate symptoms and cysts [13, 27]. In our review section, three patients were treated with antibiotics. It seems rational to us to treat PCI patients for suspected intestinal bacterial overgrowth, since this condition sometimes develops in hypomotility intestinal disorders. However, the most appropiate antibiotic dose and the optimal duration of the treatment have not yet been established.

In this context, it is notable that two patients presented with a motility disorder. One of them demanded surgery because of bowel intussusception. In celiac disease, small bowel intussusceptions are known to occur frequently, but they usually do not require surgical treatment, since they are normally nonobstructive and transient [21]. Intestinal polyposis has been shown to be an etiological factor in bowel intussusception in these patients [3, 14, 24]. It seems possible that PCI, with its submucosal and subserosal cyst formation, may lead to a mechanical barrier, causing intestinal intussusception or obstruction as seen in our patient and the one described by Frank and O'Connell [7].

Rupture of the subserosal cysts of PCI results in pneumoperitoneum, usually without clinical peritonitis—the so-called benign pneumoperitoneum, which does not require therapy. This condition occurs more frequently in small bowel (15% of cases) than in colonic pneumatosis (2% of cases) [12]. In our series, the rate of pneumoperitoneum was considerably higher, accounting for 87.5% of all patients. It is not known whether this much higher rate of pneumoperitoneum is related to the mucosal disturbances of underlying celiac disease. In contrast to benign pneumoperitoneum, portal venous gas and peritoneal and septic signs indicate a serious life-threatening infection or transmural infarction of the gastrointestinal tract that requires immediate surgical treatment. The difficulty in making the differentiation between these two extremes accounts for the high rate of negative laparotomy, which, in the past, occurred in 27% of cases [12]. In this series, rate of negative laparotomy rate was comparable, at 37%. Only the patient with intussusception was able to derive any benefit from his laparotomy.

In our patient, the clinical course with development of peritonitis in the upper abdomen as well as the high level of the acute-phase protein CRP in conjunction with proven pneumoperitoneum made surgical intervention inevitable. We decided to perform diagnostic laparoscopy which proved to be useful to identify the benign form of PCI through its characteristic laparoscopic features and to exclude intestinal perforation or infarction, thus preventing laparotomy. Other surgeons have also attempted to identify the patients that require surgery. Portal venous gas, metabolic acidosis, and hyperamylasemia have been identified as the clinical signs that are found in up to 75% of patients in whom a bowel infarction is discovered at laparotomy [17, 19].

The patients in our review section were all treated with a gluten-free diet, additional antibiotic

therapy, and high concentrations of oxygen, either alone or in combination (Table 1) [2, 5, 7, 8, 10, 16, 22, 23, 28]. All of these patients enjoyed an uneventful course, some of them with persistent or recurrent radiological signs of PCI, but without any clinical complaints [11, 25]. Once the patient becomes asymptomatic, no further treatment is required, but the gluten-free diet should be maintained in order to control celiac disease.

In summary, PCI may appear as a complication in patients with celiac disease. Due to the rupture of gas-filled subserosal cysts, pneumoperitoneum will frequently develop in these patients, mimicking a potentially life-threatening intestinal complication. Although diagnostic laparoscopy is not routinely indicated as a tool for the detection of PCI, it proved to be a safe and accurate method to differentiate between the benign type of PCI and the life-threatening form. Whenever this differentiation has to be made, we recommend that diagnostic laparoscopy be performed first rather than immediately resorting to primary laparotomy.

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Tables

Table 1. Treatment modalities and outcome of Pneumatosis cystoides intestinalis (PCI) in patients with concomitant celiac disease

Figures

Figure 1
Figure 1 (large scale)

Fig. 1. Plain chest radiograph showing free air under both diaphragms mimicking intestinal perforation.

Figure 2
Figure 2 (large scale)

Fig. 2. Plain abdominal radiograph revealing air-dilated intestinal loops and pneumoperitoneum. In the left upper abdomen, the picture is suggestive of intramural collections of gas in the small bowel wall.

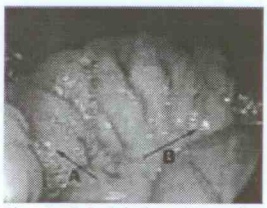

Figure 3
Figure 3 (large scale)

Fig. 3. Multiple glistening, translucent, gas-filled blebs and clusters can be appreciated in the subserosal plane of the bowel wall (**A**) and mesentery (**B**). These are the characteristic laparoscopic features of PCI.