Fibrosing Colonopathy Associated with Treatment with Enteric-coated Mesalazine Pills

To the Editor:

Fibrosing colonopathy consists of the appearance of a thickening of the submucous layer of the colon due to proliferation of connective tissue together with a variable amount of fatty tissue. The dense fibrotic proliferation may cause stenosis of the lumen. This condition was first described by Smyth et al in 1994[1] in cystic fibrosis patients who were given high doses of pancreatic enzymes in the form of pills with an enteric coating of methacrylic acid (Eudragit). This report shows that stenotic fibrosing colonopathy may also appear in other conditions treated with Eudragit-coated drugs. We report a case of a 10-year-old male with no relevant medical history who was referred to us for asthenia, bloody diarrhea, lower abdominal pain, and weight loss over a period of 2 months. He had iron-deficient anemia and increased acute phase reactants. Abdominal ultrasound and autoimmunity studies were irrelevant, except ANCA-positive and ASCA-negative. Colonoscopy was performed. The patient was diagnosed with mild ulcerative pancolitis and started treatment with prednisone (30 mg/12 h) and mesalazine (500 mg/8 h). The response to treatment was positive for 18 months, allowing for gradual removal of prednisone, whereas the treatment with mesalazine (Claversal, Faes Farma, Spain) was unchanged. The patient then reported diffuse abdominal pain, borborigms, intermittent diarrhea without blood or mucus, and weight loss. The dose of mesalazine was increased to 1 g/8 h. After an initial improvement, he lost 3–4 kg and his condition deteriorated, requiring admission. Barium enema revealed a 2–3 cm long stenosis in the ascending colon. Colonoscopy confirmed the presence of a concentric stenosis with thick edges in the ascending colon and biopsy showed nonspecific acute and chronic signs of inflammation, without evidence of malignancy. Laparotomy was then undertaken. Severe thickening of the ascending colon wall was observed and a resection was performed. The surgical specimen showed abundant fatty tissue and intense hyalinization in the submucous layer of the stenotic zone, without inflammation or vascular proliferation, and with noninvolved muscular and serosal layers (Fig. 1). After the operation the patient did well and the symptoms disappeared. One year later, he had a new outbreak of ulcerative colitis that responded well to corticosteroids.

Since 1993 a number of cases of fibrosing colonopathy associated with cystic fibrosis have been described. The main feature of this condition is the appearance of extensive fibrosis in the submucous and muscular layers of the colon with undamaged or mildly inflamed mucosa with eosinophilic and mast cell infiltration.[2] The stenosis is more often located at the ascending colon, but the terminal ileum may also be involved. These patients were receiving high doses of pancreatic enzymes for cystic fibrosis over the 12–18 months preceding the onset of the colonopathy and a causal relationship was suggested.[3] Two pathogenic interpretations were proposed: The first postulated that the proteolytic action of pancreatic enzymes caused mucosal damage[1] that evolved to fibrosis and stenosis in the process of scarring.[3] Since the pH of the intestinal secretion in cystic fibrosis is lower than in normal individuals, the enteric coating would be broken down only at the distal ileal and colonic levels. But it was later observed that colonopathy was also possible with lower doses.[4] A second interpretation suggested that the lesions might be due to the enteric coating itself.[2] Several studies addressed the association between colonopathy and certain commercial brands of enzymes presented as micro-pills with an enteric coating containing a methacrylic acid copolymer (Eudragit L30 D-55). The recommended safe dose was 150 mg/day, but this was widely exceeded in many of the cases described. Eudragit L30 is a methacrylic acid copolymer dispersion with 2 surfactants (sodium lauryl sulfate and polysorbate 80). These would act as irritants in the intestinal mucosa, favoring the passage of the active principle and methacrylic acid to the mucosa. The passage of methacrylic acid would induce fibrosis in the submucosa, as observed in some animal studies.[4] This hypothesis is supported by a strong time link, since fibrosing colonopathy was first detected shortly after this formulation was introduced into the market and there have been hardly any cases since its use was limited.[4] Other conditions have been associated with this type of stenosis: an adult patient without cystic fibrosis who received treatment with pancreatic enzymes for a pancreatoduodenectomy and newborns with meconium ileus due to cystic fibrosis who had not yet received treatment with pancreatic enzymes. These observations prompted other pathogenic interpretations for this disease.

The methacrylic acid copolymer is a component of other medications that have to be released in the small intestine, such as mesalazine. The suspicion that prolonged treatment with 5-aminosalicylate (5-ASA) may cause fibrosing colonopathy has been raised.[5,6] A patient with Crohn's disease who received mesalazine in monotherapy developed intestinal obstruction due to fibrosing colonopathy of the ascending colon.[7] Our patient was receiving treatment

DOI 10.1002/ibd.20830
Published online 18 December 2008 in Wiley InterScience (www.interscience.wiley.com).

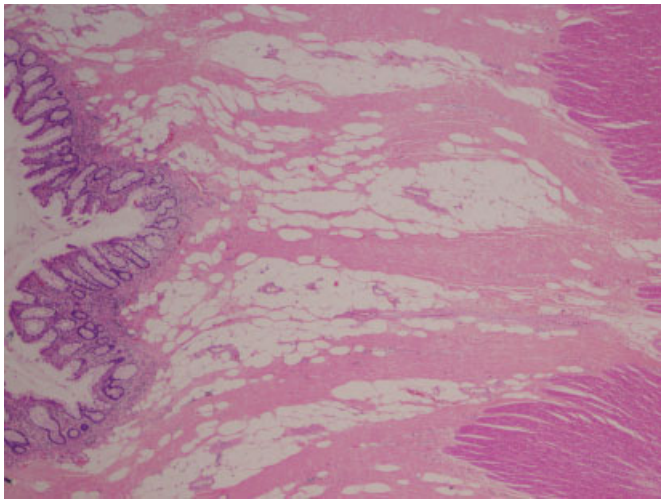

FIGURE 1. Histological study of the surgical specimen showing the characteristic findings of fibrosing colonopathy: abundant fatty tissue and intense hyalinization in the submucous of the stenotic zone, with no inflammatory component or vascular proliferation, and undamaged muscular layer (H&E 2×). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

with mesalazine with methacrylic acid copolymer as a component of the enteric coating prior to the onset of symptoms. He appears to be the first case of fibrosing colonopathy associated with mesalazine in children.

Mesalazine, an aminosalicylate considered a nonsteroidal antiinflammatory drug, may cause diaphragm-like stenosis of the small and large bowel (particularly of the ascending colon) as a consequence of the scarring of ulcerative lesions,[8] but these stenosis are different from those seen in fibrosing colonopathy.

Although the presence of methacrylic acid copolymer in the enteric coating suggested the suspicion of its role as a causative agent, an unequivocal link between this chemical and the fibrosis could not be firmly established. More cases of this nature must be analyzed in order to confirm this association.

Gerardo Prieto, MD
Begoña Pérez-Moneo, PhD
Manuel Molina, MD
Esther Ramos, PhD
Jesús Sarría, PhD
Javier Larrauri, MD
Juan Antonio Tovar, MD
Hospital Infantil La Paz
Madrid, Spain

REFERENCES

1. Smyth RL, van Velzen D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. *Lancet*. 1994;343:85–86.
2. Pawel BR, de Chadarevian JP, Franco M. The pathology of fibrosing colonopathy of cystic fibrosis: a study of 12 cases and review of the literature. *Hum Pathol*. 1997;28:395–399.
3. Powell CJ. Colonic toxicity from pancreatins: a contemporary safety use. *Lancet*. 1999;353: 911–915.
4. Prescott P, Bakowski MT. Pathogenesis of fibrosing colonopathy: the role of methacrylic acid copolymer. *Pharmacoepidemol Drug Saf*. 1999;8:377–384.
5. Borum ML, Ginsberg AL. Lack of evidence for fibrosing colonopathy by 5-ASA in humans [Letter]. *Dig Dis Sci*. 1999;44:1494.
6. Bakowski MT, Prescott P. Lack of evidence for fibrosing colonopathy by 5-ASA in humans [Letter]. *Dig Dis Sci*. 2002;47:469.
7. Gaia E, Sambatoro A, De Giuli P, et al. Adult fibrosing colonopathy associated with mesalazine treatment [Letter]. *Am J Gastroenterol*. 2001;96:2508–2509.
8. Thiéfin G, Beaugerie L. Toxic effects of nonsteroidal anti-inflammatory drugs on the small bowel, colon and rectum. *Joint Bone Spine*. 2005;72:286–294.