ABSTRACT

Chronic intestinal pseudo-obstruction is an uncommon syndrome characterized by relapsing episodes suggesting intestinal obstruction during which no mechanical causes are identified to account for symptoms. Etiologic factors may be manifold. Among them a number of neurologic conditions, gastrointestinal smooth muscle myopathies, endocrinometabolic and autoimmune diseases, and the use of selected drugs stand out. We report a case of chronic intestinal pseudo-obstruction originating in a sporadic, primary intestinal myopathy that corresponds to no type thus far described. A histological study of the intestinal wall showed disrupted muscle bundles and the presence of interstitial edema. Myocytes had severe degenerative changes, and no alterations were seen in submucosal and myenteric plexus neurons. The activity of enzyme complexes in the mitochondrial respiratory chain, and of thymidine phosphorylase was normal. No mitochondrial DNA changes were seen.

Key words: Chronic intestinal pseudo-obstruction. Visceral myopathy.

INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is an uncommon, high-morbidity syndrome that develops as a consequence of altered intestinal motility, which results in clinical manifestations that resemble intestinal obstruction but in the absence of any obstructive process (1-3). It may be primary, when it exclusively involves intestinal smooth muscle or enteric neural plexa, or secondary to other conditions. Within primary forms, even though familial forms with dominant or recessive autosomal inheritance have been reported, most cases are described as sporadic (4,5). Clinical spectrum is variable and dependent on the cause, site, and involvement extent (6,7). Major diagnostic criteria include suspicion of this condition and exclusion of mechanical obstruction. When suspicion develops, gastrointestinal manometry, radionuclide studies, and histopathological examination of all intestinal wall layers may help confirm the diagnosis, establish a prognosis, and delineate treatment (1,7). The presence of an unexplained association with neuromuscular, gastrointestinal, and other non-neuromuscular symptoms should prompt suspicion of mitochondrial changes as a reflection of mitochondrial ubiquity (8-10). Treatment is aimed at symptom improvement and sustained adequate nutrition (1,7,11). The female subject of this paper initially had sporadic, primary intestinal pseudo-obstruction symptoms, and then developed manifestations suggesting the involvement of striated muscle. However, studies of mitochondrial respiratory chain activity and mitochondrial DNA were all normal.

CASE REPORT

A 37-year-old woman with constipation since childhood and a fecal retention episode in the last six months. Moderate obesity. Her family history included two sib-
lings diagnosed with Crohn’s disease. She was first admitted for the study of persistent pain in the right iliac fosse, abdominal distention, and increased constipation. She had also lost 15 kg in 2 months, and had nausea and vomiting. Both the basic blood study and biochemical and coagulation tests were normal. Erythrocyte sedimentation rate and C-reactive protein were also normal. Thyroid hormones were within the normal range. No vitamin deficiency was identified. Non-organ-specific antibodies were negative, and fecal microbiologic studies yielded normal results. Abdominal plain X-rays showed dilated small-bowel loops with no fluid-air levels. Doppler ultrasonography and abdominal CT scans were normal. Ileocolonoscopy showed a macroscopically normal terminal ileum with no mucosal lesions in the histological exam. Enteroscopy with gastric, duodenal, and jejunal mucosa biopsy sampling revealed no pathologic findings. An opaque enema could not be assessed because of the presence of feces. Gastrointestinal follow-through revealed no pathologic findings. The study of colonic transit using radiopaque markers showed that after 7 days all of them but three remained in the right iliac fossa, within the cecal region. Gastric emptying was slow when studied using radionuclides. She had food intolerance during admission, which did not improve with the use of prokinetic drugs, and ultimately required total parenteral nutrition. Despite this, clinical manifestations worsened, which led to an exploratory laparotomy to collect transparietal tissue. In the days before surgery urinary incontinence developed, which was thoroughly assessed by the Neurology Department—physical examination was absolutely normal. A medullary or radicular lesion was ruled out by lumbosacral magnetic resonance imaging. Intravenous urography as well as cystography showed no pathologic findings.

During the surgical procedure the right colon had a delustered appearance, and the cecum’s wall was slightly thickened. There was mild ascites, which once subsequently studied was negative for malignant tumor cells, and showed no elevated tumor markers. A right hemicolectomy plus ileotransverse anastomosis was performed. Upon opening the resected specimen a hardened area 3 x 2 cm in size was macroscopically detected in the colonic wall, with loss of mucosal folds and the presence of two erosions and multiple petechiae. The appendix, ileum, and appendicocolic vessels had no gross changes. A microscopic examination of the cecocolic wall at the indurated area level showed a disruption of smooth-muscle fiber bundles from reduced myocyte size and intercellular edema, which resulted in a frayed appearance mainly of the muscularis propia layer (Fig. 1). Myocytes had irregular borders, alternating vacuolization and condensation in their cytoplasm, and scarcely patent myofibrils (Fig. 2). There were no changes in the myenteric plexus, and both the myenteric and submucosal plexus had their usual neuronal population. Mucosal erosions had no microscopic specificity. No vascular lesions were seen. An extensive sampling of the colonic wall showed similar patchy lesions with an irregular distribution and extension, which mainly involved the inner muscular layer. The ileum had thinned muscularis propria layers, but no degenerative changes in cecal or colonic myocytes. Neither intercellular fibrosis nor inflammatory infiltration were seen at any level.
Fifteen days after the procedure the patient was admitted for similar manifestations. She had urinary incontinence no more; however, an urodynamic exploration was performed, which yielded normal results. Bacterial overgrowth was excluded using the expired oxygen test. Esophageal and anorectal manometry were both normal. New abdominal X-rays were obtained following the administration of radiopaque markers, which were permanently retained apparently in the colon remnant rather than the small bowel.

Total colectomy plus ileostomy was decided upon. The surgical specimen included 8 cm of ileum. No relevant gross lesions were seen. A histological study of the colonic wall showed lesions similar to those described after the previous hemicolectomy. The submitted terminal ileum has normal characteristics. An ultrastructural study of the small intestine and colon was performed, where myocytes exhibited myofibrilar reduction and disruption in both organs (Fig. 3), as well as segmentarily distributed vacuolization in peripheral and parnuclear areas, and nonspecific mitochondrial changes. The latter had abnormal shapes and occasionally hydropic changes in their matrix (Fig. 4). A histological and ultrastructural study of samples from the gastric wall, a different small bowel portion, and abdominal wall striated muscle yielded normal results. An immunohistochemical study of the cecal wall and the small intestinal wall was performed with the markers listed in table I. Actin 1A4 expression was clearly pathological in the small and great intestinal wall. The inner (circular) muscle layer was only positive in the innermost portion of its bundles, which exhibited a positive border (Figs. 5 and 6). However, the outer (longitudinal) muscle layer was clearly stained. CD117 (c-Kit) was positive indicating the presence of normal interstitial cells of Cajal. A study of mitochondrial respiratory chain complex activity was performed in an intestinal muscular homogenate using the previously described...
technique (12), and results were normal. Using a Southern blot technique the presence of single or multiple deletions in striated muscle mitochondrial DNA was excluded. Lack of signal in the sample prevented a mitochondrial DNA study from being performed.

The patient was again admitted two months later because of pain after food ingestion, which was relieved by cisapride. In the following 6 months she had several predominating painful episodes, and hence required a continual infusion pump implanted that was connected to an intradural catheter for chronic opioid administration. Fifteen months later she remained in an acceptable clinical condition from a gastrointestinal standpoint. However, one year after initial diagnosis she started to develop strength loss in her limbs with a proximal distribution; following a complete striated muscle study and brain MRI scans, both with normal results, the patient was diagnosed with progressive, disabling tetraparesis, while the type of muscular involvement could not be documented. Approximately one year later she began with sustained urinary incontinence, and the urodynamic study was pathologic. Subsequent plasma thymidine and deoxyuridine measurements were negative, which suggested a normal thymidine phosphorlyase activity.

**DISCUSSION**

The patient reported here had a history of chronic constipation that had turned more severe in the past few months, in association with abdominal pain and distension. Severely slowed intestinal transit and dilated intestinal loops were seen. The study ruled out any obstructive process. Both CIPO diagnostic criteria were met (1,4).
In such cases, plain abdominal x-rays usually show signs suggesting paralytic ileum or dilated bowel loops similar to mechanical obstruction (7). Contrast radiographic and endoscopic studies may exclude obstruction. Endoscopic biopsies usually provide no diagnostic data—for a histological study to be useful, biopsy samples must include the full thickness of the intestinal wall (13,14), and be collected at various levels within the gut (7,13-15).

The causes of CIPO are manifold, but may be classified in two major groups: a) neuropathies; and b) myopathies. The first group includes diverse conditions, including inflammatory and degenerative diseases (4). The patient reported here could not be included in the inflammatory disease group, as no inflammation changes were revealed by histology.

Many of these CIPO-inducing visceral neuropathies fall within the degenerative type. In such cases there is degeneration of ganglion cells in the myenteric and submucosal plexa, with no inflammatory component (4,16-18). The causes of such neuronal degeneration are manifold, and comprise central nervous system neurodegenerative conditions, including mitochondrial diseases, among others. The latter conditions have mitochondrial changes that disturb oxidative phosphorylation and result in complex clinical syndromes, including multiple system (neurologic, striated muscular, smooth muscular) manifestations. The development of muscle weakness in this patient’s limbs led to consider a mitochondrial disease. As can be seen in Table II, which lists all major mitochondrial myopathies, most of these conditions manifest with neurologic symptoms. These manifestations have not developed in our patient so far; however, gastrointestinal symptoms occasionally precede in months or years the remaining manifestations of mitochondrial disease (19-25). Moreover, the striated muscle study proved it to be normal both from the histological and ultrastructural standpoint, and in relation to mitochondrial DNA or mitochondrial respiratory chain activity.

Mitochondrial conditions most often manifesting with gastrointestinal symptoms include: 1) mitochondrial neurogastrointestinal encephalopathy (MNGIE); 2) Leigh’s syndrome (subacute necrotizing encephalopathy); 3) Kearns-Sayre syndrome (progressive external ophthalmoplegia, pigmented retinal disease, ataxia, and heart block); and 4) MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, cerebrovascular accidents). Patients with gastrointestinal manifestations failing to meet diagnostic criteria for either syndrome have been reported (24,26). The best known syndrome is MNGIE. This is an autosomal recessive disease resulting from mutations in the thymidine phosphorylase gene (22,27,28), which translates into high plasma thymidine and deoxyuridine levels (29). These changes, which our patient lacked, are of diagnostic value. Secondarily, increased thymidine may result from disturbed mitochondrial DNA stability, and lead to muscle depletion (28). In the muscle fibers of these patients a cytochrome c oxidase deficiency may be identified. While the full clinical picture includes peripheral neuropathy, leukoencephalopathy, and ophthalmoparesis in addition to CIPO (30), gastrointestinal symptoms develop first in 45 to 67% of patients (23,25).

In these patients the most relevant changes are seen in enteric neurons, which exhibit degenerative changes and mitochondrial abnormalities (19). None of this was seen in our patient. However, it has been suggested that degenerative changes may compromise neurons in the autonomic extraintestinal nervous system (26).

The remaining above-mentioned syndromes –Leigh’s (31,32), Kearns-Sayre (33), and MELAS (34)— do not correspond to our patient’s picture either.

The second major group of CIPO etiologies includes visceral myopathies (Table III). Histological lesions found at the intestinal wall allow the inclusion of our patient in this etiologic group, since myenteric plexa and ganglion cells were free of involvement but muscle layers were deeply disrupted. These are sometimes intestinal smooth muscle lesions that develop secondary to other conditions (scleroderma, autoimmune disease, amyloido-
The management of CIPO is intended to improve symptoms and maintain adequate nutrition (1,7,11,42). In more serious, treatment-refractory cases a number of endoscopic or surgical therapies may be needed, including colectomy (11) and intestinal transplantation (6,7).

In the patient we report here gastrointestinal symptoms are acceptably controlled with measures adopted after colectomy, but limb muscular weakness results in greater disability when compared to gut manifestations. According to data available, we believe this case to be a chronic intestinal pseudo-obstruction syndrome resulting from a primary, sporadic visceral myopathy. Studies performed allow inclusion in no myopathy class thus far described.

ACKNOWLEDGEMENTS

We are grateful to Dr. R. Martí at CIBBIM, Hospital Universitario “Valle de Hebrón”, Barcelona, for his measurements of plasma thymidine and deoxyuridine concentrations, and to Dr. M. A. Martínez González at Service of Pathology, Hospital Universitario “12 de Octubre”, Madrid, for the ultrastructural examination of the surgical specimen.

REFERENCES


Table III. Visceral myopathies

<table>
<thead>
<tr>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleroderma / lupus / Kawasaki</td>
</tr>
<tr>
<td>Polymyositis</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Cereoidosis (vitamin E deficiency)</td>
</tr>
<tr>
<td>Progressive muscular dystrophy</td>
</tr>
<tr>
<td>Drugs (neuroleptics, haloperidol)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Absence of or selective decrease in smooth-muscle alpha-actin</td>
</tr>
<tr>
<td>Familial or sporadic visceral myopathy</td>
</tr>
<tr>
<td>Myopathies from abnormal gut morphogenesis</td>
</tr>
<tr>
<td>Myopathies from primary changes in myocytes</td>
</tr>
<tr>
<td>Autoimmune leiomyositis</td>
</tr>
</tbody>
</table>


