Acquired Myopathic Intestinal Pseudo-obstruction May Be Due to Autoimmune Enteric Leiomyositis

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We describe a previously healthy boy who developed intestinal pseudo-obstruction following an episode of gastroenteritis at age 2 years. At presentation, the patient had mildly raised erythrocyte sedimentation rate and C-reactive protein level, and elevated antineutrophil cytoplasmic antibodies, antinuclear anti-DNA, and antisMOOTH muscle antibodies. His electrocardiography was myopathic with no dominant frequency. First full-thickness intestinal biopsies showed a T lymphocytic myositis, particularly in the circular muscle. Steroid therapy resulted in clinical remission; cessation of steroids, in relapse. Further full-thickness biopsies showed an initial reduction in alpha-smooth muscle actin immunostaining in circular muscle myocytes and later atrophy and disappearance of many myocytes. Vascular and the remaining enteric smooth muscle cells showed HLA-DR and intercellular adhesion molecule 1 expression. These observations demonstrate the ability of enteric myocytes to take part in an inflammatory response and to change their phenotype, allowing them to act as antigen-presenting cells and to activate T cells. This and possible cytokine production by the myocytes play a role in their own destruction. This process responded to immunosuppressive therapy.

Chronic idiopathic intestinal pseudo-obstruction is a disorder of intestinal motility resulting in recurrent episodes of intestinal obstruction in the absence of mechanical occlusion. It is an uncommon disorder with a high morbidity and mortality that in children is usually caused by congenital enteric neuromuscular disease.1,2 In comparison, enteric neuromuscular disease causing intestinal pseudo-obstruction commencing in later childhood is much less well understood, although the fact that neuropathy may be caused by various toxic, infective, and inflammatory disorders, including Chagas’ disease3 and autoimmune enteric ganglionitis, is well known.4 In contrast, the causes of visceral myopathy are almost totally unknown, apart from a congenital absence of alpha-smooth muscle actin.5 A number of different histopathologic appearances have been described, among which replacement of the muscle coats by fibrosis is seen in both childhood and adult life.6,7 Such fibrosis may be postinflammatory in origin, although enteric myositis is rarely described in childhood.8

In this article, we describe a boy who initially presented at age 2 with apparent acute gastroenteritis, but later developed prolonged ileus requiring parenteral nutrition for survival. Full-thickness gut biopsies showed the presence of a perinuclear inflammatory process with marked leiomyositis.

Case Report

The patient (S.R.) was born after a normal full-term pregnancy with a birth weight of 3.2 kg. He was initially breast-fed and developed and grew normally until 2 years of age. No specific abnormalities were detected in normal infant health reviews. He participated uneventfully in the infant immunization program and had no reported abdominal symptoms. At age 2 years, he suffered a typical attack of acute gastroenteritis, as did other young children in his community. On cessation of diarrhea, an intestinal ileus became obvious, and he became intolerant of enteral feeding. No mechanical or metabolic cause of the obstruction could be found. The obstruction became persistent, and parenteral nutrition was required for survival. After 1 month of obstructive symptoms, a laparotomy confirmed the absence of mechanical obstruction and showed a hugely dilated small intestine. Laboratory studies performed at this time revealed normal complete blood count, blood urea nitrogen, electrolytes, and liver function tests but a marginally elevated erythrocyte sedimentation rate (13 mm/
hour). C-reactive protein level was elevated (6 mg/L), and positive non–organ-specific autoantibodies were detected: antineutrophil cytoplasmic antibody (ANCA), 1:2000; antinuclear antibodies, 1:80; anti-DNA, 1:150; and smooth muscle antibody, 1:500. Surface electrogastrography showed no dominant frequency in either the antrum or the duodenum. A repeat laparotomy was performed, and full-thickness biopsies were obtained from the ileum and colon. Histology of the full-thickness biopsies (biopsy 1, pretreatment; Figure 1) showed a panmural inflammation particularly affecting the muscularis propria in both the ileum and colon. The patient’s obstructive symptoms appeared to be a consequence of an enteric myositis.

The patient’s initial treatment involved nutritional support with total parenteral nutrition, upper gastrointestinal decompression by nasogastric tube, and nothing by mouth. Bacterial overgrowth was suppressed with ciprofloxacin and penicillin, and cisapride, 0.2 mg/kg 3 times a day, and metoclopramide, 0.5 mg/kg 3 times a day, were started to improve motility. The cisapride and metoclopramide were ineffective in resolving symptoms, and after the histology of the biopsies became known, the patient was started on immunosuppressive treatment with prednisolone, 2 mg · kg⁻¹ · day⁻¹. The obstruction then settled, and enteral feeding was slowly introduced. After 1 month, the prednisolone dose was reduced to 0.5 mg · kg⁻¹ · day⁻¹, and 1 week later, prednisolone was stopped. Abdominal distention recurred, as did vomiting. On resumption of prednisolone therapy, symptoms resolved; over the next 9 months, obstruction recurred every other month, related to reduced prednisolone dosage and infection.

One year after initiation of prednisolone therapy, another major obstructive episode occurred. Increasing the prednisolone dosage to 2 mg · kg⁻¹ · day⁻¹ did not resolve this episode. A repeat laparotomy showed multiple adhesions, and more full-thickness biopsies (biopsy 2, 1 year posttreatment) were taken. An autoimmune profile showed elevated ANCA (1:4000) and smooth muscle antibody (1:500). Erythromycin, 1 mg/kg 4 times a day, was added to the cisapride and metoclopra-
mide, but it appeared to have little effect. In view of the patient’s increased circulating autoantibody titers, other immunosuppressive agents were added: azathioprine, 2 mg·kg\(^{-1}\)·day\(^{-1}\), and cyclophosphamide, 2 mg·kg\(^{-1}\)·day\(^{-1}\). Little improvement was observed from the addition of these agents, and cyclosporin, 5 mg/kg twice a day, was introduced, with the goal of achieving a plasma cyclosporin level of 120–150 mg/L.

The combined prednisolone and cyclosporin therapy rapidly relieved the patient’s obstruction, and his smooth muscle and ANCA antibody levels decreased and then disappeared from the peripheral blood circulation. He started to tolerate enteral feeding. Over the next 2 years, the patient had intermittent episodes of obstruction, usually associated with bacterial overgrowth. He then had another major obstructive episode, along with a hemorrhagic gastritis that was controlled with intravenous omeprazole. Once again, he required parenteral nutrition. Full-thickness biopsies (biopsy 3, 2 years post-treatment; Figure 2) showed decreased bowel inflammation but markedly reduced amounts of smooth muscle. Laboratory tests revealed increased plasma creatinine levels. Because the patient had received cyclosporin therapy for approximately 2 years, a renal biopsy was performed. Histologic changes suggesting cyclosporin toxicity (i.e., vacuolation of the tubular epithelial cells) were found. As a result, the cyclosporin level decreased to around 50 mg/dL and creatinine returned to normal.

Currently, the patient still needs parenteral nutrition and receives intravenous prednisolone, 17.5 mg/day; cyclosporin, 10 mg/day; omeprazole, 20 mg/day; and metronidazole, 15 mg·kg\(^{-1}\)·day\(^{-1}\). He does not tolerate anything by mouth. His stoma prolapses continuously, creating a management problem.

**Results**

**Surface Electrogastrography**

Gastric potential differences were recorded at the skin’s surface of the upper abdomen using bipolar pregelled electrocardiogram electrodes as previously described. Gastric and duodenal activity was recorded for 1 hour and later analyzed off-line in the frequency domain using a previously described autoregressive model-
ing technique.\textsuperscript{10} No clearly dominant frequency could be found for either the gastric antrum, with variations between 3.5 and 5 cycles/minute (control frequencies of 3.0 ± 0.2 cycles/minute), or the duodenum, with variations between 9.5 and 11.5 cycles/minute (control frequencies of 11.2 ± 0.5 cycles/minute). The gastric antral recordings were similar to those previously reported.\textsuperscript{9}

Taken together, data from the electromyographic and histologic studies suggest that the whole bowel is involved in the inflammatory disorder. Further recordings were made when remission was induced with prednisolone. A normal gastric antral dominant frequency of 3.0–3.2 cycles/minute was found. When relapse occurred, the dominant frequency was once again lost. It returned at a frequency of 3.1–3.3 cycles/minute in the gastric antrum when remission was induced with prednisolone and cyclosporin.

**Histopathology**

Full-thickness intestinal samples from the ileum and colon were fixed and processed routinely into paraffin wax. Snap-frozen full-thickness tissue was also available. Sections were stained with H&E and immunostained for white blood cells, α-smooth muscle actin, class II major histocompatibility complex HLA-DR, and intercellular adhesion molecule 1 (ICAM-1) using the avidin-biotin peroxidase complex method.\textsuperscript{11} The white cell markers (Dako Ltd., Ely, England) included antibodies for T lymphocytes (CD3, CD4, and CD8), monocytes and macrophages (CD68), neutrophils (CD15), activated white cells (CD45 and CD30), and B lymphocytes (CD20).

Figure 1 shows the ileum and colon to have a normal mucosal architecture and normal enteric ganglia in the submucosal and myenteric plexuses. Other findings included a moderate increase in cellularity of the lamina propria and a more profound and florid lymphocytic inflammatory infiltrate in the muscularis propria. This infiltrate was especially dense around blood vessels in the circular muscle. Some loss of α-smooth muscle actin immunostaining was seen in the outer portion of the circular muscle layer. Immunostaining of biopsy 1 showed that in the muscularis propria of both the ileum and colon, the inflammation was predominately T lymphocytic, with the cells being largely CD3 and CD8 positive, although some CD3- and CD4-positive cells and occasional B cells were seen.

In biopsy 2, done 1 year posttreatment, the lymphocytic infiltrate seen in biopsy 1 was still present but was less marked; however, there was increased loss of α-smooth muscle actin immunoreactivity in most of the circular muscle cells, although the inner circular muscle and the longitudinal muscle appeared relatively intact. Normal actin immunostaining was seen in the muscularis mucosa and the vascular smooth muscle.

Biopsy 3, performed 2 years posttreatment, showed a profound loss of myocytes in the outermost circular muscle layer with only occasional cells remaining in the innermost circular muscle and longitudinal muscle coats. In comparison, the muscularis mucosae appeared normal. The activated T lymphocytes previously present in large numbers in the outermost circular muscle layer had largely disappeared, although some were still present. HLA-DR and ICAM-1 were markedly positive in vessels throughout the biopsies and particularly in the circular muscle. Some positivity for both HLA-DR and ICAM-1 was observed in the remaining circular muscle myocytes. HLA-DR was also positive on the apical surface of enterocytes throughout the crypt villous axis, but ICAM-1 was not.

**Discussion**

Visceral myopathy occurs in approximately 1 in 40,000 live births, presents most frequently in the first year of life (often in the neonatal period),\textsuperscript{1,12,13} and is largely congenital in nature. In about 70% of young children with congenital visceral myopathy, the bladder and urinary tract are also involved.\textsuperscript{1,13} However, in a small number of patients it is not recognized until later in life, when it presents as an end-stage motility failure disorder. In 60% of adults and in some older children presenting with intestinal pseudo-obstruction, histology most often shows a degenerative process with acrophy, vacuolation, and fibrosis occurring in either 1 or both layers of the muscularis propria.\textsuperscript{7} The etiology of the fibrotic condition is unknown, but it may be postinflammatory in origin.

We have described a boy who developed functional obstruction after an apparent attack of acute gastroenteritis. The obstruction was caused by abnormal gut dysmotility as we have previously described,\textsuperscript{1} induced by an acquired progressive enteric myositis. The myositis resulted from a severe T cell-mediated inflammatory disorder involving only the intestinal muscularis propria. This is totally unlike congenital enteric muscle disorders,\textsuperscript{6} which commonly involve the bladder. The myositis was associated with circulating autoantibodies directed against smooth muscle cells along with nonspecific antibodies to nuclear antigens and neutrophil cytoplasmic antigens. The autoimmune injury in our patient appeared clinically to be limited to the muscularis propria, particularly the outermost circular muscle layer.
It is noteworthy that our patient presented with what appeared to be gastroenteritis. We speculate that molecular mimicry with an infectious agent resulted in the initiation of the autoimmune inflammatory process, as has been previously suggested for other gastrointestinal autoimmune disorders, such as celiac disease and autoimmune hepatitis. It is of particular interest that the immune response to hepatitis viruses through molecular mimicry may result in the production of smooth muscle antibodies. Hepatitis B virus shares sequence homology with myosin and caldesmon, and hepatitis C virus does so with vimentin and myosin, but to a different sequence of myosin than hepatitis B virus. Thus, different viruses induce auto-reactivity to both different smooth muscle proteins and different parts of the same protein. It is also possible that other enteric pathogens that elicit a long-lasting inflammatory reaction (e.g., Campylobacter, Salmonella, Klebsiella) do so by inducing autoimmune responses. All of the biopsies taken showed evidence of mild mucosal inflammation. The condition seemed to be progressive, beginning with a loss of contractile proteins and progressing to loss of smooth muscle cells. The clinical progression of the disease was initially arrested with prednisolone; relapses were observed on prednisolone withdrawal and remissions on prednisolone re-introduction. Relapse and remission were also associated with the loss and return of normal slow wave frequency as detected by electrogastrography. Like other autoimmune disorders, this condition took a fluctuating course, and increased immunosuppressive treatment with cyclosporin in addition to prednisolone became necessary, providing further support to the belief that the disease was caused by T cell–mediated immune response.

Ultimately, however, the T cell–mediated inflammatory process escaped control and resulted in destruction of most of the circular muscle of our patient’s gastrointestinal tract. As a result, despite being able to tolerate enteral feeds for certain periods, he now needs supplemental parenteral nutrition to survival.

Most cases of autoimmune disease causing intestinal pseudo-obstruction have been due to an autoimmune enteric ganglionitis with circulating enteric neuronal antibodies. Such cases have been either paraneoplastic, associated with Chagas’ disease, or idiopathic. Enteric myositis has been reported in only 9 patients to date. In nearly all of these reports, the nature of the myositis was not fully investigated, and specific treatments were not used. However, in 1 of these studies, a patient with enteric myositis also had active chronic hepatitis, suggesting that autoimmunity could have played a role in the inflammatory state. The most recent report clearly describes an autoimmune process directed against both enteric and skeletal muscle responsive to immunosuppression. It does not elucidate the nature of the inflammatory process, however. This report is to our knowledge the first clear description of an autoimmune process appearing to be directed solely against smooth muscle involving both enteric muscularis propria myocytes and enteric vascular smooth muscle cells. Unlike in the patient described by Rigby et al., there was no evidence of skeletal myositis. We postulate that the apparent absence of other symptoms is because the symptoms result from local T cell–mediated responses rather than from production of an antibody, with antibody production being another consequence of the T cell response.

Recent studies suggest that the T cell–smooth muscle interaction may be bidirectional. After exposure to interferon-gamma, intestinal smooth muscle cells express surface molecules such as HLA-DR and ICAM-1, which are a prerequisite for antigen presentation to T cells. In addition, smooth muscle cells may be stimulated to produce cytokines, such as interleukin (IL)-6 and IL-1β. In egg albumin–sensitized mice, smooth muscle cells can present antigen to T cells in an HLA-DR–restricted manner, resulting in T cell activation and proliferation. Because epithelial permeability is always increased in intestinal inflammation, and because there is also evidence of increased vascular permeability and endothelial activation in the muscle layers, muscle cells likely are also exposed to luminal antigens. Thus, intestinal smooth muscle can function as antigen-presenting cells and, because they are among the most stable cell populations of the gut, may perpetuate the inflammatory process by engaging the T cells. Nonetheless, it is difficult to understand why the outermost circular muscle layer is preferentially affected. It may be that there are differences in the distribution of cell-surface proteins that can act as antigens in circular muscle myocytes but not in longitudinal and inner circular muscle cells. We do not know of any information to support this suggestion, however. Just as plausibly, the distribution of neuropeptides that are known to enhance the inflammatory response in particular areas could be responsible for this phenomenon. Substance P enhances the activation of T lymphocytes by smooth muscle cells, and vasoactive intestinal peptide, calcitonin gene-related peptide, and noradrenaline augment the IL-1β–induced secretion of IL-6. Thus, neural input may modulate the degree to which muscle cells participate in immune regulation. These properties of muscle cells make them targets of immune cell attack, which may result in the myositis.
and myopathy seen in this case as well as in previously described cases.22–25

In our patient, we found evidence of aberrant epithelial cell HLA-DR expression, muscle cell HLA-DR, and ICAM-1 expression and endothelial activation. We suggest that in this patient the inflammatory process was indeed perpetuated by changes in the muscle cells, which ultimately played a role in their own destruction.

The role of inflammation in motility disorders in humans remains controversial. But an increasing body of evidence indicates that mucosal inflammation may alter function in the deeper neuromuscular tissue, and that this is accompanied by alterations in motility.31–33 The present case demonstrates this, but also emphasizes a number of other points. Reproduction of the experimental studies showing interactions between immune cells and smooth muscle cells in this patient prompted the use of immunomodulatory and immunosuppressive therapy, which was initially successful in halting disease progression. Appreciation of the immunomodulatory potential of smooth muscle by direct cytokine production or by T cell activation through muscle cell antigen presentation raises the possibility of targeting the muscle cell for gene therapy or immunotherapy. At the present time, only conventional immunosuppressive treatment is available; nonetheless, if used aggressively early in the course of illness, this may prevent end-stage motility failure.

Our patient's clinical course suggests a number of factors that should alert the clinician to immune activation and thus to a treatable form of myopathic pseudo-obstruction. These factors include a history of enteric infection, persistently raised inflammatory markers, circulating autoantibodies, and T cell infiltrate in the muscularis on full-thickness biopsy.

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