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Management of pneumatosis cystoides intestinalis with pneumoperitoneum: 5-years systematic review

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ABSTRACT

Introduction: Pneumatosis cystoides intestinalis (PCI) is a rare condition characterized by gas-filled cysts in the intestinal wall. Although rare, it may also involve other regions, such as the mesentery. PCI is classified as primary or secondary and is associated with multiple predisposing factors. It may be associated with either a benign condition or a potentially fatal condition, such as mesenteric ischemia. The objective of this study was to review the medical literature on the rare benign presentations of PCI, excluding cases associated with intestinal ischemia.

Methods: We conducted a systematic literature review according to the PRISMA statement. We searched PubMed and LILACS databases for articles published between January 2015 and December 2020 using the following Medical Subject Headings: “pneumatosis cystoides intestinalis” and “pneumoperitoneum,” “pneumatosis intestinalis,” and “pneumoperitoneum” or “mesenteric pneumatosis.”

Results: We included 51 articles comprising 58 patients with PCI and pneumoperitoneum. Most patients were men, and mean patient age was 64.9 years. We identified an idiopathic etiology in 29.31% of cases, and the most common predisposing factor was immune dysfunction (29.31%). A total of 24.13% of patients were asymptomatic. The most commons symptoms were abdominal pain (43.10%), nausea and vomiting (41.37%), and abdominal distention (37.93%). Diagnostic surgery was conducted in 26 patients (44.82%). Only 1 patient underwent surgical treatment.

Conclusions: PCI is a clinical condition that may have a benign etiology and not require surgery. Treatment of the benign etiology is conservative. Thus, life-threatening conditions should be excluded in all cases.

Keywords: *Pneumatosis cystoides intestinalis; Pneumoperitoneum; Mesenteric ischemia*

INTRODUCTION

Pneumatosis cystoides intestinalis (PCI) is a rare benign condition characterized by the presence of gas-filled cysts in the intestinal wall in the absence of intestinal infarction[1-6]. It has a worldwide incidence of 0.03% and is more common in men, with a 3:1 male-to-female ratio[1-10]. It was first described by DuVernoi et al. in 1783, and its etiology and pathogenesis still remain unclear[2,7,8,11-16]. Pneumoperitoneum may also be observed and is secondary to subserosal bleb rupture[17]. In the absence of PCI, pneumatosis intestinalis associated with pneumoperitoneum is highly suggestive of intestinal ischemia followed by perforation, which should always be excluded by careful evaluation due to the imperative need for surgical treatment[2,11-13,17].

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The pathogenesis of PCI is not well established, and there are 4 main theories that may explain its origin: bacterial, mechanical, biochemical, or pulmonary[2,9,11,12,18-20]. PCI classically affects the digestive tract, but some studies have reported possible mesentery, omentum, and hepatogastric ligament involvement[2,21]. PCI causes a wide spectrum of mild and nonspecific symptoms, such as changes in bowel habits, nausea, and abdominal discomfort[1,4,12,18,22]. In 3% of cases, it may be associated with complications such as pneumoperitoneum, volvulus, bleeding, intestinal obstruction, and mesenteric ischemia[16-18,22,23]. There is still no consensus on the need for diagnostic laparoscopy[24].

Since benign PCI is a rare condition, its development is poorly understood, and disease management is still under debate. PCI should be carefully evaluated, given that its benign presentation is similar to intestinal ischemia, a life-threatening disease. We conducted this systematic review after treating an asymptomatic patient with pneumatosis intestinalis associated with pneumoperitoneum. Our objective is to alert clinicians that pneumatosis intestinalis is not necessarily related to intestinal ischemia or an unequivocal indication for surgery. The benign etiology of PCI should be considered in patients with a mild clinical and laboratory condition to avoid unnecessary surgery.

METHODS

We conducted a systematic review in PubMed and LILACS databases according to the PRISMA statement (Figure 1) for articles published between January 2015 and December 2020 using the following descriptors: “pneumatosis cystoides intestinalis” and “pneumoperitoneum,” “pneumatosis intestinalis,” and “pneumoperitoneum” or “mesenteric pneumatosis”. For risk of bias assessment, 2 researchers independently reviewed the titles and abstracts of the recovered articles based on predefined inclusion and exclusion criteria, as described below. Conflicts regarding study inclusion were discussed by the authors and resolved by consensus. When necessary, a third author was consulted.

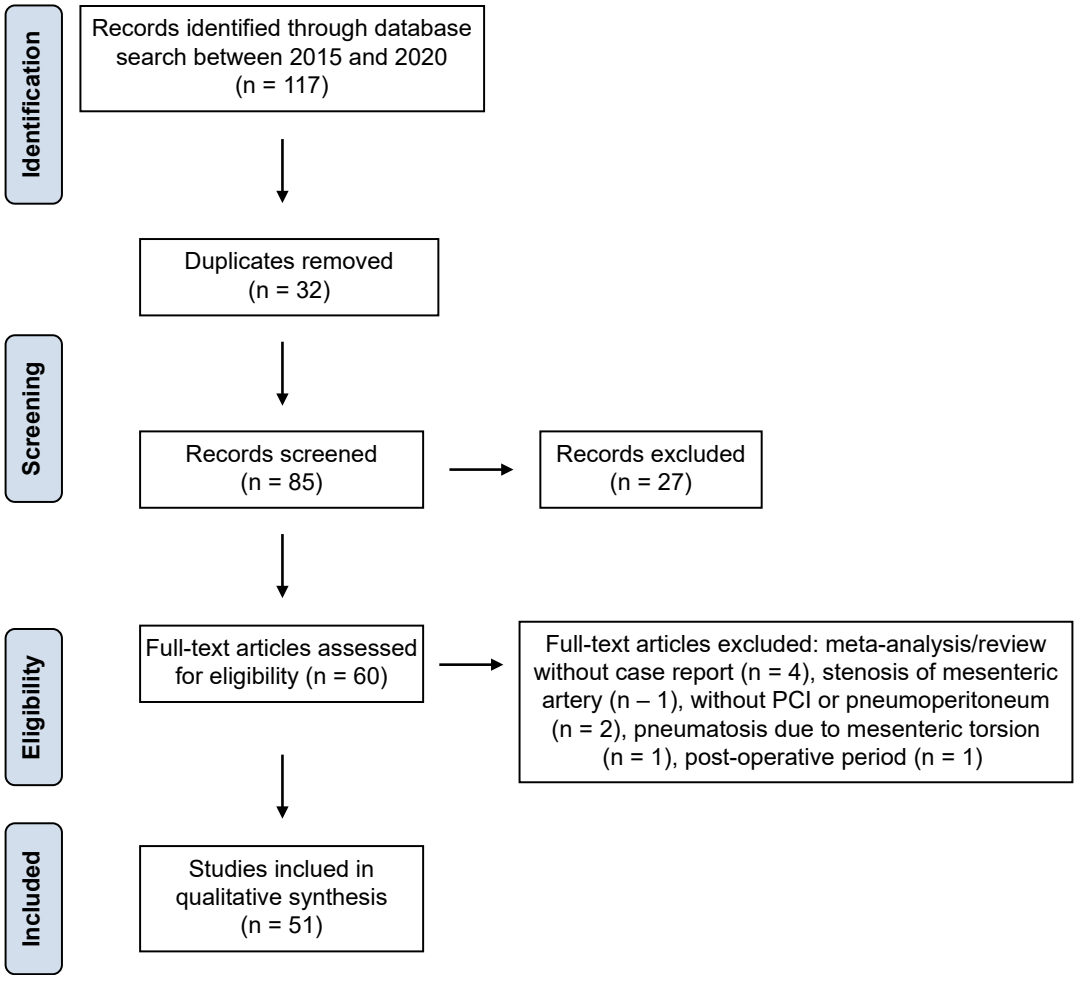

Figure 1: PRISMA flow chart.

Inclusion criteria

Data search was restricted to studies published in English reporting on adult patients with benign PCI associated with pneumoperitoneum and no obvious cause of intestinal ischemia. The abstracts were reviewed again by 2 independent researchers, who subsequently read all potentially relevant studies in full and analyzed them for eligibility. We used a standardized data extraction form to extract information from each study.

Exclusion criteria

Articles not reporting original data, such as editorials, meta-analyses, and comments, and studies addressing pneumatosis intestinalis as a progression of intestinal infarction, of iatrogenic origin, or without pneumoperitoneum were excluded. We also excluded duplicates, postoperative follow-ups of abdominal procedures, and cases of mesenteric ischemia with PCI as a classic consequence (mesenteric ischemia, volvulus, mesenteric torsion). Only articles describing PCI with pneumoperitoneum were included in the final analysis. In case of disagreement about study inclusion between the 2 researchers, the studies were reviewed and discussed by a third author until a consensus was reached.

Data extraction

We included 51 studies in the final analysis, consisting of 5 case series and 46 case reports. We retrieved the following study variables: number of patients, patient characteristics (sex, age, predisposing factors), type of study, diagnostic method, treatment, and follow-up.

RESULTS

We included 51 studies (Figure 1) and evaluated data from 58 patients with PCI and associated pneumoperitoneum.

Thirty-five patients (60.34%) were men and 23 (39.65%) were women. Mean patient age was 64.9 (SD, 17.21) years (ranging from 16 to 94 years). Among analyzed studies, an idiopathic etiology was reported in 17 patients (29.31%) because of a lack of predisposing factors. Predisposing factors for PCI were reported in 41 patients (70.68%) (Table 1). Some patients had more than 1 predisposing factor. The most common predisposing factors were immune dysfunction (n = 17, 29.3%), cancer (n = 10, 17.2%), chronic obstructive pulmonary disease (COPD) (n = 9, 15.5%), and scleroderma (n = 7, 12.0%). Malignant neoplasms included prostate (n = 3), lung (n = 2), breast (n = 1), esophagus (n = 1), pancreas neuroendocrine (n = 1), hepatocarcinoma (n = 1), and lymphoma (n = 1).

Table 1: Predisposing factors.

Characteristics	n	%
Immune dysfunction*	17	29.31
Cancer**	10	17.24
COPD	9	15.51
Scleroderma	7	12.06
Gastrointestinal dysfunction	4	6.89
Glucocorticoids	4	6.89
Lung transplantation	4	6.89
SIBO	4	6.89
Liver transplantation	3	5.17
Alpha-glucosidase inhibitor	2	3.44
Bone marrow transplantation	1	1.72
Heart transplantation	1	1.72
Heroin addiction	1	1.72
Amyloidosis	1	1.72
Crohn's disease	1	1.72
Abdominal trauma	1	1.72
Mixed connective tissue disease	1	1.72

COPD: chronic obstructive pulmonary disease; SIBO: small intestinal bacterial overgrowth.

*Immune dysfunction: using immunosuppressive drugs, corticosteroids in immunosuppressive doses, and chemotherapy; **Cancer: prostate (3), breast (1), lung (2), esophagus (1), pancreas neuroendocrine (1), hepatocarcinoma (1), and lymphoma (1).

During evaluation, 14 patients (24.13%) were asymptomatic. Clinical manifestations were observed in 44 patients (75.86%) (Table 2). The most common symptoms were abdominal pain (n = 25; 43.10%), nausea and vomiting (n = 24; 41.37%), and abdominal distension (n = 22; 37.93%). One patient (1.72%) had melena, in whom unremarkable colonoscopy and upper gastrointestinal endoscopy revealed ischemic abnormalities in the duodenum. A biopsy was performed, and amyloid deposition was confirmed by Congo red stain. Laboratory tests were normal in 50 patients (86.2%), whereas 2 (3.4%) had acidosis and 5 (8.6%) had leukocytosis with increased C-reactive protein (CRP). All patients underwent computed tomography (CT) evaluation, which revealed PCI with pneumoperitoneum. CT was the definitive diagnostic method for PCI in all patients. Diagnostic laparoscopy or laparotomy was conducted in 26 patients (44.8%) to resolve any doubts about the presence of intestinal ischemia. Intestinal loops without ischemic abnormalities were observed in 25 patients (43.1%), intestinal ischemia was observed in 1 patient (1.7%), and perforation was not observed in any patient. One patient underwent enterectomy during diagnostic laparoscopy for pathological analysis, with no treatment purpose.

Table 2: Clinical manifestations of patients with pneumatosis cystoides intestinalis.

Clinical manifestations	n	%
Abdominal pain	25	43.10
Nausea and vomiting	24	41.37
Abdominal distention	22	37.93
Asymptomatic	14	24.13
Diarrhea	10	17.24
Constipation	7	12.06
Weight loss	5	8.62
Fever	2	3.44
Melena	1	1.72

*Some patients had more than one clinical manifestation.

Twenty-seven patients (46.55%) received conservative treatment, without medical or surgical intervention. Medical management was conducted in 30 patients (51.72%), among whom antibiotic therapy was employed in 16 (27.58%). Six patients (10.34%) received combined therapy with antibiotics, oxygen, and bowel rest. Treatment of choice was isolated oxygen therapy in 3 patients (5.17%), bowel rest alone in 3 patients (5.17%), hyperbaric therapy in 1 patient (1.72%), and laxative therapy in 1 patient (1.72%). The only patient to undergo surgical treatment was the one diagnosed with intestinal ischemia during laparoscopy. All patients had good recovery, with symptom recurrence in only 5 cases. Complications were described in 2 cases, including a case of sigmoid volvulus 13 months after hospital discharge and a case of mesenteric ischemia 1 month after discharge. For the latter, we were not able to determine the etiology.

DISCUSSION

The etiology of PCI may be classified as idiopathic (15%) or secondary (85%), the latter possibly resulting from lung disease, gastrointestinal disease, abdominal trauma, abdominal surgery, connective tissue diseases, drugs, or malnutrition[2,7,12,13,22,25-27]. The pathogenesis of PCI is still uncertain, and there are 4 main theories that could explain its origin: 1) bacterial – the presence of gas-producing bacteria inside the intestinal wall; 2) mechanical – increased intraluminal pressure or epithelial injury allowing gas passage from the lumen into the intestinal wall; 3) biochemical – increased hydrogen gas production from carbohydrate fermentation exerts pressure within the intestinal lumen and is forced through the mucosa; 4) pulmonary diseases such as COPD and interstitial pneumonia may cause alveolar rupture leading to gas release, which travels along the mesenteric vessels into the mesentery. Coughing with abrupt changes in intra-abdominal pressure may also be an important contributing factor[2,3,5,7,9,11-13,15,19-21,26,28-30].

Some predisposing factors may be involved, including scleroderma, systemic lupus erythematosus, granulomatosis with polyangiitis, amyloidosis, myeloma, dermatomyositis, COPD, Crohn's disease, nutritional imbalances, dysbacteriosis, gastrointestinal dysmotility, alpha-glucosidase inhibitor, glucocorticoid, kinin, immunosuppressant inhibitor, bone marrow transplantation, lung transplantation, graft versus host disease, and use of trichloroethylene[1,2,3,7,11,14,23,28,31,32]. Changes in immune function appear to be among the most significant predisposing factors, considering their relation with post-transplant organ status, corticotherapy, rheumatic disease treatment, and chemotherapy[2,33,34].

The pathophysiology of some predisposing factors is well related to the theories previously described. Glucocorticoids may favor the onset of PCI by inducing atrophy and fibrosis of the intestinal mucosa, in addition to altering immune function[8,20]. Chemotherapeutics and antiangiogenic monoclonal antibodies appear to increase the intestinal capillary permeability, allowing the passage of air from the lumen into the intestinal wall[35,36]. Chronic constipation may promote bacterial overgrowth, leading to increased intraluminal hydrogen production and resulting in leakage into the intestinal wall, according to the biomechanical theory[3,37]. Conversely, alpha-glucosidase inhibitors reduce carbohydrate absorption, which will be fermented by the gut microbiota, resulting in gas production and peristaltic dysfunction. Diabetes promotes peristaltic dysfunction as a consequence of autonomic neuropathy. Both diabetes and alpha-glucosidase inhibitors increase intraluminal pressure, allowing gas to infiltrate the bowel through the intestinal wall, further supporting the biomechanical theory[9].

The colon is affected in 36%-78% of cases, whereas the small intestine is affected in 20%-51.6% of cases. Both organs may be affected in 2%-22% of cases, but the most affected organ has not yet been determined, and there is no consensus among case series[2,7,24,27]. The presentation may be clinically chronic or acute, consisting of abdominal pain, abdominal distention, nausea, vomiting, diarrhea, constipation, anorexia, weight loss, and flatulence[4,7,13,18,24,27]. The diagnosis may be achieved by complementary tests, especially in asymptomatic patients or those with mild and recurrent symptoms[38-40].

CT is the test of choice for detecting the main diagnostic feature of PCI (figures 2 and 3), that is, multiple grape-like cystic injuries in the intestinal wall, especially when using a lung window setting[7,24,41,42]. Similar abnormalities may be observed in the mesentery, omentum, and ligaments. In addition, CT may determine the underlying etiology or identify complications that may alter the course of therapy, such as gas inside the portal vein, volvulus, and ischemia[4,5,11,12,42].

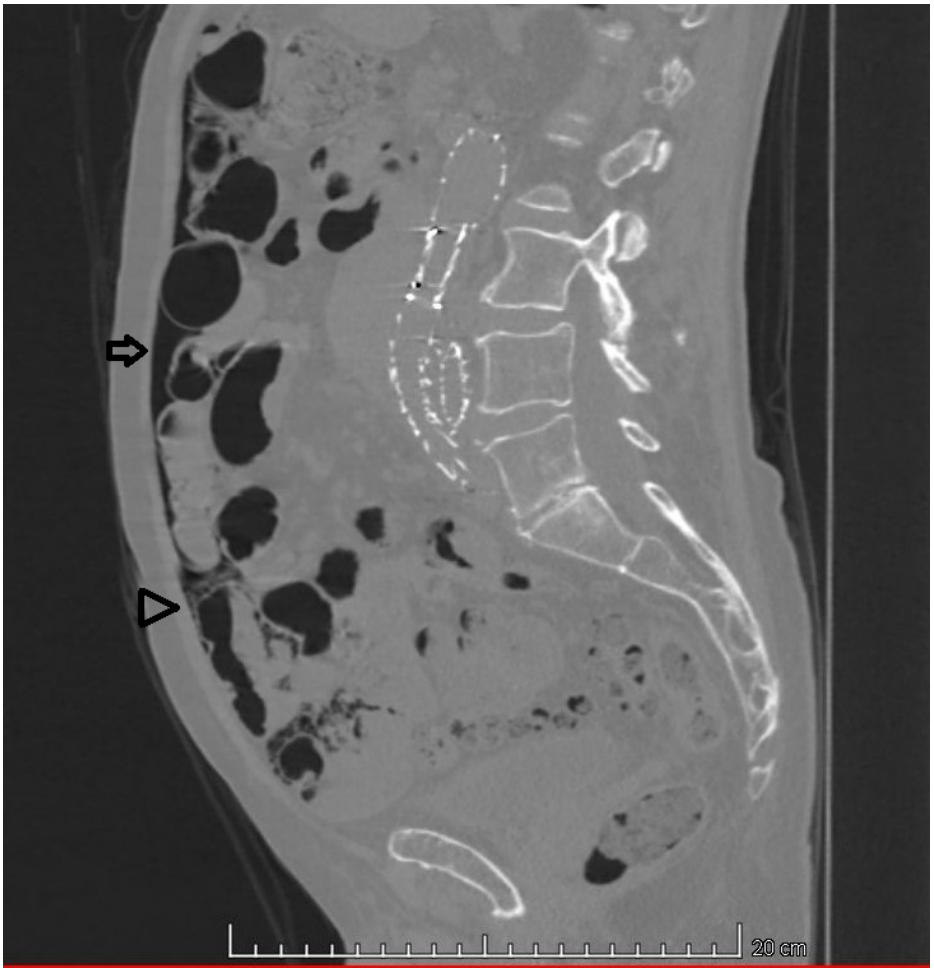

Figure 2: Sagittal CT image in lung window: (arrow) pneumoperitoneum and (arrowhead) “bubbles” within the walls of small intestine segment and the adjacent mesentery, featuring pneumatosis cystoides intestinalis and mesenteric.

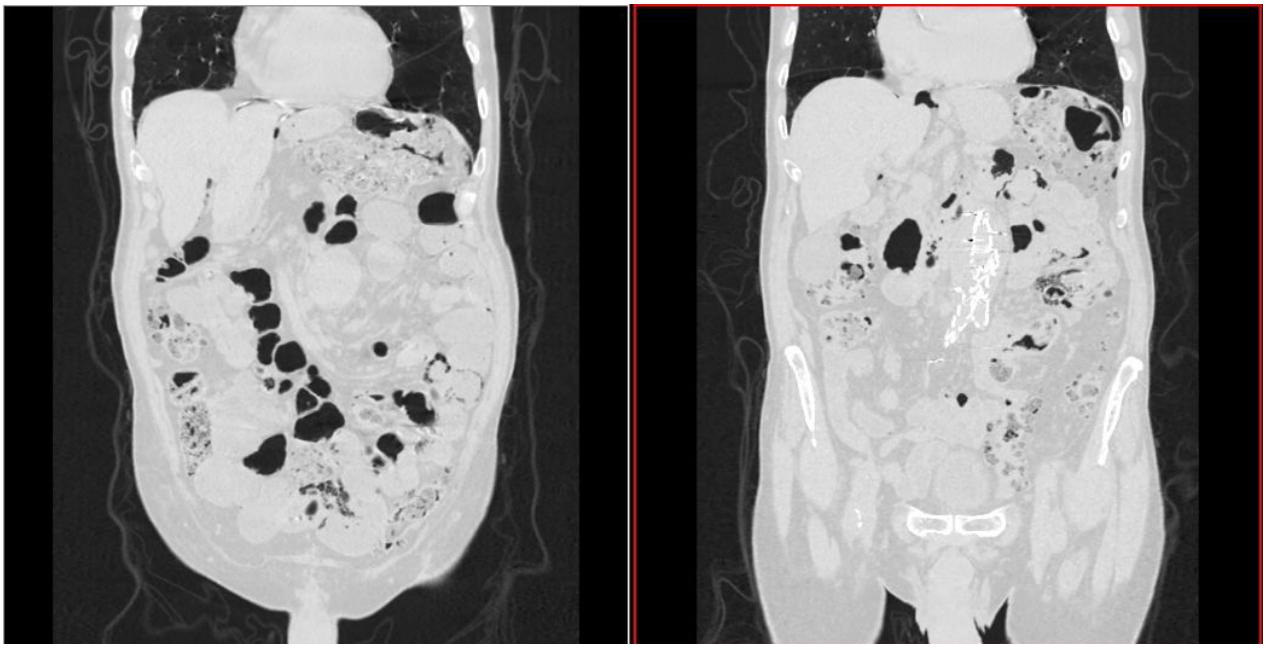

Figure 3: Transversal CT images in lung window showing pneumoperitoneum, "bubbles" within the walls of small intestine and in the mesentery.

CT findings are not pathognomonic of PCI. Intestinal perforation caused by an ischemic process should be excluded[24]. Detailed medical history, physical examination, and laboratory tests are pivotal to establish the correct diagnosis[24]. Elevated leukocytosis, elevated systemic inflammation markers such as CRP, and lactate > 2 also suggest that pneumoperitoneum may be associated with a secondary life-threatening disease[10,27,29,43]. Laparoscopy is often conducted, even in stable patients, to determine whether the case is benign, especially because pneumatosis and pneumoperitoneum heavily influence the decision to operate[8,18,44,45]. This procedure has the advantage of directly evaluating the intestine and safely excluding ischemic processes associated with perforation[24,46]. However, the increase in PCI recognition has reduced the number of unnecessary surgical procedures[7].

A multidisciplinary evaluation with a physician, radiologist, and surgeon is effective to determine the benign and spontaneous origin of pneumoperitoneum and to avoid unnecessary invasive procedures[12,14,17,20,47,48]. Pathological examination of the resected cyst wall often shows a chronic inflammatory process[3].

Endoscopic procedures are important to investigate the presence of submucosal cysts and exclude the presence of associated pathologies or differential diagnoses, such as lymphoma, liquid cysts, dysbacteriosis, carcinoma, inflammatory disease, polyps, and polyposis[27]. During colonoscopy, polypoid grape-like masses protruding through the mucosa may be indicative of PCI[49]. Such findings should be biopsied, and polyposis or neoplasia should be excluded. In the absence of rheumatologic diseases, we suggest that an evaluation should be conducted by an in- or out-of-hospital specialist after emergency resolution, which helps to identify predisposing factors.

PCI may be self-limited, and conservative treatments are effective in 90% of cases, consisting of oxygen and antibiotic use as needed and individualized management[3,12,13,16,22,24,30,50,51]. Although hyperbaric oxygen therapy has been used, its efficacy has not been established. Some authors have reported an efficacy of 50% in patients with PCI undergoing treatment with hyperbaric oxygen therapy[12,13,24]. High-flow inhaled oxygen creates a PaO_2 diffusion gradient that promotes gas outflow through the cyst wall. In addition, high O_2 tissue concentrations are toxic to gas-producing anaerobic bacteria[10]. Patients should be appropriately informed of their illness and especially of the need for future medical evaluations, considering that benign pneumoperitoneum may persist for years or forever[17]. Predisposing factors or secondary causes should be investigated and managed accordingly.

Laparoscopy should be considered in patients with PCI and pneumoperitoneum if leukocytosis and metabolic acidosis are present or if there is clinical worsening. Ischemia and hollow visceral perforation should be excluded[6,7,11,16,20,24,26,42,44,45]. Long-term outcomes are still not well known, with reports of complications that may or may not be

associated with PCI, such as intestinal ischemia secondary to volvulus[24,47].

PCI is a challenging and rare condition to diagnose and manage. It should be suspected in patients with pneumoperitoneum and mild symptoms. A precise diagnosis should be established to avoid unnecessary surgical procedures.

Diagnosis may be achieved by CT combined with endoscopic evaluation. Clinical observation is essential, with serial reassessment of the patient, given that PCI management is not well established. Increased recognition of this benign form of pneumatosis intestinalis and pneumoperitoneum may reduce the number of unnecessary surgical procedures.

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