

Case Report

DOI: 10.5582/irdr.2012.v1.1.35

Chronic intestinal pseudo-obstruction due to lymphocytic intestinal leiomyositis: Case report and literature review**Keiichi Uchida^{1,*}, Kohei Otake¹, Mikihiro Inoue¹, Yuhki Koike¹, Kohei Matsushita¹, Toshimitsu Araki¹, Yoshiki Okita¹, Koji Tanaka¹, Katsunori Uchida², Noriko Yodoya³, Shotaro Iwamoto³, Katsuhiko Arai⁴, Masato Kusunoki¹**¹Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Tsu, Mie, Japan;²Department of Pathology, Mie University Graduate School of Medicine, Tsu, Mie, Japan;³Department of Pediatrics, Mie University Graduate School of Medicine, Tsu, Mie, Japan;⁴Division of Gastroenterology, Department of Medical Specialties, National Center for Child Health and Development, Tokyo, Japan.**Summary**

Lymphocytic intestinal leiomyositis is a rare entity, which causes chronic intestinal pseudo-obstruction (CIPO) in children. We present the first case of a boy who had pure red cell anemia 1 year before onset. Prolonged ileus developed after gastroenteritis and the patient was diagnosed using a biopsy of the intestinal wall. Findings from the present case indicate that there are three important factors for accurate diagnosis: history of enteritis, positive serum smooth muscle antibody, and lymphocyte infiltration with muscle destruction in the muscularis propria in the intestinal wall. Earlier diagnosis and induction of immunosuppressive therapy may be essential for a better outcome.

Keywords: Chronic intestinal pseudo-obstruction (CIPO), pseudo-obstruction, leiomyositis, intestine

1. Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare intestinal dysmotility disorder characterized by repetitive or continuous bowel obstruction without mechanical causes (1-3). CIPO may be classified either as primary or secondary. Secondary CIPO is classified as a disease of gastrointestinal smooth muscle, nervous system, endocrine system, metabolism, and others (2). Smooth muscle fibers of the intestinal wall are affected by connective tissue disorders, muscular dystrophies, infiltrative disease, and mitochondrial myopathy.

Lymphocytic intestinal leiomyositis (LIL) in which lymphocytic infiltration causes muscle degeneration and fibrosis has been rarely reported in the literature (3-8). We present a rare case of a boy with CIPO due to T-lymphocytic intestinal leiomyositis (T-LIL).

He suffered from pure red cell anemia (PRCA) and T-cell lymphocytosis 1 year before onset of T-LIL. Prolonged ileus developed after a gastroenteritis attack and accurate diagnosis was performed using a histopathological immunostaining study of full-thickness biopsies. We also review T-LIL cases in the literature and discuss the pathogenesis of T-LIL.

2. Case report

A 2.5-year-old boy was diagnosed with PRCA and T-cell lymphocytosis. A complete response was obtained with steroid therapy. Steroids were ceased 1 year after the initial therapy. He was then admitted to a hospital with diarrhea and abdominal distension with symptoms of acute gastroenteritis. Laboratory data demonstrated leukocytosis (white blood cell count, 42,000/mm³) and mild elevation of C reactive protein (CRP). Crohn's colitis was suspected and 5-ASA 60 mg/kg/d and prednisone 1 mg/kg/d were started. However, any attempt of oral feeding resulted in severe abdominal distention and vomiting due to paralytic ileus. Complete response was not obtained for 5 months; the patient was given prednisone 2

*Address correspondence to:

Dr. Keiichi Uchida, Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan.
E-mail: ucchie@clin.medic.mie-u.ac.jp

mg/kg/d with administration of azathioprine 1 mg/kg/d and tacrolimus (target trough: 10 ng/mL) and total parenteral nutrition. Since abdominal symptoms deteriorated after prednisone tapering, prednisone was never discontinued. The patient was transferred to our hospital for further examination. A plain abdominal X ray film demonstrated a huge dilatation of the small intestine with air fluid levels. Small bowel follow through indicated no apparent stricture. No mechanical cause of obstruction and normal mucosal findings were observed by esophagogastroduodenoscopy, colonoscopy, and double balloon enteroscopy. Mucosal biopsy showed mild non-specific inflammation in ileal and colonic mucosa. Laboratory data demonstrated no abnormal findings in blood counts, biochemical studies, CRP, and positive smooth muscle antibody.

We decided to perform laparotomy and a full-thickness biopsy to confirm the suspicion of intestinal disorder related to autoimmune disease because the patient suffered from CIPO with a response to prednisone and immunomodulators, and he had positive smooth muscle antibody A. Laparotomy revealed a huge dilated small intestine without the absence of mechanical obstruction. Enterostomy was created for intestinal decompression and irrigation. Full-thickness biopsies were performed in multiple locations of the small intestine and colon.

Histological findings (Figure 1) in the colon and all small intestine specimens demonstrated massive mononuclear infiltration and muscle fiber degeneration in the muscularis propria and lamina muscularis mucosae in the intestinal wall. Mononuclear cells moderately infiltrated the mucosal and submucosal layers. Ganglion cells in the submucosal and myenteric plexuses were normal. Immunostaining of a small intestine specimen predominantly showed T lymphocytic inflammation consisting of T lymphocytes (CD3, CD4, and CD8), monocytes and macrophages (CD68), and activated white cells (CD45RO). B lymphocytes (CD20, CD30) and NK cells (CD56) were absent. The specimen was also characterized by inflammatory targets that were not smooth muscles of vessels, but they were the muscularis propria and lamina muscularis mucosae in the intestinal wall. Based on the histopathological and immunological findings, the final diagnosis was confirmed as T-LIL.

Postoperatively, the patient began to orally ingest food with regular decompression and irrigation through enterostomy. However, he had intermittent episodes of obstruction associated with intestinal bacterial overgrowth. One year later, the pseudo-obstruction was gradually resistant to treatments and he died from sepsis due to bacterial translocation 1.5 years later.

3. Discussion

CIPO is a rare, severe, disabling disorder characterized

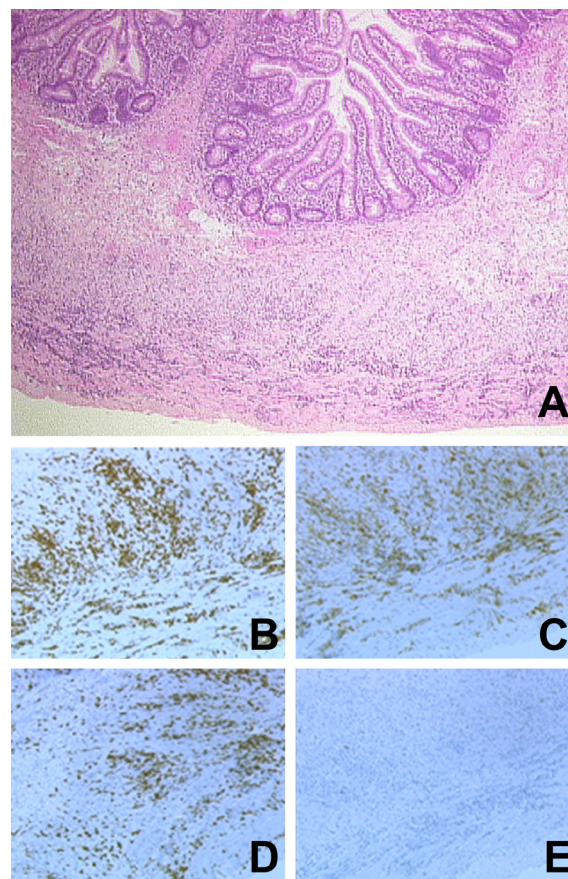


Figure 1. Immunostaining of the biopsy samples. (A), Full-thickness biopsy of the small intestine. Histological findings show inflammation in the muscularis propria of the small intestine. Intestinal mucosa and submucosa were mostly normal. Ganglion cells in the submucosal and myenteric plexuses were normal. Immunostaining of a biopsy sample showed predominantly T lymphocytic inflammation consisting of T lymphocytes (B, CD3; C, CD4; D, CD8). B lymphocytes (E, CD20) are absent. (Original magnification 100×)

by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic documentation of a dilated bowel with air-fluid levels, in the absence of a fixed, lumen-occlusive lesion (2). CIPO may be classified as either congenital or acquired (1,2). Acquired CIPO is classified according to presumed underlying pathogenesis to facilitate an organized approach to evaluation (9). Autoimmune reactions to smooth muscle fibers or nerve plexuses have also been reported as very rare causes of acquired CIPO (7,10). CIPO due to true T-LIL, such as in the present case, has only been reported in six cases of specific histopathological findings by full-thickness biopsy (4-8).

The clinical and histopathological characteristics of this entity are summarized in Tables 1 and 2. It is noteworthy that almost all patients have a preexisting episode of gastroenteritis, and intestinal ileus and abdominal distension occur. Anti-yersinia pseudotuberculosis antibodies were detected in one case (4). Molecular mimicry with infectious agents resulting in the initiation of the autoimmune

Table 1. Clinical characteristics in lymphocytic intestinal leiomyositis

Items	Age/Sex	Preexisting disease	Abnormal laboratory findings	Treatment	Progress
Case 1 (4)	6 mth./M	ns	Anti- <i>Yersinia pseudotuberculosis</i>	Steroid	4 yr. follow, death
Case 2 (5)	1 yr./M	ns	SMA	Steroid	ns
Case 3 (5)	2.5 yr./F	ns	SMA	Steroid	ns
Case 4 (6)	2 yr./M	AIH, gastroenteritis	SMA, ANCA, ANA	Steroid, AZA, Cyclosporin, enterostomy	3 yr. follow, TPN, relapsing obstruction
Case 5 (7)	5 yr./F	Enteritis	SMA	Steroid, AZA, FK 506	1.5 yr. follow, relapsing obstruction after steroid tapering
Case 6 (8)	16 yr./F	Enteritis	ns	Steroids, AZA, budesonide	2 yr. follow, normal oral diet
our case (2011)	3.5 yr./M	PRCA, TCLC, enteritis	SMA	Steroid, AZA, budesonide, FK 506, enterostomy	1.5 yr. follow, death

mth., month; yr., year; M, male; F, female; AIH, autoimmune hepatitis; ns, not specified; PRCA, pure red cell aplasia; TCLC, T cell lymphocytosis and cytopenia; SMA, smooth muscle antibody; ANCA, anti-neutrophil cytoplasmic antibody; ANA, antinuclear antibody; AZA, azathioprine; FK506, tacrolimus; TPN, total parenteral nutrition.

Table 2. Pathological characteristics in lymphocytic intestinal leiomyositis

Items	Affected digestive Organ	Histopathological findings of small intestine			
		MSM	LPM	MP	NP
Case 1 (4)	Small intestine	Atrophic	ns	Mono infil, degeneration, fibrosis	
Case 2 (5)	Small/large intestine	ns	ns	Severe T-lym infil, degeneration, fibrosis	Intact
Case 3 (5)	Small/large intestine	ns	ns	Severe T-lym infil, degeneration, fibrosis	Intact
Case 4 (6)	Ileum, large intestine	Mild inflammation	Moderate T-lym infil	Severe T-lym infil, degeneration	Intact
Case 5 (7)	Small/large intestine	Moderate T-lym infil	Moderate T-lym infil	Severe T-lym infil, degeneration	Intact
Case 6 (8)	Small intestine	Intact	Intact	T-lym infil, fibrosis, degeneration	Intact
our case (2011)	Small/large intestine	Mild T-lym infil	Moderate T-lym infil, degeneration	Severe T-lym infil, degeneration, fibrosis	Intact

MSM, mucosa and submucosa; LPM, lamina propria mucosae; MP, muscularis propria; NP, nerve plexus; ns, not specified; Mono infil, monocyte infiltration; T-Lym infil, T-lymphocytic infiltration.

inflammatory process has been previously suggested for other gastrointestinal autoimmune disorders (6, 11, 12). Myositis is associated with circulating autoantibodies directed against smooth muscle cells with or without nonspecific antibodies to nuclear antigens and neutrophil cytoplasmic antigens.

Diagnosis of LIL was performed by full-thickness biopsy of the small and large intestines. Mucosal and submucosal biopsy through endoscopy never results in a definite diagnosis. Severe T-lymphocyte inflammation is found in the muscularis propria, and there is no significant inflammation in the mucosal and submucosal layers. Although the pathogenesis and mechanism of LIL remain unclear, autoreactive cross-reactivity between pathogens and T-lymphocytes with smooth muscle fibers of the intestinal wall may cause a reaction. However, it is unknown why smooth muscle fibers of vessels are completely intact, while the muscularis propria of the intestinal wall is affected.

In this series, two patients had autoimmune disease as a preexisting disease: autoimmune hepatitis (AIH, case 4) and PRCA (our case). Several diseases such as type I diabetes, Addison's disease, and autoimmune thyroiditis are closely associated with AIH in children. In case 4, autoreactive T-lymphocytes promoted the

development of LIL under immunosuppressive therapy for AIH (6).

PRCA has been associated with a variety of clinical disorders, and various autoimmune mechanisms have been described to account for red cell suppression because of its frequent association with thymoma and successful responses to thymectomy and immunosuppressive agents (13). Generally, the pathogenesis of PRCA is considered to be due to the expansion of B-lymphocytes producing immunoglobulins (IGs), which suppresses erythropoiesis, and IGs are thought to be antibodies against erythropoietin or erythroblasts (14). However, another report demonstrated that suppressor/cytotoxic T-lymphocytes can inhibit erythropoiesis (15). Recent evidence using gene rearrangement studies has indicated that PRCA with T-lymphocytosis is a clonal chronic T cell lymphoproliferative disorder in which the T cells suppress erythropoiesis (16). This disorder has a unique feature of T cell lymphocytosis. The present case had PRCA with T cell lymphocytosis as preexisting disorders of LIL. Additionally, an autoimmune inflammatory reaction, mainly on the muscularis propria in the intestinal wall, was shown by T lymphocytic inflammation using immunostaining. The present case is considered to be the first case of T-LIL with preexisting PRCA. Katabami *et al.*

(17) reported an adult female case with polymyositis associated with thymoma who subsequently developed PRCA. They considered that cytotoxic T cells may play an important role in the pathogenesis of polymyositis and PRCA.

Immunosuppressive therapies including steroids and immunomodulators are recommended and they were performed in previous reports. The patient's clinical course is eventful and their quality of life is deteriorated by recurrent relapsing, paralytic ileus, insufficient oral intake, intestinal infections, complications of fluid therapy, and prolonged hospitalizations. Abdominal distension and vomiting recurred after prednisone withdrawal in our case, which is similar to other cases. Oton *et al.* recommended AZA and budesonide while tapering off conventional steroids, if the clinical response continues, to avoid steroid complications (8).

Uncontrolled inflammation induces degenerative, atrophic, and fibrotic changes in smooth muscle fibers in the intestinal wall. In case 1, histopathological findings demonstrated a diminished nerve plexus together with mononuclear infiltration, muscle degeneration, and fibrosis proliferation in the muscularis propria. Impairment of the myenteric plexuses is explained as the final histopathological findings (4). These seven previous cases and our reports may have consisted of different phenotypes of LIL between the early and end stages. Ruuska *et al.* (7) described that disease progress may be prevented resulting in end-stage intestinal motility failure, if immunosuppressive treatments are used aggressively early in the course of illness.

Prognosis of CIPO is generally poor. Generally, liver disease and sepsis due to bacterial overgrowth and complications of TPN are the most common causes of death in CIPO (18). Bacterial overgrowth often causes malabsorption and may be associated with increased mucosal permeability and bacterial translocation across the bowel (19-21). In the present case, uncontrolled CIPO due to LIL easily caused bacterial overgrowth under immunosuppressive conditions.

Clinicians should be aware of lymphatic intestinal leiomyositis for the differential diagnosis of CIPO. Three important factors for accurate diagnosis are a history of enteritis, positive serum smooth muscle antibody, and T-cell infiltration in the muscularis propria in intestinal full-thickness biopsies. Earlier diagnosis and induction of immunosuppressive therapy may be essential for a better outcome.

References

- Connor FL, Di Lorenzo C. Chronic intestinal pseudo-obstruction: Assessment and management. *Gastroenterology*. 2006; 130 (2 Suppl 1):S29-36.
- Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, Di Lorenzo C, Flores AF, Hillemeier AC, McCallum RW, Vanderhoof JA. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: Report of consensus workshop. *J Pediatr Gastroenterol Nutr*. 1997; 24:102-112.
- Mann SD, Debinski HS, Kamm MA. Clinical characteristics of chronic idiopathic intestinal pseudo-obstruction in adults. *Gut*. 1997; 41:675-681.
- Nezelof C, Vivien E, Bigel P, Nihoul-Fekete C, Arnaud-Battandier F, Bresson JL, Arhan P, Ricour C. Idiopathic myositis of the small intestine. An unusual cause of chronic intestinal pseudo-obstruction in children. *Arch Fr Pediatr*. 1985; 42:823-828. (in French)
- Smith VV, Milla PJ. Histological phenotypes of enteric smooth muscle disease causing functional intestinal obstruction in childhood. *Histopathology*. 1997; 31:112-122.
- Ruuska TH, Karikoski R, Smith VV, Milla PJ. Acquired myopathic intestinal pseudo-obstruction may be due to autoimmune enteric leiomyositis. *Gastroenterology*. 2002; 122:1133-1139.
- Haas S, Bindl L, Fischer HP. Autoimmune enteric leiomyositis: A rare cause of chronic intestinal pseudo-obstruction with specific morphological features. *Hum Pathol*. 2005; 36:576-580.
- Oton E, Moreira V, Redondo C, Lopez-San-Roman A, Foruny JR, Plaza G, de Vicente E, Quijano Y. Chronic intestinal pseudo-obstruction due to lymphocytic leiomyositis: Is there a place for immunomodulatory therapy? *Gut*. 2005; 54:1343-1344.
- De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. *Gut*. 2004; 53:1549-1552.
- Smith VV, Gregson N, Foggensteiner L, Neale G, Milla PJ. Acquired intestinal aganglionosis and circulating autoantibodies without neoplasia or other neural involvement. *Gastroenterology*. 1997; 112:1366-1371.
- Kagnoff MF, Paterson YJ, Kumar PJ, Kasarda DD, Carbone FR, Unsworth DJ, Austin RK. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. *Gut*. 1987; 28:995-1001.
- Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: Virtuous intentions, malign consequences. *Liver*. 2001; 21:225-232.
- Tötterman TH, Nisell J, Killander A, Gahrton G, Lönnqvist B. Successful treatment of pure red-cell aplasia with cyclosporin. *Lancet*. 1984; 22:693.
- Marmont A, Peschle C, Sanguineti M, Condorelli M. Pure red cell aplasia (PRCA): Response of three patients of cyclophosphamide and/or antilymphocyte globulin (ALG) and demonstration of two types of serum IgG inhibitors to erythropoiesis. *Blood*. 1975; 45:247-261.
- Litwin SD, Zanjani ED. Lymphocytes suppressing both immunoglobulin production and erythroid differentiation in hypogammaglobulinaemia. *Nature*. 1977; 3:57-58.
- Nidorf D, Saleem A. Immunosuppressive mechanisms in pure red cell aplasia – A review. *Ann Clin Lab Sci*. 1990; 20:214-219.
- Katabami S, Sugiyama T, Kodama T, Kamijo K, Azuma N, Tamaki T, Katanuma A, Fujisawa Y, Kinoshita H, Imai K, Yachi A. Polymyositis associated with thymoma and the subsequent development of pure red cell aplasia. *Intern Med*. 1995; 34:569-573.
- Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo

- C. Long-term outcome of congenital intestinal pseudoobstruction. *Dig Dis Sci.* 2002; 47:2298-2305.
19. Vantrappen G, Janssens J, Hellems J, Ghoo Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. *J Clin Invest.* 1977; 59:1158-1166.
20. Pignata C, Budillon G, Monaco G, Nani E, Cuomo R, Parrilli G, Ciccimarra F. Jejunal bacterial overgrowth and intestinal permeability in children with immunodeficiency syndromes. *Gut.* 1990; 31:879-882.
21. Lichtman SN, Keku J, Schwab JH, Sartor RB. Hepatic injury associated with small bowel bacterial overgrowth in rats is prevented by metronidazole and tetracycline. *Gastroenterology.* 1991; 100:513-519.

(Received December 14, 2011; Accepted January 25, 2012)