Pneumatosis cystoides intestinalis induced by acarbose

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Abstract

Pneumatosis cystoides intestinalis is a rare disorder with multiple submucosal or subserosal gas-filled cysts along the gastrointestinal wall.

Pneumatosis intestinalis can be classified as either primary (idiopathic) or secondary. In the latter form, a causal relationship has been established with chronic obstructive pulmonary disease, amyloidosis, infectious colitis, intestinal obstruction, ischemia, Crohn's disease and iatrogenic conditions (drugs, surgery and endoscopy).

Most commonly reported presentations include abdominal pain, subacute intestinal obstruction, diarrhea and bloody stools. Nevertheless, it is usually asymptomatic and found incidentally during investigation of unrelated symptoms.

The authors report a case of pneumatosis intestinalis associated with the use of an oral antidiabetic - acarbose (alpha-glucosidase inhibitor)

Key words: pneumatosis cystoides intestinalis, diabetes mellitus, alfa-glucosidase inhibitor, acarbose, gastrointestinal bleeding, colonoscopy.

INTRODUCTION

Pneumatosis cystoides intestinalis is a rare pathology characterized by the presence of multiple submucosal or subserosal gas-filled cysts in the gastrointestinal wall. It was first described in 1730 by DuVernoi.[1]

Most cases occur without any known reason, while in some situations a causal relationship occurs with chronic obstructive pulmonary disease, connective tissue disease, amyloidosis, infectious colitis, bowel obstruction, ischemia, Crohn's disease and drugs. The mechanical and traumatic causes with repercussions on the digestive tube may also be related to the emergence of pneumatosis cystoides intestinalis.[2,3]

The spectrum of clinical manifestation includes abdominal pain, constipation, bowel obstruction, diarrhea, tenesmus, the feeling of constantly needing to pass stools, and gastrointestinal bleeding. However, it is frequently asymptomatic and is normally found incidentally during an unrelated investigation. Computed Tomography is the exam that shows the highest specificity in the diagnosis, but simple abdominal x-ray, sonography and endoscopy, with collection of biopsy samples for anatomic and histopathological examination, also contribute to the documentation of pneumatosis intestinalis.[4,5]

Medical treatment is required, consisting of an increase in partial oxygen pressure using hyperbaric oxygen therapy, reserving surgery for complicated forms of bowel obstruction, perforation, peritonitis and severe bleeding.[2,4]

The authors present a clinical case of a female patient with pneumatosis cystoides intestinalis associated with the consumption of an oral antidiabetic drug – acarbose (alpha-glucosidase inhibitor).

CLINICAL CASE

Sixty-six year-old Euro-caucasian woman, admitted to hospital with diarrhea. She reported watery diarrhea for four month before hospitalization, with about 6-10 bowel movements per day, during day and night, without blood, mucus or pus, associated with diffuse abdominal cramps, and with no relief or worsening factors. The pain would start immediately after a bowel movement, and continue during them, growing progressively worse. Isolated episodes of rectal bleeding were also present after the bowel movements, in small quantities and associated with the feeling of a need to pass a stool. During this period, non-selective anorexia was verified, with significant weight loss of 15 kg in the 4-month period. Patient reported no other problems, including fever, nausea

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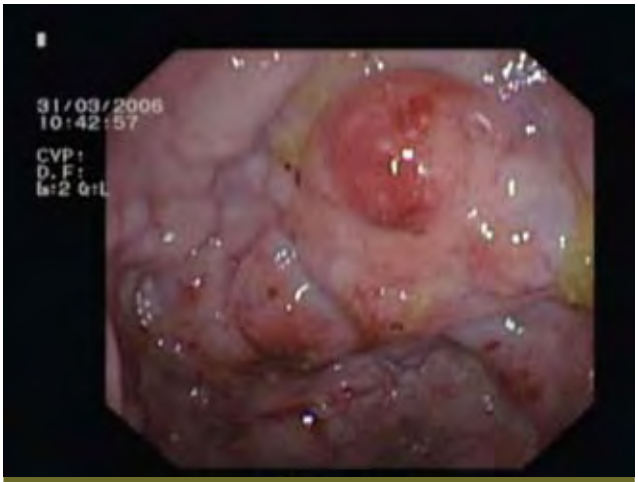
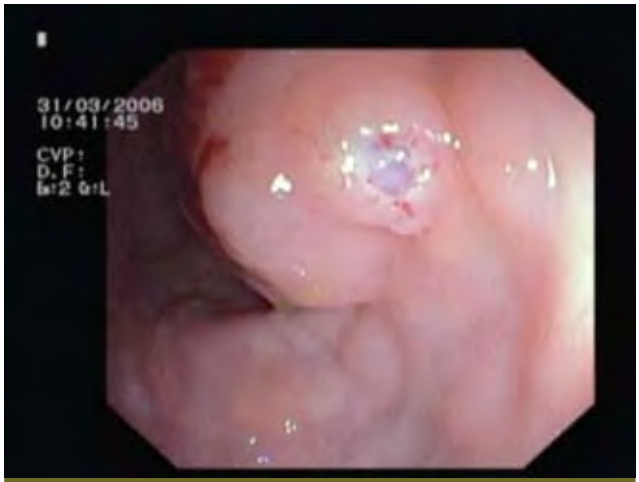


Colic mucosa with diffuse nodular appearance, covered with normal mucosa, suggesting *pneumatosis cystoides intestinalis.*

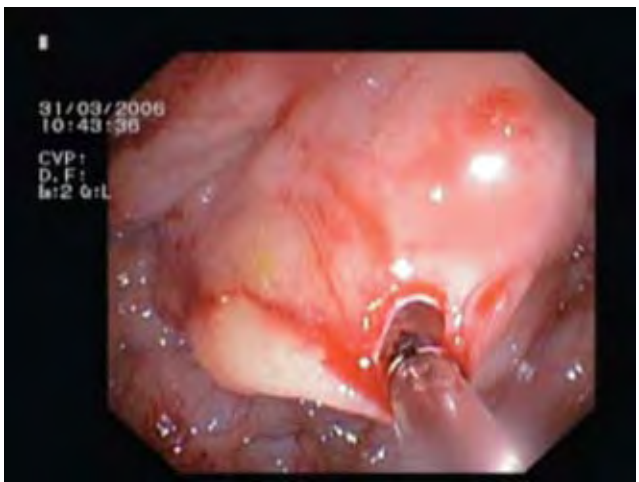
FIG. 1



Translucent aspect of a nodular lesion, suggesting the presence of submucosal gas, typical of this condition.

FIG. 2

or vomiting. She reported no skin, joint or muscle alterations. She had no previous history of recent surgical or endoscopic iatrogenesis. Personal history: elective cholecystectomy due to cholelithiasis at the age of 36; hysterectomy due to fibroleiomyoma at the age of 45; and type 2 Diabetes Mellitus since that time, which was initially controlled through diet, and which has been treated with arcabose for 6 months, apparently with good metabolic control and no clinical evidence of peripheral and autonomic neuropathy, nephropathy, retinopathy, peripheral and cardiovascular arterial disease. No other usual medication, except for the oral antidiabetic drug. In the objective examination revealed: weight 55 Kg, height 1.65m, Body Mass Index – 20.2 Kg/m^2, good color, hydrated, no fever; normal lung, cardiovascular, abdominal and neurological observations; digital rectal exam with palpation of a multilobulated polyp with a smooth surface and elastic consistency. Laboratory tests without alterations. Simple abdominal x-ray, in the standing position, did not reveal any pathological findings. Computed tomography of the abdomen/pelvis revealed: a sessile polyp in the rectum, and absence of adenopathies. Stool culture and test for eggs, cysts and parasites in the feces were negative. Patient was submitted to colonoscopy, which showed: starting 2 cm from the anus, multiple sessile polyps with smooth mucosal surface and appearance suggesting the existence of submucosal air, causing stenosis and



Collapse of nodular lesion after puncture with biopsy forceps, confirming the diagnosis.

FIG. 3

impeding the passage of the colonoscope further than 20cm; biopsy was carried out in some of the lesions, and some were perforated using sclerosis needles, causing immediate drainage. From the histology, the following is highlighted: "distal bowel mucosa with fibrosis and chronic inflammation of the chorion associated with slight architectural distortion and small cysts covered by inflammatory cells compatible with pneumatosis cystoides". sic. Acarbose was suspended, with remission of diarrhea and rectal

bleeding by the end of one week. Colonoscopy was repeated two weeks later, showing resolution of the endoscopic alterations.

DISCUSSION

Pneumatosis intestinalis is a rare clinical condition. It occurs in both genders and in any age group, being more frequent between patients aged between 40 and 50 years old.[2]

Morphologically, it is characterized by the presence of multiple submucosal or subserosal gas-filled cysts in the bowel walls, stomach, mesentery or omentum. In endoscopy, the mucosa has a diffuse nodular appearance, covered by normal mucosa, showing polyps that collapse after puncture with a sclerosis needle or biopsy forceps, showing the cysts to be of the "false polyp" type.[6]

In pneumatosis intestinalis, the left colic segment is the most commonly affected, however, any part of the gastrointestinal tract may be involved.[2-4]

Two types of pneumatosis intestinalis are considered: the primary form, which is idiopatic (15% of cases); and the secondary form, where an association with a known underlying condition can be established (85% of cases) [7,8].

Two situations associated with pneumatosis intestinalis were identified, in which a causal intervention occurs *(Table I)*. The available literature reports an association between immunosupression conditions induced by chemotherapy and other immunosuppressant drugs (e.g., cyclosporine, prednisone) and pneumatosis intestinalis, the genesis of which lies in the loss of structural integrity of the mucosa, in the Peyer plates, with a consequent increase in intestinal wall permeability and the entry of gas. The ingestion of carbohydrates, such as lactulose and sorbitol, was also identified as a predisposing factor for pneumatosis intestinalis, since it promotes the production of intestinal gas.[9,10]

The etiopathogenisis is still unclear, but it is assumed that the gas is forced to penetrate the intestinal walls through diverse routes (the lungs – alveolar rupture with perivascular gas dissection; breaks in the mucosa, or an increase in intraluminal pressure) – mechanical theory. There is also a bacterial theory, which postulates that the excess hydrogen resulting from bacterial metabolization of carbohydrates in the lumen is absorbed and sequestered by the wall of the digestive tract, producing gas-filled cyst collections

TABLE I

"Causes" of *Pneumatosis intestinalis*

Lung Disease
Chronic Obstructive Pulmonary Disease
Asthma
Cystic fibrosis
Chest trauma
Disruption of the mucosa
Peptic ulcer
Ingestion of caustic products
Bowel obstruction
Ruptured diverticulum
Abdominal trauma abdominal, Volvulus
Surgery
Endoscopy
Mucosa lesion due to inflammation or ischemia
Necrotizing enterocolitis
Ischemia and infarction
Appendicitis
Crohn's disease
Ulcerative colitis
Systemic amyloidosis
Collagen vascular diseases
Immune diseases
"Graft *vs.* host" disease
Organ transplant
Hemodialysis
Polyarteritis nodosa
Dermatomyositis
Systemic lupus erythematosus
Infection
Clostridium
Cytomegalovirus
Human immunodeficiency virus
Cryptosporidium
Mycobacterium tuberculosis
Tropherima whippeli
Parasites
Drugs
Therapy with steroids
Immunosuppressant drugs
Nitric oxide anesthesia
Lactulose/Sorbitol

that are typical of this entity.[11,12]

In our clinical case, there was no evidence of any lung disease of obstructive nature, according to the clinical history, physical examination, or findings in the additional diagnostic exams carried out. From the investigation, we highlight chest CT, blood culture and bronchial secretions, with no relevant findings, and biopsies of the colon negative for inflammatory lesions of the mucosa. Stool cultures and tests for eggs, cysts and parasites in feces with no isolation of microbiological agents, making a probable contribution to colic pneumatosis in this case. Autoimmune test negative. No reports of alterations in serum levels of B12 or folate. No recent history of invasive gastrointestinal procedure. After excluding possible associated causes during the investigation process, the only remaining suspicion of nexus causal was the acarbose treatment.

Alpha-glucosidase inhibitors interfere in the digestion of carbohydrates, hindering their absortion by the bowels through the inhibition of alpha-glucosidase in the cell membrane of the enterocyte. Well-known adverse effects of acarbose are abdominal distension and flatulence, which result from the increase in production of intestinal gas arising from the fermentation of the ingested carbohydrates, forming carbon dioxide, methane and hydrogen.[4,11] This results in an increase in intraluminal pressure of the bowel and excessive production of hydrogen, which may be the origin of pneumatosis intestinalis.

In the case described, the recent start of treatment using acarbose was verified, and the patient used the medication until the date on which *pneumatosis cystoides intestinalis* was diagnosed. Two weeks after interruption of the treatment, in the absence of other therapeutic interventions, the clinical situation was reverted, i.e., the elimination of the probable etiophatogenic factor subsequently led to the disappearance of the lesions.

Remission of symptomatology avoided the need for medical therapy, such as the use of hyperbaric oxygen and surgery, which should be reserved for refractory symptomatic cases and in the event of complications.[4]

There is the possibility that the patient had the idiopathic form of pneumatosis intestinalis with spontaneous remission, coinciding with the suspension of the drug. However, if we consider that the probability of occurrence of idiopathic penumatosis intestinalis, which is only 15%, and that spontaneous remission of the clinical status coinciding with the interruption of the drug is another low-probability situation, the combination of both events is statistically unlikely.

In conclusion, in our patient we interpreted the treatment with acarbose, in the absence of other know causes, as the event that triggered *pneumatosis cystoides intestinalis,* based on the rationale behind both theories that attempt to explain its etiopathogeny.

The hypothesis of pneumatosis intestinalis should be considered in diabetic patients treated with alpha-glucosidase inhibitors with gastrointestinal complaints, and an investigation plan within this context should be considered. ■

References

1. Pear BL et al. Pneumatosis intestinalis: a review. Radiol 1998; 207: 13-19.

2. Sartor RB et al. Miscellaneous inflammatory and structural disorders of the colon. In: Yamada T eds. Textbook of gastroenterology. 4th edition. Philadelphia: Lippincott Williams & Wilkins; 2003: 1809-1811.

3. Saito M, Tanikawa A et al. Additive contribution of multiple factors in the development of pneumatosis intestinalis: a case report and review of the literature. Clin Rheumatol 2007; 26: 601-603.

4. Shawn D, Maher A et al. The spectrum of pneumatosis intestinalis. Arch Surg 2003; 138: 68-75.

5. Caudill JL, Rose BS et al. The role of computed tomography in the evaluation of pneumatosis intestinalis. J Clin Gastroenterol 1987; 9: 223-226.

6. Hoer J, Truong S et al. Pneumatosis cystoides intestinalis: confirmation of diagnosis by endoscopic puncture: a review of pathogenesis, associated disease and therapy and a new theory of cyst formation. Endoscopy 1998; 30: 793-799.

7. Hisamoto A, Mizushima T et al. Pneumatosis cystoides intestinalis after alpha-glucosidase inhibitor treatment in a patient with interstitial pneumonitis. Intern Med 2006; 45: 73-76.

8. Heng Y, Schuffler MD et al. Pneumatosis intestinalis: A review. Am J Gastroenterol 1997; 90:1747-1758.

9. Galm O, Fabry U et al. Pneumatosis intestinalis following cytotoxic or immunosuppressive treatment. Digestion 2001; 64: 128-132.

10. Cabrera GE, Scopelitis E et al. Pneumatosis cystoides intestinalis in systemic lupus erythematosus with intestinal vasculitis: treatment with high-dose prednisone. Clin Rheumatol 1994; 13: 313-316.

11. Christl SU, Gibson GR et al. Impaired hydrogen metabolism in pneumatosis cystoides intestinalis. Gastroenterology 1993; 104: 392-397.

12. Florin TH et al. Alkyl halides, super hydrogen production and the pathogenesis of pneumatosis cystoides coli. Gut 1997; 41: 778-784.