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Review Article

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Time is Gut. Approaching Intestinal Leiomyositis: Case Presentation and Literature Review

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ABSTRACT

T-lymphocytic intestinal leiomyositis is a rare cause of "pediatric intestinal pseudo-obstructions." Diagnosis may be difficult and requires full-thickness bowel biopsies during laparotomy or laparoscopy with possible enterostomy. Currently, immunosuppressive therapy is the only available treatment. A delay in diagnosis and therapy may negatively affect the prognosis because of ongoing fibrotic alterations; therefore, early diagnosis and consequent treatment are crucial. This review summarizes the available information on the nosology, diagnostic steps, and treatment modalities. Here, we report the youngest case of enteric leiomyositis reported in the last two decades and analyze its management by reviewing previous cases.

Keywords: Pediatric intestinal pseudo-obstruction; Chronic intestinal pseudo-obstruction; Leiomyositis; Intestines; Functional bowel disorder; Intestinal motility disorder

INTRODUCTION

Intestinal lymphocytic leiomyositis (ILL) is characterized by an inflammatory reaction with lymphocytic infiltration of the muscularis propria along the bowel wall [1-3]. Clinical appearance of ILL fulfilled all criteria for chronic intestinal pseudo-obstruction (CIPO) or pediatric intestinal pseudo-obstruction (PIPO) [4-7]. In 2018, PIPO was specified for pediatric cases by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) as an independent entity because of fundamental differences between adults and children [7]. Since the first documented ILL case in adults in 1958 and in children in 1985, much new information on clinical management has led to a more structured approach and treatment of this condition [1,2,4].

Rare reports of the condition in children, adults, and dogs have not helped gain profound knowledge of the pathology or define a structured approach [1-6,8-10]. Furthermore, classification of ILL as the cause of primary or secondary PIPO remains uncertain [7,10-12]. Further, ILL is degenerative and leads to intestinal failure due to underlying fibrosis [5,8,10,12]. To date, diagnosis can only be established through full-thickness bowel biopsies,

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Conflict of Interest
The authors have no financial conflicts of interest.

and therapeutic modalities include combined immunosuppressive treatment accompanied by parenteral substitution [11,13,14].

Here, we present the case of a 21-month-old infant with lymphocytic intestinal leiomyositis showing signs and symptoms of PIPO. Prolonged ileus without an apparent cause led to full-thickness bowel biopsies with immunostaining, confirming the diagnosis. Therefore, immunosuppressive therapy was established. We also reviewed data from all published cases of ILL.

METHODS

The patient's history was analyzed, and a review of the existing literature in PubMed, Cochrane, and Embase was conducted. Articles referring to leiomyositis and intestinal myopathy, CIPO, or PIPO were evaluated, and recommendations for the treatment and management of PIPO were analyzed. Patients with adult-onset disease, involvement of other bowel layers, and articles in which demographic data or the type of infiltration were not documented were excluded. The patient's family was asked for permission to publish this case report.

CASE REPORT

A 21-month-old girl presented with a 3-week history of worsening abdominal distension. Anamnesis revealed an uneventful neonatal period. The patient was born after 36 3/7 weeks of gestation and had passed meconium uneventfully in the first 24 hours of life. The patient was administered topical corticosteroids for an atopic dermatitis. She had no history of gastrointestinal infections or constipation and had participated fully in the national immunization program. Her family history did not reveal any gastrointestinal or immune diseases.

The clinical assessment revealed hypoactive bowel sounds and atopic skin lesions. Laboratory tests revealed eosinophilia and elevated serum immunoglobulin IgG. Serum Markers of systemic inflammation, including leukocytes and C-reactive protein were negative. Cystic fibrosis was excluded, and calprotectin and elastase levels in stool were averaged. Plain abdominal radiography and ultrasonography revealed distinct dilated bowel loops, coprostasis, and reduced peristalsis (**Fig. 1**). After the enema, a significant portion of the stool was passed, and with oral laxatives, she continued voiding soft stools. Rectal biopsies excluded Hirschsprung's disease. Gastroscopy and colonoscopy revealed infiltration of eosinophil granulocytes in the duodenum, whereas the examination for *Helicobacter pylori* was negative. A stool sample culture was positive for *Clostridium difficile* toxins A and B without adequate clinical symptoms or endoscopic evidence. Magnetic resonance imaging (MRI) of the central nervous system and differential blood counts excluded the neurological origin of the symptoms or malignancy. A comprehensive blood test for autoimmune diseases revealed a titer of 1:100 for anti-nuclear antibodies and was negative for smooth muscle antibodies (SMA).

Neostigmine (Carinopharm GmbH) i.v. 1 mg (0.1 mg/kg) as prokinetic was administered with positive results. Because of the side effects (choking, bradycardia, and paleness), erythromycin (InfectoPharm) (1 mg/kg three times a day) was administered without any

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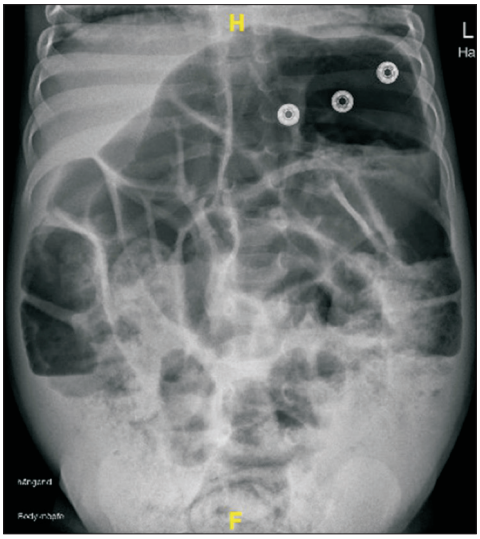

Fig. 1. Plain abdominal radiography with contrast showing massive dilated bowel.

clinical response. Off-label use of prucalopride (Takeda Pharmaceuticals) (0.3 mg/kg/d orally) showed remarkable results with the successful establishment of enteral feeding. Under this treatment, and with a possible diagnosis of eosinophilic enteropathy, the patient was discharged. Additionally, intermittent oral metronidazole was used as prophylaxis for bacterial overgrowth.

Excessive abdominal distension and deterioration of oral feeding led to readmission five weeks later with radiological findings of ileus. Due to persistent massive abdominal distension and acute abdominal pain, emergency laparotomy was performed, which revealed a dilated small intestine and colon, and 700 mL of liquid stool was suctioned. Full-thickness biopsies from the colon and ileum were obtained, and an enterostomy was performed 15 cm before the ileocecal valve. The patient was transferred to intensive care unit, a central venous catheter was inserted, and broad-spectrum antibiotic treatment was initiated.

Histological examination showed T lymphocytic infiltration of the lamina propria in the ileum and colon, whereas the mucosa and submucosa showed non-specific eosinophilic infiltration (**Fig. 2**). There was some myocyte degeneration, but the submucosal and myenteric plexuses were normal. The final diagnosis of leiomyositis was established after immunohistological examination of lymphatic infiltrations. An extensive immunological diagnosis was made to exclude blood malignancy. Testing for viruses was only positive for adenovirus, and the urine metabolic profile did not reveal any pathological findings.

An intravenous treatment with prednisolone (STADA Arzneimittel AG) 2 mg/kg was followed 3 weeks later by a combination of infliximab (Pfizer) 10 mg/kg and methotrexate (Pfizer) subcutaneously, and total parenteral nutrition (TPN) was administered. For long-term parenteral nutrition, a permanent central venous line (Broviac catheter; Bard) was inserted. The patient's overall condition improved quickly after steroid therapy, with reduced abdominal distention and regular voiding of the ileostomy and rectum. Bowel movement normalized, and oral feeding could be established quickly; thus, restoration of bowel continuity was performed six weeks after stoma formation.

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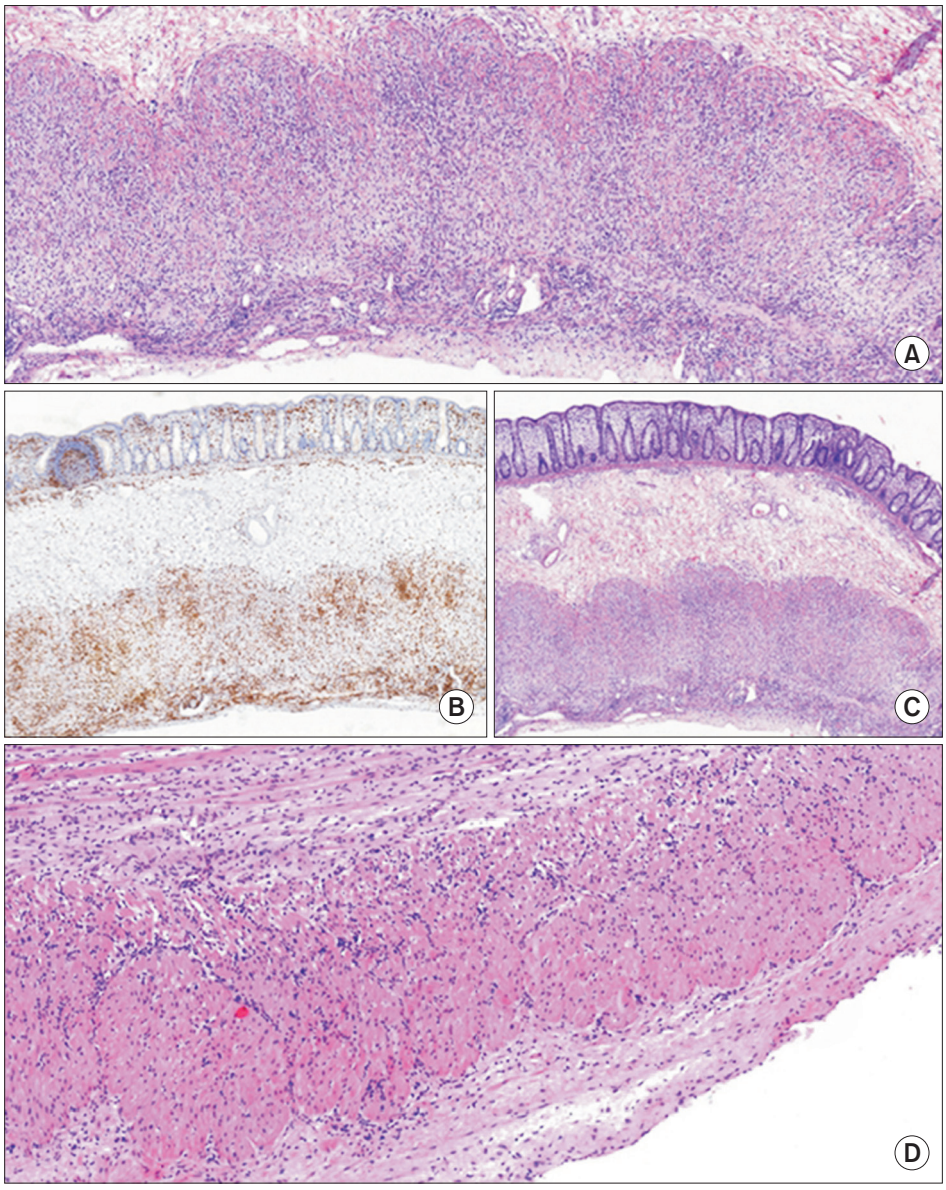

Fig. 2. (A) Biopsy of the ileum during ileostomy formation showing severe infiltration of the muscularis propria with lymphocytes. (B) Biopsy of the colon during ileostomy formation, with dye indicating T-lymphocyte infiltration in the muscularis propria. (C) Biopsy of the colon during ileostomy formation showing lymphocytic infiltration of both the mucosa and muscularis. (D) Biopsy of the ileum taken at ileostomy closure after treatment with immunosuppressants, showing a reduced lymphocytic infiltration and remaining muscle cells in the muscularis propria. Hematoxylin eosin (H&E), magnification is 40× for (A) and (D), 10× for (B) and (C).

After a 2-month hospital stay, the patient was discharged with an adequate oral diet, substitutional parenteral nutrition, and total weight equal to that at admission. Prednisolone treatment could be steadily reduced and ended three weeks later, methotrexate (Pfizer) was administrated weekly and infliximab (Pfizer) every eight weeks. Physiotherapy, nutritional, and psychological support were provided.

Weaning from steroid therapy slightly worsened her atopic dermatitis without any recurrence of intestinal symptoms. The child thrived well with total enteral nutrition, and signs of malnutrition disappeared. The permanent central venous line was removed after six months.

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Two years after diagnosis and treatment with infliximab and methotrexate, the patient was in good condition. Infliximab therapy was discontinued. To date, 2 1/2 years after the diagnosis, the child remains fine with adequate weight gain, uneventful follow-ups, and regular bowel habits.

REVIEW OF THE LITERATURE

Six articles—case reports and reviews—documented the condition of intestinal leiomyositis [1-3,5,8,9]. Seventeen similar cases have been described, including their clinical presentation and histological findings. Nine cases were excluded because of adult-onset [10-15]. In the remaining eight cases, one did not clearly mention the type of cell infiltration; therefore, only seven cases were finally included in our review [1-3,5,8,9].

Age distribution was six months to 16 years. PIPO symptoms and histological findings of lymphocytic infiltration of the muscularis propria were observed in all the patients. Immunostaining revealed T-lymphocytic inflammation, confirming the diagnosis of ILL. Four patients presented with gastroenterological infections [3,5], and two of them had pre-existing autoimmune diseases [16,17]. An overview of the patient's demographic and clinical characteristics is presented in **Table 1** [2,3,5,8,10,11].

All published patients received steroid therapy, followed by four immunosuppressive therapies or were combined [3,8,10,11]. Smooth cell antibodies were present in five cases [3,5,10,11], and enterostomy was performed in two cases [10,11]. Follow-up between 1.5 and 4 years was documented in five patients [2,3,8,10,11]; two of these patients died due to septic complications [2,10].

Table 1. Cumulative characteristics of pediatric published cases with intestinal lymphocytic leiomyositis

	Year							
	1985 [2]	1997 [5]		2002 [8]	2005 [3]	2005 [11]	2012 [10]	2021
Age/sex	6 mo/M	1 yr/M	2.5 yr/F	16 yr/F	5 yr/F	2 yr/M	3.5 yr/M	21 mo/F
Preexisting diseases	NR	NR	NR	NR	GI	AIH/GI	PRCA/GI	AD
Abnormal laboratory findings	Yersinia pseudo-tuberculosis antibodies +	SMA +	SMA +	NR	SMA +	SMA + ANCA + ANA +	SMA +	ANA borderline value
Histological findings	FTB	FTB	FTB	FTB	FTB	FTB	FTB	FTB
Affected bowel	Small intestine	Small/large intestine	Small/large intestine	Small intestine	Small/large intestine	Ileum/large intestine	Small/large intestine	Small/large intestine
Mucosa/submucosa	Atrophy	NR	NR	Intact	TL infil	Mild inf	TL infil	Eosinophilic infil
Muscularis propria	Mononuclear infil fibrosis	Severe TL infil fibrosis	Severe TL infil fibrosis	TL infil, fibrosis	Severe TL infil	Severe TL infil	Severe TL infil fibrosis	Severe TL infil fibrosis
Nerval plexus	Intact	Intact	Intact	Intact	Intact	Intact	Intact	Intact
Drugs	Steroid	Steroid	Steroid	Steroid AZA budesonide	Steroid AZA FK506	Steroid AZA ciclosporin	Steroid AZA budesonide	Prucalopride steroid MTX infliximab
Operations	None	None	None	None	None	Enterostomy	Enterostomy	Enterostomy
Follow-up	4 y	NR	NR	2 y	1.5 y	3 y	1.5 y	2 yr
Progress	Death	NR	NR	EN	TPN	TPN	Death	EN

M: male, F: female, NR: not reported, AIH: autoimmune hepatitis, GI: gastrointestinal infection, PRCA: pure red cell anemia, AD: atopic dermatitis, SMA: smooth muscle antibodies, ANCA: anti-nuclear cytoplasmic antibodies, ANA: anti-nuclear antibodies, FTB: full-thickness biopsies, infil: infiltration, TL: T-lymphocytic, AZA: azathioprine, FK506: tacrolimus, MTX: methotrexate, TPN: total parenteral nutrition, EN: enteral nutrition.

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DISCUSSION

ILL is an inflammatory myopathy that belongs to a heterogeneous group of disorders that clinically present as PIPO, according to the diagnostic criteria set by the expert group of ESPGHAN [5,7,10]. PIPO has also been associated with gene mutations associated with smooth muscle function and structure [18]. Although T-lymphocytic intestinal leiomyositis (T-ILL) can be classified as primary or secondary when triggering factors such as infections, toxins, or paraneoplastic syndromes are present, little is known about the pathophysiological mechanisms that affect only the intestinal muscular layer [8,10,18,19].

The exact prevalence of PIPO remains unknown; some surveys report a similar sex distribution, with 80% affected by one year of age [19]. The age of intestinal leiomyositis onset has been reported to be between 6 months and 16 years. Three patients developed symptoms during infancy and four between one and five years of age. Disease-free intervals after birth range from six months to 2.5 years [1-3,5,8,9].

Diagnosing T-ILL is challenging because of the heterogeneity of symptoms [1-3,5,9,10]. However, abdominal distension, vomiting, and hypoactive bowel sounds were present in all patients, and abdominal pain was infrequent [1-3,5,8,9,10]. Imaging studies such as abdominal radiography, ultrasound scan, and contrast studies depicted in all patients with intestinal dysmotility and entero-MRI could also provide helpful information but require time and sedation [8,10,14,20]. Laboratory tests show systemic signs of inflammation, and circulating autoantibodies against smooth muscle cells (SMC) are found in most reported cases of leiomyositis [1-3,5,9,10]. However, the key to diagnosing intestinal leiomyositis is full-thickness biopsies, which should follow in the absence of evidence of other known motility disorders [13,17,18,21-23]. Decompressive enterostomy can be indicated in patients with ILL during recurrent pseudo-obstructive episodes, providing an opportunity for additional bowel biopsies to control therapeutic effects [20,24].

Medical therapy for ILL mainly aims to suppress inflammation and bacterial overgrowth and promote gastrointestinal motility to restore enteral feeding [25,26]. Parenteral nutrition is paramount for optimizing the nutritional status; however, its related complications can be devastating [25,27-29]. Steroid therapy was initiated in all leiomyositis patients and was mainly effective during the acute phase [4,9,10,11,17,21]. The combination of steroid tapering and immunosuppressants should prevent recurrence or complications [11,25-27]. In our case, the improvement in bowel motility and oral feeding tolerance persisted during steroid tapering, and under immunosuppressive treatment, only recurrence of atopic skin lesions was noted. Others have suggested early and more aggressive immunosuppressive therapy to preserve sufficient muscle cell mass and improve prognosis [11,25,27,28]. 5-Hydroxytryptamine receptor 4 receptor agonists (prucalopride and metoclopramide) had remarkable effects in our patient; thus, off-label use should be considered. In cases of leiomyositis, prokinetics, antibiotics, and probiotics may improve peristalsis but are only supplementary medications [19,25]. However, there is no recommended drug treatment for PIPO that improves gastrointestinal motility [7,11,19].

In three patients, unspecific enteritis was previously diagnosed, one patient had already been treated for autoimmune hepatitis, and another for red cell aplasia [3,10,11]. In our patient, symptoms of infection were not reported on diverse endoscopic and histological tests.

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Although her atopic dermatitis highlights an autoimmune predisposition, it does not clarify the nosology of this situation.

Although the trigger factor in ILL remains unknown, molecular mimicry with infectious agents or cross-reactivity between pathogens and T-lymphocytes has been previously suggested for other gastrointestinal autoimmune disorders [8,10,30,31]. Inflammation is mediated by a localized reaction with T cells, resulting in the production of antibodies [10]. Another pathophysiological theory suggests that the symptoms result from local T cell-mediated responses rather than antibody production [8,10,14,23]. Furthermore, in all reported leiomyositis cases, the stomach, esophagus, and other smooth muscle organs were unaffected. Neural inputs may modulate how muscle cells participate in immunoregulation, explaining why smooth muscles at other body sites are unaffected [15,16].

Furthermore, immunostaining revealed that abnormal intestinal motility was derived from dense inflammation restricted to the muscularis propria and was mediated by T cells with a cytotoxic phenotype [8,20,21]. In the present case, the CD4 and CD8 T-lymphocytes ratio was 2:1. In contrast, the mucosa and submucosa revealed nonspecific eosinophilic infiltration, and endoscopic mucosal biopsies were unsuccessful in establishing a diagnosis of leiomyositis [19,21,22]. An alternative to laparotomy for histological diagnosis was proposed by Valli et al. [22], who presented endoscopic full-thickness wall resection results for colonic tissue sampling, which might also be a helpful tool for follow-up [20,24]. Biopsies in previous cases have reported atrophy and fibrosis of muscle cells during symptom recurrence, revealing the degenerative nature of the disease [11,13,18,32]. This demonstrates that early control of inflammation reduces intestinal muscle loss, which is necessary for a better prognosis.

Martire et al. [18] reported phenotypic changes in the SMCs of patients with primary PIPO. SMCs show low expression of alpha smooth muscle actin (aSMA) during this process, which is mainly observed in the circular layer. Analogous investigations should also be performed in cases of secondary PIPO to provide insights into the underlying mechanism and help in structuring an effective therapeutic protocol.

SMA may be elevated in ILL; however, their levels can differ during therapy and their absence cannot exclude this condition [3,10,11,13]. The mass of SMCs in biopsies appears to be the only prognostic factor; however, clinical conditions remain a helpful tool for clinicians in deciding on further management. The combined interpretation of histopathological evidence and blood test results could provide more information regarding the progression of the condition and the remaining SMC mass. We strongly believe that faster diagnostic strategies and effective therapeutic modalities are milestones in preserving bowel function.

Until now, reported cases have not provided much information about the lifelong impact and prognosis of this condition, especially in the period after medical treatment ends. Further issues to address in the future would be the de-escalation's tempo of the immunosuppression, protocols about laboratory or histological follow-ups, and finally, dietary recommendations for these patients. The degenerative nature and devastating consequences of this condition underline the need for a quick diagnosis and effective treatment. Meticulous documentation of these cases and a center of expertise for interpreting the histological findings are the primary steps for this purpose.

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CONCLUSION

ILL is a rare inflammatory myopathy presenting as PIPO. Early diagnosis using full-thickness biopsies requires a high degree of suspicion. The priority in these patients is to preserve a sufficient mass of SMC, as this can result in degenerative leiomyopathy and end-stage motility failure in TPN-dependent patients with high morbidity and mortality. The early application of immunosuppressive therapy can improve the prognosis, and intestinal decompression with nutritional substitution can facilitate the early restart of oral feeding. However, the long-term impact on patients and changes in permanent remedies remain unclear.

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