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CASE REPORT

Pneumatosis Cystoides Intestinalis in Intestinal Pseudoobstruction

Resolution after Therapy with Metronidazole

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Spontaneous pneumoperitoneum usually indicates perforation of a hollow abdominal organ. In a small percentage of patients, there is no clinically significant abnormality, and surgery is not indicated (1). The most common abdominal cause of pneumoperitoneum without perforation is pneumatosis cystoides intestinalis (2). This uncommon condition, which is characterized by multiple cystic accumulations of gas located in the submucosa or subserosa of the intestine, is associated with many diseases. Few patients with pneumatosis secondary to chronic intestinal pseudoobstruction have been described (3), in particular in systemic sclerosis (4, 5).

Primary chronic intestinal pseudoobstruction constitutes a group of propulsive disorders without mechanical occlusion and without recognized underlying disease. Cases in which no visceral neuropathy or regressive myopathy is discerned are extremely unusual (6).

We present a 66-year-old man with a primary chronic intestinal pseudoobstruction without visceral neuropathy or regressive abnormalities of the smooth muscle. This disorder was complicated by pneumatosis cystoides intestinalis and pneumoperitoneum. The latter conditions were successfully treated with metronidazole.

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CASE REPORT

A 66-year-old man had a history of a myocardial infarction in 1981 and ankylosing spondylitis since 1988. In 1986 chronic intestinal pseudoobstruction was diagnosed on the basis of radiological studies. An underlying disorder could not be demonstrated. There was no pneumatosis or pneumoperitoneum. Bacterial overgrowth with secondary vitamin B_{12} deficiency was treated with tetracycline for four weeks and supplementation of vitamin B_{12} intramuscularly. In May 1990 the patient was admitted to our hospital for subileus and pneumoperitoneum. He was not treated with antibiotics at that time.

In June 1990 he was readmitted for evaluation of recurrent postprandial nausea and vomiting, abdominal distension, progressive constipation, and weight loss of over 10 kg. There were no urinary symptoms. He has had nonspecific complaints of postprandial abdominal distension of 50 years duration. No other family members were affected. His medication included fenprocoumon, acebutolol, antacids, lactulose, and vitamin B_{12} supplementation.

Examination revealed a man in no apparent distress with a weight of 63 kg, a height of 1.83 m, a blood pressure of 130/90 mm Hg in upright and supine position, and a pulse rate of 86/min. The abdomen was distended. Bowel sounds and liver dullness to percussion were decreased. No tenderness or palpable masses were noted. Rectal examination was negative. There were no neurological abnormalities.

Admission laboratory data showed a hemoglobin of 6.4 mmol/liter (10.3 g/liter), MCV of 77 fl, a normal ferritin and folic acid, and a serum albumin of 28 g/liter. On the plain abdominal film a marked dilatation of small bowel loops with a pneumoperitoneum was demonstrated (Figure 1A). In addition, radiolucent clusters of cysts were detected in the small bowel wall, indicating pneumatosis cystoides intestinalis. An enteroclysis was performed using a Miller-Abbott tube. Despite the use of metoclopramide intravenously, hardly any propulsive peristalsis was observed. Besides the dilated small bowel loops, at least two segments suggestive of stenosis were seen.

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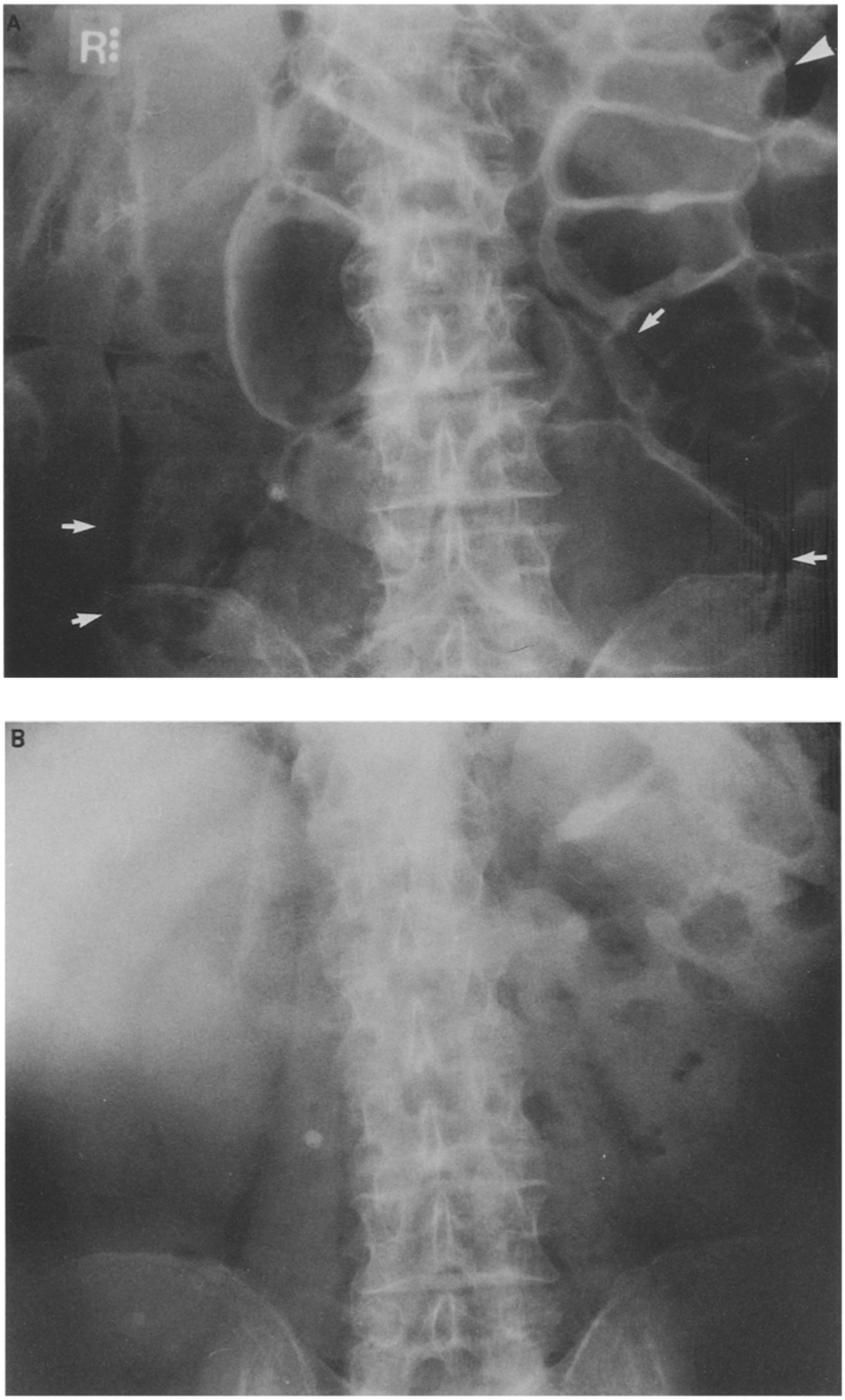

Fig 1. (A) Plain abdominal film showing marked dilatation of small bowel loops, air-filled cysts in the small bowel wall, indicating pneumatosis cystoides intestinalis (arrows), and pneumoperitoneum (arrow head). (B) Resolution of pneumatosis cystoides intestinalis and pneumoperitoneum after therapy with metronidazole.

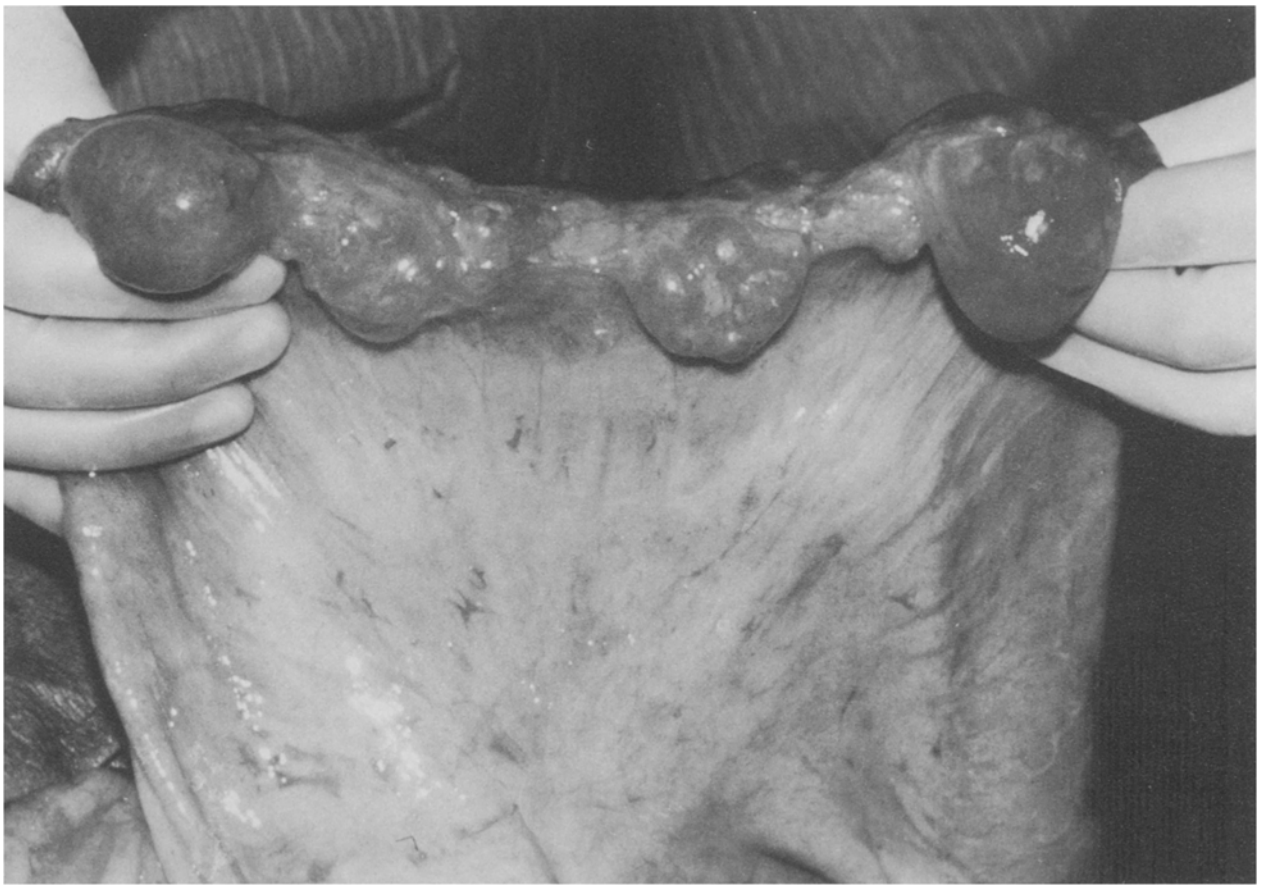

Fig 2. Photograph taken at exploratory laparotomy, showing multiple subserosal air cysts along the small intestine.

The lower esophageal sphincter pressure was 8 mm Hg and contractions of the esophagus were absent, as shown by an esophageal manometric study. Upper gastrointestinal endoscopy showed retention of fluid in the stomach and candidiasis of the esophagus. In mucosal specimens of the proximal duodenum and the jejunum no abnormalities could be demonstrated. In particular, the findings were not suggestive of a neoplasm, amyloidosis, or villous atrophy. Dysfunction of the vagus nerve assessed by means of the plasma pancreatic polypeptide response to hypoglycemia could not be identified (7). Laboratory tests could not detect a disorder known to cause intestinal pseudoobstruction: blood glucose, thyroid function tests, creatinine phosphokinase, antinuclear antibody tests, and viral antibodies were normal. The results of the urinary excretion of indican and the glucose hydrogen breath test were compatible with bacterial overgrowth.

To exclude mechanical obstruction, the patient underwent laparotomy. Along the small intestine multiple subserosal air cysts were found (Figure 2). There was generalized absence of peristalsis and gross dilatation of the small bowel with a proximal to distal gradient, but no mechanical stenosis. Full-thickness biopsy specimens were taken of the hypomotile small bowel, but not near the air cysts, and the abdomen was closed. Histopathological examination of these biopsies revealed mucosa with normal villous height, normal enterocytes, and slight increase of mononuclear inflammatory cells in the lamina propria. The submucosa showed dilated lymphatic vessels lined by normal endothelial cells. The muscle layer appeared to consist of somewhat hypertrophic myocytes. No abnormalities were found in the myenteric plexus, even in slides stained by special enzyme and immunohistochemical methods (neurofilament, acetylcholinesterase). There was a normal number of neurons, and the axons showed no pathological changes. There was no evidence of amyloid deposition (Congo red stain). Electron microscopy of the muscle layer revealed thickened smooth muscle fibers with thickened myofilaments (diameter 10.5 nm, in the myocytes of an adjacent artery 5.7 nm), indicating hypertrophy of the smooth muscle cells. This might be secondary to obstruction, or caused by a long-standing increase of the muscle tone.

Primary chronic intestinal pseudoobstruction complicated by pneumatosis cystoides intestinalis and pneumoperitoneum was diagnosed. Presumably, one or more cysts had ruptured, causing pneumoperitoneum. The patient was treated with supplementary parenteral nutrition. On admission all medication had been discontinued without any clinical effect. Postoperatively cisapride 10

mg four times daily orally was started. This did not result in a clinical improvement. After two weeks this prokinetic drug was stopped and metronidazole 500 mg three times daily orally was started to treat bacterial overgrowth. After a week of antibiotic therapy, there was a marked clinical improvement and the patient could tolerate solid food without postprandial complaints. Concurrently, a plain film showed an impressive reduction of pneumatosis and pneumoperitoneum (Figure 1B). The glucose hydrogen breath test had normalized, indicating suppression of bacterial overgrowth.

At seven weeks, during continuous therapy with metronidazole, there was still no recurrence of pneumatosis and pneumoperitoneum. This was confirmed by a repeated abdominal plain film. Since the esophageal abnormalities are probably representative of the propulsive disorder in the small bowel (8), another esophageal manometric study was performed under these conditions. The results were similar to the previous one: a low lower esophageal sphincter pressure of about 8 mm Hg and absent contractions of the esophagus. Administration of erythromycin (250 mg intravenously), known to have prokinetic effects as a motilin receptor agonist (9) and cisapride (10 mg intravenously), which probably facilitates release of acetylcholine in the myenteric plexus (10), did not improve the contractions of the esophagus. Neither was the orocecal passage time shortened with these drugs, as measured by a lactulose hydrogen breath test. No further treatment with these drugs was instituted.

After three months of therapy, the metronidazole was discontinued. Within a week the symptoms of postprandial nausea and abdominal distension recurred. The plain abdominal film showed again marked dilatation of small bowel loops with pneumoperitoneum. Therapy with metronidazole 500 mg three times a day was reinstituted. The symptoms disappeared within two days. After one week, the plain film showed a marked decrease of dilatation and pneumoperitoneum. Another week later, the plain film had normalized. Metronidazole therapy was continued.

DISCUSSION

In this 66-year-old man an unusual combination of two rare conditions was present: primary chronic intestinal pseudoobstruction and pneumatosis cystoides intestinalis, complicated by pneumoperitoneum. The pneumatosis and pneumoperitoneum resolved after therapy with metronidazole. A favorable effect of administration of erythromycin or cisapride on the underlying propulsive disorder could not be demonstrated.

In chronic intestinal pseudoobstruction the motility disorder may affect every part of the gastrointestinal tract (11). Regardless of the underlying causes, the patient has recurrent signs and symptoms of intestinal obstruction (8).

The secondary form of chronic intestinal pseudoobstruction may be associated with several underlying systemic conditions (8). Since mechanical obstruction is much more common than intestinal pseudoobstruction, the diagnosis can be made after excluding a stenosis using radiology (6), endoscopy (12), and if necessary, operative data. Esophageal manometric studies are helpful, since the disorder produces an esophageal motor abnormality in more than half of the cases (8). The myopathic type of intestinal pseudoobstruction seems to be associated with low-amplitude pressure activity, as seen in this patient. The neuropathic type tends to produce excessive or uncoordinated pressure activities on manometry (11). Laboratory tests may be useful in detecting underlying disease (8, 12). If surgery is indicated to rule out mechanical obstruction, neuropathic or myopathic abnormalities may be identified in full-thickness specimens (11). Neurological testing provides further information in the case of clinical features, suggestive of an underlying neurological disease. Medication that may be associated with pseudoobstruction should be discontinued. In this patient no underlying disorder could be demonstrated.

The primary form of chronic intestinal pseudoobstruction can be divided into familial and nonfamilial types, which can both be further divided into visceral myopathies and visceral neuropathies (8). Rarely, regressive visceral myopathy and visceral neuropathy are absent in the nonfamilial type of primary intestinal pseudoobstruction (13–16), as in this case.

Several drugs have been used unsuccessfully in patients with pseudoobstruction. Possibly, new prokinetic drugs such as erythromycin (9, 17) and cisapride (18, 19) offer therapeutic possibilities for some patients. However, we could not demonstrate any favorable effect of these drugs in this case. There was no clinical improvement after therapy with cisapride orally; neither was there improvement of the esophageal contractions after administration of cisapride and erythromycin intravenously.

Pneumatosis cystoides intestinalis is associated with several diseases (20, 21). There is strong circumstantial evidence that the gas produced in this condition is of bacterial origin (22). In hypomotility in chronic intestinal pseudoobstruction, bacterial overgrowth and bowel distension can cause elevated intraluminal pressure and force gas into the wall of the intestine (4, 21). The diagnosis of pneumatosis cystoides intestinalis may be made on plain films or barium enema (1). The condition is generally asymptomatic, although complications,

such as pneumoperitoneum may occur (23, 24), as in this patient.

Our findings suggest that pneumatosis cystoides intestinalis further added to the obstructive symptoms (25), forming a vicious cycle. In our patient treatment of bacterial overgrowth resulted in concurrent resolution of pneumatosis and pneumoperitoneum, improvement of the obstructive symptoms, and radiologically diminished dilatation of small bowel loops. Discontinuation of the metronidazole therapy resulted in recurrence of these symptoms and radiological abnormalities, including pneumoperitoneum, with a subsequent resolution after reinstitution of this therapy. If treatment of pneumatosis is felt necessary, resolution of the cysts may be achieved by oxygen therapy (26, 27), elemental diet (28), or antibiotics (29–31). The therapeutic effect of metronidazole, as described by Jauhonen et al (29) and as shown in this case, lends support to the view that anaerobic gas-forming bacteria play a role in the pathogenesis of pneumatosis. To our knowledge, this is the first reported case of successful treatment of pneumatosis cystoides intestinalis in primary chronic intestinal pseudoobstruction.

SUMMARY

A 66-year-old man with chronic idiopathic intestinal pseudoobstruction was admitted for pneumatosis cystoides intestinalis, complicated by pneumoperitoneum. The latter conditions resolved after treatment with metronidazole. There was no favorable effect of the prokinetic agents cisapride and erythromycin. To the authors' knowledge, this is the first reported case of successful treatment of pneumatosis cystoides intestinalis with metronidazole in primary chronic intestinal pseudoobstruction.

REFERENCES

1. Rice RP, Thompson WM, Gedgaudas RK: The diagnosis and significance of extraluminal gas in the abdomen. Radiol Clin North Am 20:819–837, 1982
2. Fick ThE, Van Oorschot FHAM, Mallens WMC, Kitselaar PJEHM: Pneumoperitoneum without peritonitis. Neth J Surg 40:152–154, 1988
3. Pennoit H, Barbier F, Schoofs R, Van den Brande L: Pneumatosis cystoides intestinalis met chronische idiopathische intestinale pseudoobstructie—voorstelling van een geval. Tijdschr Gastroenterol 15:116–124, 1972
4. Stafford-Brady FJ, Kahn HJ, Ross TM, Russell ML: Advanced scleroderma bowel: Complications and management. J Rheumatol 5:869–874, 1988
5. Meihof WE, Hirschfield JS, Kern F: Small intestinal scleroderma with malabsorption and pneumatosis cystoides intestinalis. JAMA 204:102–106, 1968
6. Schuffler MD, Rohrmann CA, Chaffee RG, Brand DL, Delaney JH, Young JH: Chronic intestinal pseudoobstruction. Medicine (Baltimore) 60:173–196, 1981
7. Schwartz TW, Holst JJ, Fahrenkrug J, Lindkear Jensen S, Nielsen OV, Rehfeld JF, Schaffalitzky de Muckadell OB, Stadil F. Vagal: Cholinergic regulation of pancreatic polypeptide secretion. J Clin Invest 61:781–789, 1978
8. Anuras S: Intestinal pseudo-obstruction syndrome. Annu Rev Med 39:1–15, 1988
9. O'Dorisio TM, Thomas FB, Mekhjian HS: Erythromycin exerts a prokinetic effect in patients with chronic idiopathic intestinal pseudoobstruction. Gastroenterology 99:A375, 1990
10. MacColl C, MacCannell KL, Baylis B, Lee SS: Treatment of acute colonic pseudoobstruction (Ogilvie's syndrome) with cisapride. Gastroenterology 98:773–776, 1990
11. Colemont LJ, Camilleri M: Chronic intestinal pseudoobstruction: Diagnosis and treatment. Mayo Clin Proc 64:60–70, 1989
12. Stanghellini V, Corinaldesi R, Barbara L: Pseudoobstruction syndromes. Baillieres Clin Gastroenterol 2:225–254, 1988
13. Rossowski WJ, Ertan A, Rice J, Ozden A, Covington S, McCord R: Alterations in cholinergic muscarinic and somatostatin binding sites in a patient with idiopathic intestinal pseudo-obstruction. Am J Med Sci 296:399–405, 1988
14. Bannister R, Hoyes AD: Generalised smooth-muscle disease with defective muscarinic-receptor function. Br Med J 282:1015–1018, 1981
15. Keshavarzian A, Isaacs P, McColl I, Sladen GE: Idiopathic intestinal pseudo-obstruction and contaminated small bowel syndrome—treatment with metronidazole, ileostomy, and indomethacin. Am J Gastroenterol 78:562–565, 1983
16. Sarna SK, Daniel EE, Waterfall WE, Lewis TD, Marzio L: Postoperative gastrointestinal electrical and mechanical activities in a patient with idiopathic intestinal pseudoobstruction. Gastroenterology 74:112–120, 1978
17. Berger SA, Keshavarzian A, DeMeo MT, Mobarhan S: Erythromycin in chronic intestinal pseudo-obstruction. J Clin Gastroenterol 12:363, 1990
18. Camilleri M, Malagelada JR, Abell TL, Brown ML, Hench V, Zinsmeister AR: Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. Gastroenterology 96:704–712, 1989
19. Graham JR: Cisapride for severe non-ulcer dyspepsia, pseudoobstruction and constipation. Med J Aust 150:667, 1989
20. Vlasveld LT, Peters WG, Thompson J: Pneumatosis intestinalis bij een patient met acute monocytenleukemie. Ned Tijdschr Geneeskd 132:171–173, 1988
21. Sequeira W: Pneumatosis cystoides intestinalis in systemic sclerosis and other diseases. Semin Arthritis Rheum 19:269–277, 1990
22. Ellis BW: Symptomatic treatment of primary pneumatosis coli with metronidazole. Br Med J 280:763–764, 1980

23. Galandiuk S, Fazio VW: Pneumatosis cystoides intestinalis. A review of the literature. Dis Colon Rectum 29:358–363, 1986
24. Mathus-Vliegen EMH, Rutgeerts L, Tytgat GNJ: Pneumatosis cystoides intestinalis. Ned Tijdschr Geneeskd 127:2272–2277, 1983
25. Soutter DI, Paloschi GB, Prentice RS: Pneumatosis cystoides intestinalis. Can J Surg 28:272–273, 1985
26. Down RHL, Castleden WM: Oxygen therapy for pneumatosis coli. Br Med J 1:493–494, 1975
27. Forgacs P, Wright PH, Wyatt AP: Treatment of intestinal gas cysts by oxygen breathing. Lancet 1:579–581, 1973
28. Van der Linden W, Marsell R: Pneumatosis cystoides intestinalis associated with high H_2 excretion: Treatment with an elemental diet. Scand J Gastroenterol 14:173–174, 1979
29. Jauhonen P, Lehtola J, Karttunen T: Treatment of pneumatosis coli with metronidazole. Endoscopic follow-up of one case. Dis Colon Rectum 30:800–801, 1987
30. Rogy MA, Mirza DF, Kovats E, Rauhs R: Pneumatosis cystoides intestinalis (PCI). Int J Colorect Dis 5:120–124, 1990
31. Goulet JR, Hurtubise M, Senecal JL: Retroperitoneum and pneumatosis intestinalis in 2 patients with mixed connective tissue disease and the overlap syndrome. Clin Exp Rheumatol 6:81–85, 1988