Ⅳ. 研究成果の刊行物・別刷

Pediatr Surg Int (2012) 28:239–244
DOI 10.1007/s00383-011-3013-2

ORIGINAL ARTICLE

The utility of muscle sparing axillar skin crease incision for pediatric thoracic surgery

Tomoaki Taguchi · Kouji Nagata · Yoshiaki Kinoshita · Satoshi Ieiri · Tatsuro Tajiri · Risa Teshiba · Genshiro Esumi · Yuji Karashima · Sumio Hoka · Kouji Masumoto

Accepted: 3 October 2011 / Published online: 19 October 2011

Abstract
Background Posterolateral or standard axillar incisions for the pediatric thoracic surgery are occasionally associated with poor motor as well as cosmetic results, including chest deformities and large surgical scars. A muscle sparing axillar skin crease incision (MSASCI) was initially proposed by Bianchi et al. (in J Pediatr Surg 33:1798–1800, 1998) followed by Kalman and Verebely (in Eur J Pediatr Surg 12:226–229, 2002) resulting in satisfactory cosmetics. However, they performed operations through the third or fourth intercostals space (ICS), therefore the target organs were restricted in the upper two-thirds of the thoracic cavity.
Patients and methods Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old). There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. A thoracotomy was performed through the appropriate ICS (from third to eighth).
Results In all patients, the expected procedures, including pulmonary lower lobectomy, were successfully performed by MSASCI throughout the thoracic cavity. A good operational field was easily obtained in neonates and infants. Most of the patients achieved excellent motor and aesthetic outcomes.
Conclusions MSASCI may become the standard approach for the thoracic surgery for small children.

Keywords Axillar skin crease · Thoracotomy · Pulmonary lobectomy · Neonate · Infant

Introduction

Advances in antenatal diagnosis, surgical technique and perioperative care have improved survival rate for neonatal surgical diseases. The mortality rate has become less than 10% [1]. It is now important to consider the long-term good "quality of life" (QOL) in neonatal surgical disease. Therefore, surgeons have sought to establish procedures that leave no scars, using the natural skin crease such as axillar crease and umbilical crease [2–4].

Posterolateral or standard axillar incisions for the pediatric thoracic surgery sometimes cause poor functional as well as cosmetic results, including chest deformities (scoliosis, shoulder deformity, and winged scapula) and large surgical scars. Muscle sparing axillar skin crease incision (MSASCI) was initially proposed for neonates by Bianchi et al. [5] in 1998, and then Kalman and Verebely [6] extended this approach for children in 2002, thus resulting

T. Taguchi · K. Nagata · Y. Kinoshita · S. Ieiri · T. Tajiri · R. Teshiba · G. Esumi
Department of Pediatric Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

T. Taguchi (✉)
Department of Pediatric Surgery, Reproductive and Developmental Medicine, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan
e-mail: taguchi@pedsurg.med.kyushu-u.ac.jp

Y. Karashima · S. Hoka
Department of Anesthesiology and Critical Care Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

K. Masumoto
Department of Thoracic, Endocrine, and Pediatric Surgery, Fukuoka University School of Medicine, Fukuoka, Japan

in a good postoperative cosmetic results. However, they performed surgery through the third or fourth intercostals space (ICS), therefore the performed operations were restricted in the upper two-thirds of the thoracic cavity.

Patients and methods

Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old) from December 2006 to February 2011. There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. The performed operations were 10 primary esophageal anastomoses, 12 pulmonary lobectomies (including lower lobectomies) or partial resections, 2 subtotal neuroblastoma resections, 1 diaphragmatic repair, 1 pulmonary biopsy, and 1 exploratory thoracotomy.

This study was performed, according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan on 30 July 2003 and complies with the Helsinki Declaration of 1975 (revised 1983). Regarding this retrospective study, properly informed consent was obtained from the parents.

The patient was placed in the lateral position. The uppermost arm was extended to about 130°, drawn forward, and placed on an arm-rest. A pulse-oxymeter was applied on hand of the extended arm.

A skin incision was made just on the axillar skin crease, and the pectoralis major and latissimus dorsi muscles were retracted superiorly and medially, respectively. Either of these muscles could be partially incised in case. The incision was deepened and the axillary fat pad and lymph nodes were pushed upward. The long thoracic nerve was preserved in the posterior part of the wound (Fig. 1). The anterior serratus muscle was split along its fibers just on the targeted costa. The thoracic cavity was entered through the appropriate ICS. The peripheral pulse was monitored by the pulse-oxymeter of the extended arm avoid a circulatory failure of the arm.

Thoracotomy for esophageal atresia was performed through the fourth ICS and the upper and lower esophagus was exposed via an extrapleural approach. After cutting The azygos vein was cut and the Tracheoesophageal fistula (TEF) was closed by 5-0 polydioxanon (PDS) transfixing sutures and cut. Esophageal end-to-end anastomosis was performed with one layer stitch sutures. Both lateral sides were approximated using 5-0 PDS, and a transanastomotic tube was inserted from the nose to the stomach through the anastomosis. The anterior and the posterior aspects were sutured with 6-0 PDS in stitch.

One-lung ventilation was attempted in order to obtain adequate operational field for pulmonary lower lobectomy [7]. Briefly, bronchial blockade with a 4Fr or 5Fr Fogarty embolectomy catheter was attempted in each case. Children were initially intubated with a Fogarty embolectomy catheter under direct laryngoscopy. Then, immediately, an endotracheal tube was placed alongside the catheter in the trachea. After securing the tube, a pediatric fiberoptic bronchoscope (2.2 mm in diameter) was passed through to set a Fogarty embolectomy catheter to the mainstem bronchus. And then, bronchial blockade was performed with its balloon inflated with an appropriate volume of normal saline. Thoracotomy was done through the fifth or sixth ICS, and then the lung was deflated. The pulmonary arteries were ligated and cut and then the bronchus was cut and closed with 5-0 PDS sutures. Finally, the pulmonary vein was doubly ligated and cut, and the pulmonary ligament was dissected.

One-lung ventilation was also performed for the pulmonary sequestration. Thoracotomy was performed via the seventh or eighth ICS in order to approach the abnormal artery in pulmonary ligament at first. One-lung ventilation allowed lower lobe to be easily lifted for the dissection of pulmonary ligament and the ligation of abnormal artery. This abnormal artery was ligated, before ligation of pulmonary vein in order to avoid lung volume expansion.

A rolled vicryl sheet was inserted between the costa during thoracic closure, in order to avoid bony adhesion in some cases. Both the thoracic and subcutaneous tubes were inserted through both ends of wound; therefore, no additional wounds were necessary for tubes.

Results

Thoracotomy was successfully done through from the third and eighth ICS using MSASCI. All of the expected procedures, including pulmonary lower lobectomies, were able to be performed adequately. A good operational field was easily obtained in neonates and infants in comparison to that in elder children. The incision was extended caudally, about 1 cm in only one infant with pulmonary sequestration. Two patients died due to the severe cardiopulmonary anomalies, and one patient with right diaphragmatic hernia showed recurrence and required reoperation using an abdominal approach. The other patient with a right diaphragmatic hernia showed no right lung; therefore, no procedure was performed (exploratory thoracotomy).

Surgical complications included wound disruption in the four cases and transient arm paralysis in the two cases. The wound disruptions were treated by vacuum therapy and healed about 1 week, and the transient arm paralysis

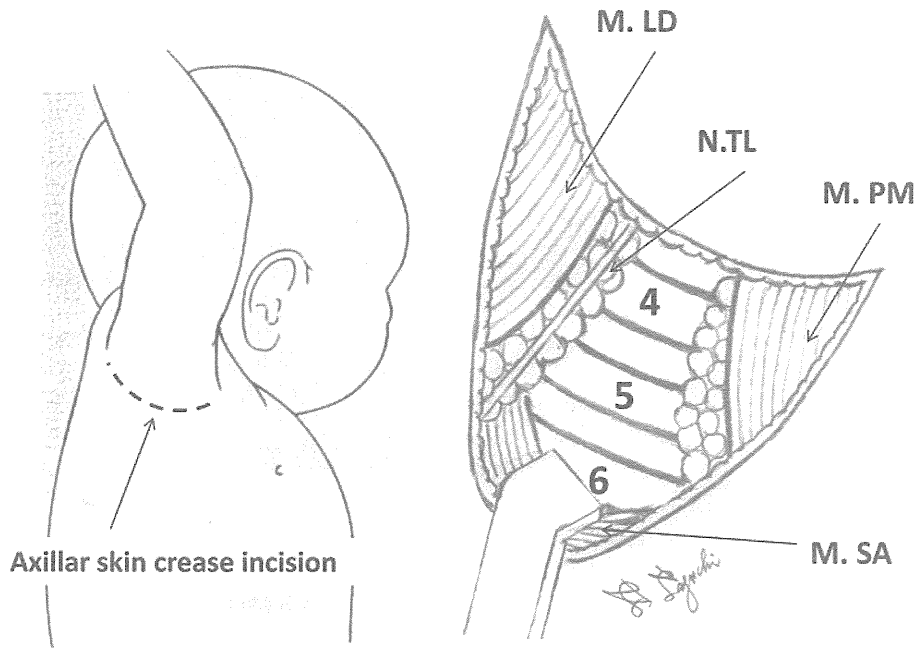


Fig. 1 Operation schema for MSASCI. *M.LD* lattismus dorssi muscle, *N.TL* long thoracic nerve, *M.PM* pectoralis major muscle, *M.SA* serratus anterior muscle, The *numbers* are labeling in the individual ribs.

recovered spontaneously in a few weeks. All of the patients showed uneventful postoperative course and achieved excellent motor and aesthetic outcomes after 1 month. The surgical scar was almost hidden by the axillar skin crease in a year (Figs. 2, 3). So far, there have been no patients showing thoracic deformity, in a relatively short-term follow-up (no more than 4 years). The outcome of each patient is shown in Table 1.

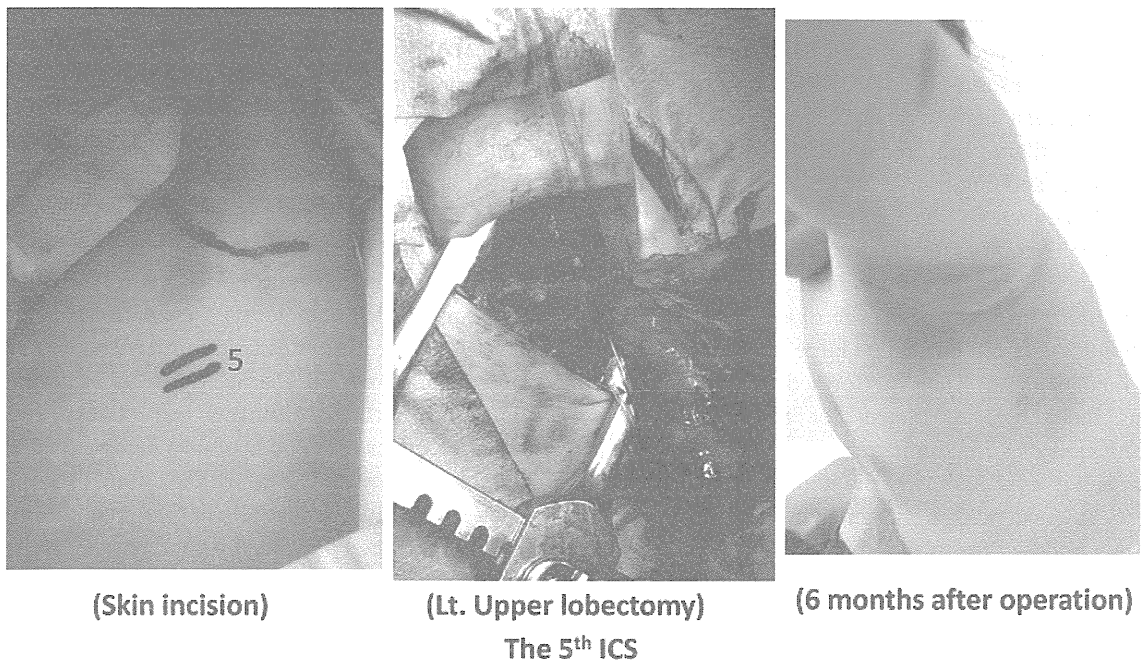


Fig. 2 Pre, intra, and postoperative appearance of Case 15. Congenital cystic adenomatoid malformation in Lt. upper lobe. *Left* skin incision on the axillar crease. *Middle* Lt. upper lobectomy of lung was performed through the fifth ICS at 1-month old. *Right* operative wound was almost hidden 6 months after operation

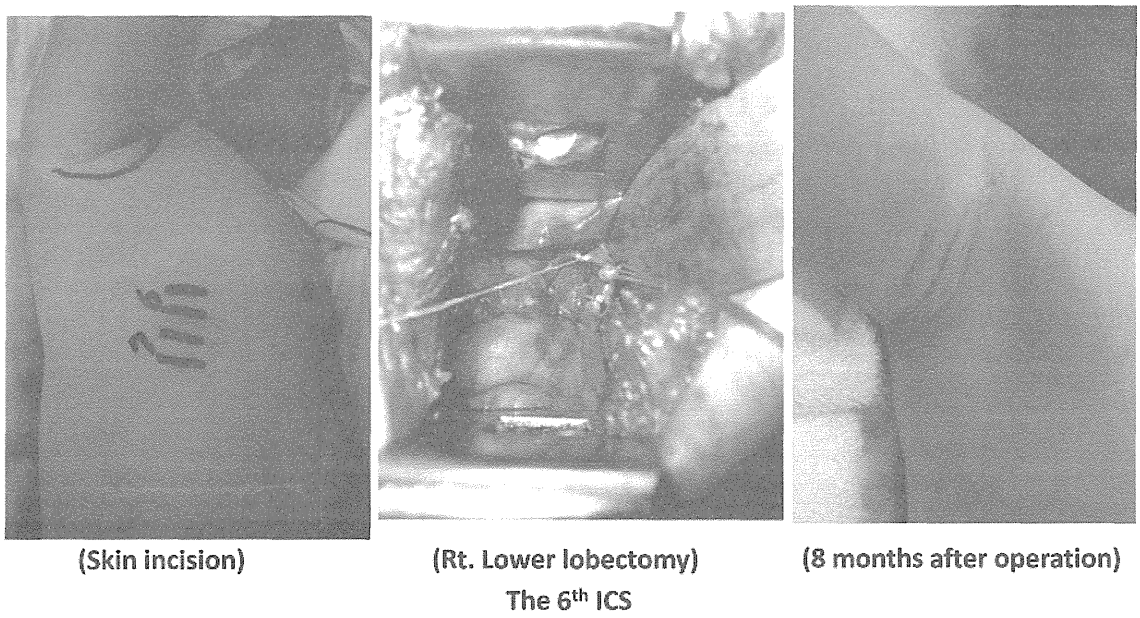


Fig. 3 Pre, intra, and post operative appearance of Case 17. Intralober lung pulmonary sequestration in Rt. lower lobe. *Left* skin incision on the axillar crease. *Middle* Rt. lower lobectomy of lung was performed through the sixth ICS at 3-month old. *Right* operative wound was almost hidden 8 months after operation

Discussion

Axillary skin crease incision for thoracic surgery was initially reported by Atkinson as "peraxillary approach" for dissection of the upper thoracic and stellate ganglia through the second ICS in adult in 1949 [8]. Bianchi et al. [5] reported using "high axillary skin crease, muscle-sparing to right lateral thoracotomy" for children in 1998. They operated on 29 neonates including 27 esophageal atresia and two patent ductus arteriosus (PDA) through the third or fourth ICS. Kalman and Verebely [6] also reported this approach as "axillary skin crease incision" for thoracotomy of neonates and children in 2002. They performed 17 operations in neonates (8 esophageal atresia, 8 PDA, 1 CCAM) and 9 operations in children (3 neuroblastoma, 1 teratoma, 5 pulmonary operations including lobectomies) through the third or fourth ICS. The oldest patient of this report was a 15-year-old girl with a large teratoma from the anterior mediastinum. They performed five pulmonary operations including one biopsy for histiocytosis, one marsupialization of an inflammatory cyst, one cystectomy of a congenital cyst and two pulmonary resections for bronchiectasia (one S2-3-4 trisegmentectomy on the left side and one middle lobe lobectomy). They concluded that it ensured unrestricted access to the upper two-thirds of the thoracic cavity through the third or fourth ICS. They did not perform any pulmonary lower lobectomies.

These reports indicate that the term MSASCI is appropriate. The approach was extended downward up to the eighth ICS in the current series to perform the expected procedures in all cases, including pulmonary lower lobectomy and intralobular pulmonary sequestration. This technique is feasible for almost all kinds of pediatric thoracic surgery from third to eighth ICS. The appropriate ICS for thoracotomy depends on the target organ. For example, the fourth ICS is used for esophageal atresia, the fifth ICS is for standard pulmonary lobectomy, and the seventh or eighth ICS for pulmonary sequestration. We experienced technical difficulties in patch closure of right diaphragmatic hernia in one case. The medial margin of diaphragmatic defect was difficult to be exposed for suturing, because liver and intestine interfered to the operation field. Right diaphragmatic hernia might not be indication for MSASCI from our restricted experience.

There were initially several complications, such as wound disruption and transient arm paralysis. In 18 out of the 27 patient, thoracotomy was performed below the fourth ICS. The wound disruption occurred in four cases (Cases 5, 7, 9 and 26). These four were operated through fifth, fourth, sixth, and fifth ICS, respectively. Three out of four cases underwent thoracotomy below the fourth ICS. Therefore, downward hyperextension of skin by metal retractor may cause wound disruption. In addition, the case five was extremely premature infant and the modified gestational age at operation was 40 weeks. Cases 7, 9 and 26 were operated in their neonatal period. And the three out of these four cases showed cyanosis in perioperative period due to their congenital heart disease and the subsequent pulmonary hypertension. Therefore, hyperextension of the skin as well as vulnerable factors of each child may cause

Table 1 Summary of 27 pediatric patients performed thoracotomies with MSASCI

Case	Sex	Diagnosis	Type or site	Age at op.	Operation	Intercostal space	Complication	Prognosis
1	M	EA	Gross type A	1 year 3 month	Esophageal EEA	Rt. 4th intercostal	Minor leakage	Alive
2	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	Stenosis	Alive
3	M	EA, AA, TAC	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
4	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	None	Alive
5	F	EA, ELBWIPA stenosis	Gross type C	3 months	Esophageal EEA	Rt. 5th intercostal	TEF recurrence wound disruption	Died[b]
6	F	EA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
7	M	EA, TA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	Wound disruption transient paralysis	Died[c]
8	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 5th intercostal	Stenosis	Alive
9	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 6th intercostal	Wound disruption	Alive
10	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
11	M	CCAM	Rt. middle lobe	8 months	Partial resection	Rt. 5th intercostal	None	Alive
12	M	LPS	Rt. lower lobe	4 days	LPS resection	Rt. 5th intercostal	None	Alive
13	F	CCAM	Lt. upper lobe	1 month	Partial resection	Lt. 5th intercostal	None	Alive
14	F[a]	LPS	Lt. lower lobe	8 months	LPS resection	Lt. 8th intercostal	None	Alive
15	M	CCAM	Lt. upper lobe	1 month	Lt. upper lobectomy	Lt. 5th intercostal	Pneumothorax	Alive
16	F	CCAM	Lt. lower lobe	4 months	Lt. lower lobectomy	Lt. 5th intercostal	None	Alive
17	M	LPS	Rt. lower lobe	3 months	Rt. lower lobectomy	Rt. 6th intercostal	None	Alive
18	F	CTA with LPS	Lt. lower lobe	4 months	Rt. lower lobectomy	Rt. 6th intercostal	Transient paralysis	Alive
19	M	CCAM	Lt. lower lobe	3 months	Lt. lower lobectomy	Lt. 6th intercostal	None	Alive
20	M	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Rt. 5th intercostal	None	Alive
21	M	LPS	Lt. lower lobe	7 months	LPS resection	Lt. 7th intercostal	None	Alive
22	F	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Lt. 5th intercostal	None	Alive
23	M	Mediastinal NB	Lt. upper lobe	6 years 1 month	Subtotal excision	Lt. 4th intercostal	None	Alive
24	F	Mediastinal NB	Lt. upper lobe	9 years 4 months	Subtotal excision	Lt. 3th Intercostal	None	Alive
25	M	Pulmonary HT	Lt. upper lobe	5 years 11 months	Biopsy	Lt. 6th intercostal	None	Alive
26	M	Rt. CDH		5 days	Repair	Rt. 5th intercostal	Wound disruption CDH recurrence	Alive
27	F	Rt. CDH Rt. lung agenesis		5 days	Exploratory thoracotomy	Rt. 7th intercostal	None	Alive

EA esophageal atresia, *AA* anal atresia, *TAC* truncus arteriosus communis, *ELBW* extremely low birth weight infant, *PA* pulmonary artery, *TA* tricuspid atresia, *CCAM* congenital cystic adenomatoid malformation, *LPS* lung pulmonary sequestration, *CTA* congenital tracheal atresia, *NB* neuroblastoma, *CDH* congenital diaphragmatic hernia, *HT* hypertension, *EEA* end to end anastomosis, *TEF* tracheoesophageal fistula

[a] Incision was extended caudally about 1 cm

[b, c] Two patients died due to the severe cardio-pulmonary anomalies

the wound disruption. In order to prevent this complication, a wound retractor XS has been currently applied to protect the surgical wound. This instrument can prohibit skin and subcutaneous tissue damage during surgery. Postoperative subcutaneous negative-pressure drainage is also an effective for avoiding or treating wound disruption.

The transient arm paralysis occurred in the case 7 and 18. They were operated through the fourth ICS and the sixth ICS, respectively. Therefore, the transient paralysis is not considered to be related to the level of thoracotomy. Actually, there were no complications in the patients operated from the seventh to eighth ICS. Currently, a pulse-oxymeter has been applied, on the hand, of the extended arm for monitoring peripheral blood pulse and saturation of oxygen. During operation blood pulse and saturation of oxygen has been kept in normal range. Since then, no patient has experienced transient arm paralysis. Therefore, transient arm paralysis is considered to be vascular origin caused by the hyperextension of arm or the hyperextension of wound.

The surgical field is relatively small; therefore, there are a few technical methods in order to overcome this disadvantage. One-lung ventilation is required for pulmonary lower lobectomy during the dissection of the pulmonary ligament and pulmonary vein. Furthermore, one-lung ventilation provides adequate operative field in ligation of the abnormal artery during surgery of pulmonary sequestration. One-lung ventilation has been technically feasible in infant, using Fogarty embolectomy catheter [7]. Hemoclips facilitate the ligation of pulmonary arteries. The proximal site is ligated by 3-0 or 4-0 silk suture and the distal site is closed by a hemoclip, to provide sufficient distance for a safe cut. A long and fine-tip needle holder and forceps are required for dissection of the TEF and anastomosis of the esophagus in esophageal atresia. Fine monofilament absorbable 5-0 or 6-0 PDS with the two needles in both ends are useful for full thickness stitch suture using an inside-to-outside and inside-to-outside manner.

In conclusions, MSASCI for pediatric thoracic surgery resulted in excellent motor and aesthetic outcomes. MSASCI may become the standard approach for thoracic surgery for the small children, especially for neonates and infants.

Acknowledgments The authors thank Mr. Brian Quinn for proof reading the manuscript. This work was partly supported by a Grant-in-aid for scientific research from the Japanese Society for the Promotion of Science and also supported by a Grant of Kyushu University Interdisciplinary Programs in Education and Projects in Research Development.

Conflict of interest No competing financial interest exists.

References

1. Taguchi T (2008) Current progress in neonatal surgery. Surg Today 38:379–389
2. Taguchi T (2008) Scar less surgery and reconstructive surgery in neonates (Plenary Lecture 7). In: 15th congress of the federation of Asia and oceania perinatal societies, 20th–24th May 2008, Program & Abstract pp 69–70
3. Tajiri T, Ieiri S, Kinoshita Y, Masumoto K, Nishimoto Y, Taguchi T (2008) Transumbilical approach for neonatal surgical diseases: woundless operation. Pediatr Surg Int 24:1123–1126
4. Takahashi Y, Tajiri T, Masumoto K, Kinoshita Y, Ieiri S, Matsuura T, Higashi M, Taguchi T (2010) Umbilical crease incision for duodenal atresia achieves excellent cosmetic results. Pediatr Surg Int 26:963–966
5. Bianchi A, Sowande O, Alizai NK, Rampersad B (1998) Aesthetics and lateral thoracotomy in the neonate. J Pediatr Surg 33:1798–1800
6. Kalman A, Verebely T (2002) The use of axillary skin crease incision for thoracotomies of neonates and children. Eur J Pediatr Surg 12:226–229
7. Camci E, Tuğrul M, Tuğrul ST et al (2001) Techniques and complications of one-lung ventilation in children with suppurative lung disease: experience in 15 cases. J Cardiothorac Vasc Anesth 15:341–345
8. Atkins HJB (1949) Peraxillary approach to the stellate and upper thoracic sympathetic ganglia. The Lancet 254:1152

Original Paper

Digestion

Digestion 2012;86:12–19
DOI: 10.1159/000337528

Received: September 9, 2011
Accepted: February 25, 2012
Published online: June 15, 2012

An Epidemiologic Survey of Chronic Intestinal Pseudo-Obstruction and Evaluation of the Newly Proposed Diagnostic Criteria

Hidenori Ohkubo[a] Hiroshi Iida[a] Hirokazu Takahashi[a] Eiji Yamada[a] Eiji Sakai[a] Takuma Higurashi[a] Yusuke Sekino[a] Hiroki Endo[a] Yasunari Sakamoto[a] Masahiko Inamori[a] Hajime Sato[b] Kazuma Fujimoto[c] Atsushi Nakajima[a]

[a]Gastroenterology Division, Yokohama City University School of Medicine, Yokohama, [b]Department of Health Policy and Technology Assessment, National Institute of Public Health, Wako, and [c]Gastroenterology Division, Saga University School of Medicine, Saga, Japan

Key Words
Chronic intestinal pseudo-obstruction · Diagnostic criteria · Algorithm

Abstract
Background and Aims: Chronic intestinal pseudo-obstruction (CIPO) is an intractable disease in which clinical symptoms of intestinal obstruction appear without mechanical cause. No clear diagnostic criteria have been established; therefore, we proposed diagnostic criteria to facilitate the diagnosis of this rare disease and aim to evaluate their usefulness and validity. ***Materials and Methods:*** A questionnaire was sent to 378 institutions belonging to the Japanese Society of Gastroenterology between December 2009 and February 2010. We summarized the returned data and performed a statistical analysis. ***Results:*** A total of 160 cases were included, and 141 cases (88.1%) fulfilled the criterion of disease duration of >6 months, 157 cases (98.1%) the criterion of the clinical symptoms of abdominal pain and/or bloating and 154 cases (96.2%) fulfilled the criterion of imaging findings. Eventually, 138 cases (86.3%) fulfilled all criteria. ***Conclusions:*** The proposed diagnostic criteria were useful, with a high sensitivity of 86.3% for Japanese patients. Improved recognition of CIPO and practical use of the criteria are desired. The criteria should be appropriately modified by additional researchers to make them more practical and internationally applicable.

Introduction

Intestinal pseudo-obstruction (IPO), first reported by Dudley et al. [1] in 1958, is a rare, serious digestive syndrome characterized by failure of the intestinal tract to propel its contents appropriately, resulting in recurrent clinical episodes of intestinal obstruction in the absence of any mechanical cause [1–5]. Acute or chronic abdominal pain and distension are the most common symptoms. Furthermore, nausea, vomiting, constipation and diarrhea are also seen at various frequencies. Based on the pattern of onset, IPO is classified as acute or chronic. The acute type, especially acute pseudo-obstruction of the colorectum, is referred to as Ogilvie syndrome, which encompasses several colonic obstructive syndromes caused

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0012–2823/12/0861–0012$38.00/0

Accessible online at:
www.karger.com/dig

Atsushi Nakajima, MD, PhD
Gastroenterology Division
Yokohama City University School of Medicine
3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004 (Japan)
Tel. +81 45 787 2640, E-Mail nakajima-tky@umin.ac.jp

Table 1. Diagnostic criteria for CIPO proposed by the Research Group of the Ministry of Health, Labour and Welfare

Definition of CIPO
Chronic bowel obstruction not explained by structural abnormalities
Criteria for CIPO
Must include all of the following four points:
1. Onset of one or more symptoms of bowel obstruction[1] at least 6 months prior to the diagnosis
2. One or both of the following for the previous 12 weeks
   a. Abdominal bloating
   b. Abdominal pain
3. Dilatation and/or air-fluid level of the intestine on abdominal X-ray, echo and/or CT imaging
4. No evidence of structural disease (by upper and lower gastrointestinal endoscopy, computed tomography, barium enema, and small-bowel follow-through) that could explain the dilatation and/or air-fluid level of the intestine

Important notice
1. Congenital and/or onset at under 15 years of age must be excluded. Only adult onset is included
2. Surgical history, except surgery for CIPO, within the 6 months prior to the diagnosis must be excluded to rule out Ogilvie syndrome
3. CIPO is defined at two levels: primary CIPO or secondary CIPO. Primary CIPO consists of three types: the myogenic type, neurogenic type and idiopathic type. Secondary CIPO consists of two types: the SSc type and the unclassified type
4. Family accumulation may exist
5. Neuropathy, such as problems with urination, may exist
6. Some psychosocial disorder may be present

[1] Symptoms of bowel obstruction include: abdominal pain, nausea, vomiting, abdominal bloating, abdominal fullness, lack of gas and/or passing gas.

by acute functional transit failure. It is speculated that this syndrome is caused by collapse of the regulation of autonomic nerves distributed in the colorectum. The Ogilvie syndrome is secondary to various diseases and has been mainly reported to occur after abdominal surgery [6].

The chronic type of IPO is the so-called 'CIPO'. Although there are no specific laboratory findings, malabsorption due to bacterial overgrowth, anemia, hypocalcemia, hypolipidemia, folic acid deficiency, iron deficiency and hypoalbuminemia are often observed in CIPO patients due to malnutrition [2–4]. CIPO may affect the entire gut from the esophagus to the rectum in the broad sense, but predominantly, the small intestine is affected. CIPO can be categorized as primary or secondary [7]. Primary CIPO includes the myogenic, neurogenic, mesenchymopathic (arising from the dysfunction of the interstitial cells of Cajal) and the mixed or unclassifiable type (inflammation). Secondary CIPO includes a subtype that is secondary to underlying diseases such as systemic sclerosis (SSc) or mitochondrial encephalomyopathy as well as a subtype that is related to antipsychotic or antidepressant drug use. The subtype of CIPO that is not associated with any apparent underlying disease has been called 'chronic idiopathic intestinal pseudo-obstruction' (CIIP).

At present, the diagnostic criteria for CIPO are not well established. The Research Group for the Survey of the Actual Conditions of Epidemiology, Diagnosis, and Treatment of CIIP in Japan (chief investigator, Atsushi Nakajima), Research Project for Overcoming Intractable Disease, Health Labour Sciences Research Grant in the fiscal year 2009, proposed Japanese diagnostic criteria for CIPO in order to facilitate the diagnosis of this rare disease by the general physician. The criteria are composed of four mandatory requirements and an important note for the diagnosis, as shown in table 1. Recently, Iida et al. [8] investigated the reported data of a total of 121 Japanese CIPO cases between 1983 and 2009 and calculated the sensitivity of the proposed diagnostic criteria, under the assumption that the case reports used contained sufficient information about each patient; therefore, all cases were considered to be correctly diagnosed as having CIPO. However, very little is still known about the pathophysiology of CIPO and the status of CIPO patients in Japan; therefore, we conducted an epidemiologic survey to assess the present status of this rare disease in the Japanese population following the investigation of previous case reports. We investigated the recognition rate of the disease in certified gastroenterology institutions as well as its epidemiology, including the clinical symptoms and

Table 2. Patient questionnaire sent to 378 institutions belonging to the JSGE

I. Patient information									
Sex:	Male	Female							
Age, years:	≤14	15–19	20–29	30–39	40–49	50–59	60–69	70–79	≥80
II. Clinical presentations at first hospital visit									
Abdominal pain for the previous 12 weeks:				Yes			No		
Vomiting for the previous 12 weeks:				Yes			No		
Abdominal bloating for the previous 12 weeks:				Yes			No		
Dilatation of the bowels on radiological imagings:				Yes			No		
Disease duration:				More than 6 months			Within 6 months		
Type of CIPO:				Primary			Secondary		
If secondary CIPO:				Secondary to SSc			Secondary to others		
III. Treatment									
Selected method of treatment:	Diet		Medication		Surgery		Others	No treatment	
Medication drugs: (multiple answers allowed)	Mosapride[1]		Erythromycin		Pantothenic acid		Metoclopramide	Sulpiride	
	Domperidone		Daikenchuto[2]		Somatostatin analogue		Kanamycin	Metronidazole	
	Polymixin B		Probiotics		Itopride		Calcium polycarbophil		
	Magnesium oxide		Other laxatives		Loperamide		Albumin tannate		
	Dimethicone		PPI		H2RA		Mucosal protective drugs		

JSGE = Japanese Society of Gastroenterology; PPI = proton pump inhibitors.
[1] Mosapride is the 5-HT4 receptor agonist. [2] Daikenchuto is a herbal medicine.

radiological imaging findings; then, we evaluated the validity and usefulness of the diagnostic criteria for CIPO newly proposed by this research group.

Materials and Methods

A questionnaire was sent to 378 institutions belonging to the Japanese Society of Gastroenterology between December 2009 and February 2010. At first, we enquired whether or not each of the participating institutions was aware of CIPO as a disease entity or had encountered patients with CIPO. While enquiring about the institutions' recognition of this disease, CIPO was defined as a disease characterized by recurrent clinical episodes of intestinal obstruction in the absence of mechanical obstruction, as confirmed by clinical examinations, including radiological imaging and gastrointestinal endoscopy. The institutions that had knowledge about the disease entity were asked to fill out the questionnaire, based on the premise that the gastrointestinal specialists in the institutions had certainly performed the aforementioned examinations to exclude mechanical obstruction and made a correct diagnosis of CIPO. The details of the questionnaire are shown in table 2. Here, the term 'dilatation of the bowels on radiological imagings' indicates not only dilatation of the small intestine, but also of the colon. We decided to use the simplistic term 'the bowels' because of the following reasons: (1) our intention in establishing these diagnostic criteria is to facilitate the diagnosis of CIPO by the general physician without any need for complicated or specialized discussions, such as 'which is the dilated bowel, the small intestine or the colon?'; (2) the colon should not be excluded, because special cases such as the colorectal localized type (chronic colonic pseudo-obstruction (CCPO)) sometimes exist.

Table 3. Disease type of a total of 160 CIPO cases

Classification of CIPO	Cases
Primary CIPO	117 (73.1)
Secondary CIPO	41 (25.6)
SSc	23 (56.1)
Non-SSc	18 (43.9)
DM	4 (9.8)
MCTD	3 (7.3)
SjS	1 (2.4)
Amyloidosis	2 (4.9)
Others	8 (19.5)
Unknown	2 (1.3)

Figures in parentheses are percentages. DM = Dermatomyositis; MCTD = mixed-connective tissue disease; SjS = Sjögren syndrome.

Table 4. Clinical presentations at first hospital visit (**a**) and disease duration prior to the diagnosis (**b**) (n = 160)

a Clinical presentation

	Cases		
	Yes	No	Unknown
Clinical symptoms			
Abdominal pain	107 (66.9)	53 (33.1)	0 (0)
Vomiting	81 (50.6)	79 (49.4)	0 (0)
Abdominal bloating	156 (97.5)	4 (2.5)	0 (0)
Abdominal pain and/or bloating	157 (98.1)	3 (1.9)	0 (0)
Radiological imaging findings			
Dilatation and/or air-fluid level of the bowel	154 (96.2)	3 (1.9)	3 (1.9)

b Disease duration

	Cases
Disease duration	
>6 months	141 (88.1)
<6 months	16 (10.0)
Unknown	3 (1.9)

Figures in parentheses are percentages. Of the total CIPO cases, 138 (86.3%) fulfilled all the diagnostic criteria, including abdominal pain and/or bloating, dilatation and/or air-fluid level of the bowel, as well as disease duration >6 months.

The closing date for the receipt of the questionnaire responses was 19 February 2010. We aggregated the data on the type of CIPO (primary or secondary), age at the time of the first hospital visit, clinical symptoms, radiological imaging findings, duration of disease and method of treatment in each patient and conducted a statistical analysis.

Results

Recognition of CIPO and Experience with CIPO at Each Institution

Overall, 216 (57.2%) of the 378 institutions responded to our questionnaire, and of these, 200 (92.6%) were aware of CIPO as a distinct disease entity and 103 (51.5% of those aware of CIPO as a distinct disease entity) had encountered cases of CIPO. None of the institutions that were unaware of CIPO have encountered CIPO cases. The number of cases was 0 in 97 (48.5%), 1 in 52 (26.0%), 2 in 17 (8.5%), 3 in 7 (3.5%), 4 in 1 (0.5%), 5 in 2 (1.0%), 6 in 3 (1.5%), 7 in 2 (1.0%), 8 in 1 (0.5%), 10 in 2 (1.0%), and 27 in 1 (0.5%) of the institutions. A total of 213 patients were accumulated from 103 institutions until 19 February 2010. Of the 213 patients, 53 for whom detailed information (e.g., sex, clinical symptoms) was not available from the questionnaire were excluded. Eventually, the data of a total of 160 patients were included in our study.

Type of CIPO

Data analysis of the 160 cases revealed that 77 (48.1%) were males and 83 (51.9%) were females. The type of CIPO was primary in 117 cases (73.1%), secondary in 41 cases (25.6%) and unknown in 2 cases (1.3%), as shown in table 3. The underlying cause in the cases with secondary CIPO was SSc in 23 cases (56.1%) and non-SSc in 18 cases (43.9%). Collagen diseases were prominent among the non-SSc cases and included dermatomyositis in 4 cases (9.8%), mixed connective tissue disease in 3 cases (7.3%) and Sjögren syndrome in 1 case (2.4%). The other causes of non-SSc CIPO were amyloidosis in 2 cases (4.9%) and 'others' in 8 cases (19.5%).

Age at the Time of First Hospital Visit

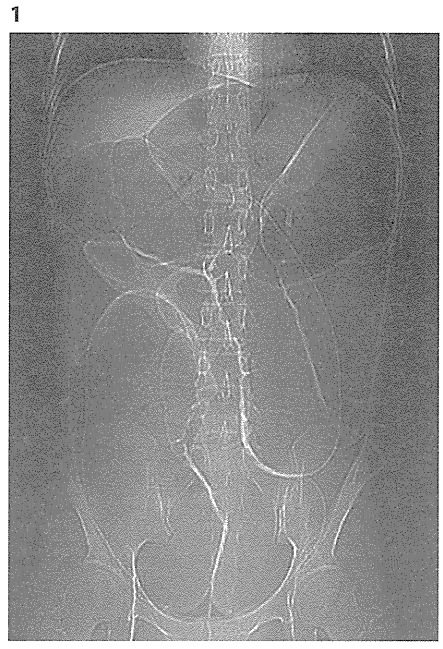
The majority of the patients of both sexes were in their 60s at the time of their first hospital visit (25.7% males, 24.1% females).

Clinical Symptoms

Our evaluation of the clinical symptoms in 160 cases showed that abdominal bloating was the most common symptom, recorded in 156 cases (97.5%), and that abdominal pain and vomiting were relatively common symptoms, recorded in 107 (66.9 %) and 81 cases (50.6%), respectively (table 4). Overall, 157 cases (98.1%) had at least one of these two symptoms, which fulfilled the diagnostic criterion 2.

Radiological Imaging Findings

In this survey, we defined positive imaging findings as the presence of dilatation and/or air-fluid levels of the bowels. Figure 1 shows a typical abdominal radiograph of a CIPO patient with marked distention of the small



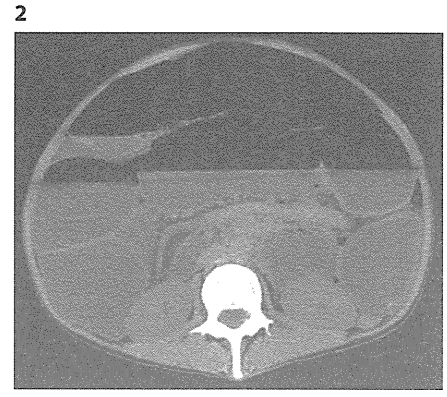


Fig. 1. Abdominal radiograph: marked distention of the intestine filled with a large amount of intestinal gas.
Fig. 2. Abdominal CT: markedly dilated intestinal loops and multiple air-fluid levels are observed. A large amount of small-intestinal gas occupies the greater part of the abdomen.

intestine and a large amount of intestinal gas. Figure 2 shows a typical CT image of a CIPO case. Among the 160 patients, 154 (96.2%) had positive imaging findings and 3 (1.9%) showed no positive findings; the status with regard to this finding was unknown in 3 cases (1.9%) (table 4a). Thus, 154 of the 160 cases (96.2%) showed dilatation of the bowel loops and/or air-fluid levels of the intestine on plain radiographs or CT images of the abdomen, which is included as a positive diagnostic criterion.

Duration of Disease

The number of patients with the criterion of disease duration >6 months was 141 (88.1%), and 16 (10.0%) had a disease duration <6 months; disease duration was unknown in 3 cases (1.9%) (table 4b).

Selected Method of Treatment

Our summarization of the responses to the questionnaire, where multiple answers were allowed, in relation to the selected method of treatment for each patient in the total of 160 cases (table 5) showed that medical conservative (drug) therapy was the most commonly selected treatment: it was selected in 135 cases (84.4%), diet in 107 cases (67.1%) and surgical treatment in 36 cases (22.5%). A total of 46 cases (28.8%) were treated by other methods, including home parenteral nutrition (intravenous hyperalimentation) in 33 cases (20.6%) and endoscopic intestinal decompression, ileus tube placement and enema in a few cases. One case (0.6%) received no treatment. The most commonly used drugs were mosapride citrate (5-HT4 receptor agonist), probiotics, Daikenchuto (herbal medicine), magnesium oxide, and others. Antacids such as proton pump inhibitors and H2 receptor antagonists were sometimes used in the cases treated conservatively (table 6).

As a result, 138 patients fulfilled all the diagnostic criteria, and the sensitivity of the proposed criteria for the diagnosis of CIPO in Japanese patients was 86.3%.

Table 5. Selected method of treatment (n = 160)

Treatment	Cases
Medication	135 (84.4)
Diet	107 (67.1)
Surgery	36 (22.5)
Others	46 (28.8)
Home parenteral nutrition	33 (20.6)
Endoscopic decompression	4 (2.5)
Ileus tube placement	2 (1.3)
Enema	1 (0.6)
No treatment	1 (0.6)

Figures in parentheses are percentages.

Table 6. Drugs used for treatment (n = 160)

Drugs	Cases
Mosapride citrate[1]	101 (63.1)
Daikenchuto[2]	83 (51.9)
Magnesium oxide	69 (43.1)
Probiotics	62 (38.8)
Proton pump inhibitor	45 (28.1)
Erythromycin	41 (25.6)
Pantothenic acid	36 (22.5)
Metoclopramide	34 (21.3)
Mucosal protective drugs	23 (14.4)
Domperidone	20 (12.5)
H2 receptor antagonist	19 (11.9)
Metronidazole	18 (11.3)
Itopride	16 (10.0)
Dimethicone	12 (7.5)
Calcium polycarbophil	11 (6.9)
Kanamycin	10 (6.3)
Somatostatin analogue	7 (4.4)
Loperamide	5 (3.1)
Sulpiride	5 (3.1)
Polymixin B	3 (1.9)
Albumin tannate	3 (1.9)
Other laxatives	45 (28.1)

Figures in parentheses are percentages.
[1] Mosapride is the 5-HT4 receptor agonist.
[2] Daikenchuto is a herbal medicine.

Discussion

CIPO is a serious digestive disease characterized by the disturbance of intestinal propulsive motility, which results in clinical features mimicking mechanical obstruction, in the absence of any mechanical occlusion [1–5]. Long-term outcomes are generally poor, with disabling and potentially life-threatening complications developing at a high frequency over time [9]. The diagnosis of CIPO is difficult and often delayed owing to the lack of biological markers and the symptomatic overlap with several other forms of digestive syndromes associated with similar gut motor dysfunction but different natural histories. The delay of correct diagnosis leads to repeated, useless and potentially dangerous surgical procedures.

Whole-gut transit scintigraphy and antroduodenal manometry are often performed in Western countries to evaluate gastrointestinal motility disorders [2]. In 1999, Di Lorenzo [10] proposed an algorithm for the evaluation of patients presenting with signs and symptoms suggestive of pseudo-obstruction. According to this algorithm, diagnosis of CIPO requires exclusion of mechanical obstruction by an abdominal X-ray series and/or contrast X-rays in patients with chronic signs and symptoms of bowel obstruction, as well as exclusion of potentially underlying causes of pseudo-obstruction. Manometory, scintigraphy and exploratory surgery with full-thickness biopsy are not absolutely necessary but may help confirm the diagnosis. On the other hand, Lacy [11] has proposed yet another diagnostic algorithm. For the diagnosis of CIPO, patients should have had symptoms for at least 6 months, and a stepwise approach is used to make the diagnosis of CIPO, generally including laboratory studies, radiological studies to exclude mechanical obstruction, tests to measure the gastrointestinal transit time and, if necessary, specialized tests of gastrointestinal motility, such as esophageal and antroduodenal manometry. In summary, previous algorithms emphasize that the diagnosis of CIPO requires at least chronic symptoms of bowel obstruction and exclusion of mechanical obstruction and, if necessary, manometry and scintigraphy to confirm the diagnosis.

Full-thickness biopsy of the small bowel should be performed in all patients with severe dysmotility of unknown etiology who are scheduled to undergo surgery for any reason, because of the potential to elucidate the pathophysiology of CIPO. Adoption of this procedure has revealed that neurogenic CIPO can be classified into two major forms, including degenerative neuropathy with hypoganglionosis, characterized by evidence of damage and/or marked reduction in the ganglion cells in the intestinal wall, and inflammatory neuropathy characterized by myenteric infiltration by inflammatory cells, and that myogenic CIPO is characterized by fibrosis or vacuolization of the inner circular muscle and/or the longitudinal muscle of the intestine [12–14]. Although full-thickness biopsy may not be absolutely necessary, it is an important procedure that helps to confirm the diagnosis of CIPO.

As mentioned above, gastrointestinal motility function tests, including whole-gut transit scintigraphy and manometry, and exploratory surgery with full-thickness biopsy of the small bowel are important; however, they are invasive in terms of patient tolerability. This is the reason why we were prompted to develop diagnostic criteria that would not necessitate the use of these special examinations.

Although a few diagnostic algorithms have been reported, no clear diagnostic criteria for CIPO have been established. Iida et al. [8] revealed that it took an average of >7 years from the initial symptoms before a correct

diagnosis of CIPO could be established, and therefore, emphasized the importance of a greater degree of awareness of this disease among physicians and the necessity of diagnostic criteria in order to shorten the period from the initial symptoms to correct diagnosis. Hongo et al. [6], who were co-researchers of the Survey Group, drafted interim diagnostic criteria referring to several textbooks and case reports. In addition, they discussed the usefulness of the interim diagnostic criteria with other collaborators specialized in gastrointestinal motility disorders, soliciting their opinions by e-mail, and laid down the proposed diagnostic criteria as shown in table 1. In our study, we investigated the clinical features of 160 patients and examined the validity of the proposed diagnostic criteria by calculating the diagnostic sensitivity. All the registered patients were diagnosed as CIPO based on the findings on plain abdominal X-ray, CT imaging, gastrointestinal endoscopy and, where necessary, barium enema and small-bowel follow-through. None of the patients underwent manometry, scintigraphy or exploratory surgery with full-thickness biopsy. Of the 160 patients, 138 fulfilled all the diagnostic criteria, and the sensitivity of the proposed criteria for the diagnosis of CIPO in Japanese patients was 86.3%. If the criteria included only 'No evidence of structural disease' (criterion 4) and 'Showing at least one of abdominal pain and abdominal bloating in the previous 12 weeks' (criterion 2), they would have shown higher sensitivity, but lower specificity, because patients with chronic constipation might be included as false-positives. However, most of these false-positives could be excluded based on criterion 1, i.e. 'Onset of one or more symptoms of bowel obstruction at least 6 months prior to the diagnosis', and on criterion 3, i.e. 'Dilatation and/or air-fluid levels of the bowels on plain abdominal X-ray, echo and/or CT images'.

The recognition rate of CIPO is not more than 92%, even in specialized gastroenterology institutes in Japan, which is not optimal. There seems to be an even poorer recognition rate among physicians and surgeons who are not specialized in gastroenterology. The recognition rate of CIPO in foreign countries does not seem to be too satisfactory either, given that no large-scale epidemiological studies have been reported and no clear diagnostic criteria for CIPO have been established. A greater awareness of the clinical features of CIPO among physicians would help limit unnecessary surgical procedures to the minimum.

Both the proposed diagnostic criteria and the previously described diagnostic algorithms have their own advantages and limitations. Previously described diagnostic algorithms are superior in terms of allowing systematic differential diagnosis; however, they are difficult to use for general physicians and need specialized invasive examinations. On the other hand, our proposed diagnostic criteria are superior to the previously described algorithms in terms of the ease of use for the diagnosis of CIPO by the general physician without specific examinations, and also the ease of use in clinical practice; however, they are inferior to the previously described algorithms in that they do not provide a stepwise diagnostic approach or systematic differential diagnosis. New diagnostic algorithms are needed that can complement the shortcomings of the proposed diagnostic criteria and can be used in combination with them.

The main limitation of this study is the lack of a previous gold standard with which to compare the results, and the lack of assessment of fulfillment of the criteria among other gastrointestinal motility disorders. The most important aim of establishing diagnostic criteria is to shorten the interval from the initial symptoms to correct diagnosis and referral to a specialist and to minimize the performance rate of unnecessary surgical procedures. Improved recognition of CIPO and practical use of the diagnostic criteria are urgently desired. In addition, further investigation is required to determine whether or not the proposed diagnostic criteria might also show a high sensitivity for patients in other countries. The proposed diagnostic criteria should be appropriately modified by consultation with additional researchers to make them more practical and internationally applicable.

Acknowledgement

This work was supported in part by Health and Labour Sciences Research Grants for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan to A.N.

Disclosure Statement

There are no conflicts of interest.

References

1 Dudley HA, Sinclair IS, McLaren IF, McNair TJ, Newsam JE: Intestinal pseudo-obstruction. J R Coll Surg Edinb 1958;3:206–217.

2 Manten HD: Pseudo-obstruction; in Haubrich WS, Schaffner F, Berk JE (eds): Bockus Gastroenterology, ed 5. Philadelphia, Saunders, 1995, pp 1249–1267.

3 Sutton DH, Harrell SP, Wo JM: Diagnosis and management of adult patients with chronic intestinal pseudoobstruction. Nutr Clin Pract 2006;21:16–22.
4 Anras S: The colon in the pseudo-obstructive syndrome. Clin Gastroenterol 1986;15:745–762.
5 Connor FL, Di Lorenzo C: Chronic intestinal pseudo-obstruction: assessment and management. Gastroenterology 2006;130:S29–S36.
6 Nakajima Group Research Report, Fiscal Year 2009 (chief investigator: Atsushi Nakajima). Research Group for the Survey of the Actual Conditions of the Epidemiology, Diagnosis and Treatment of CIIP in Japan. Research Project for Overcoming Intractable Diseases, Health Labour Sciences Research Grant. Yokohama, Sanou Printing Ltd, 2010, pp 1–42.
7 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.
8 Iida H, Inamori M, Sekino Y, Sakamoto Y, Yamato S, Nakajima A: A review of the reported cases of chronic intestinal pseudo-obstruction in Japan and an investigation of proposed new diagnostic criteria. Clin J Gastroenterol 2011;4:141–146.
9 Stanghellini V, Cogliandro RF, De Giorgio R, Barbara G, Cremon C, Antonucci A, Fronzoni L, Cogliandro L, Naponelli V, Serra M, Corinaldesi R: Natural history of intestinal failure induced by chronic idiopathic intestinal pseudo-obstruction. Transplant Proc 2010;42:15–18.
10 Di Lorenzo C: Pseudo-obstruction: current approaches. Gastroenterology 1999;116:980–987.
11 Lacy BE: Chronic intestinal pseudo-obstruction. The Association of Gastrointestinal Motility Disorders, Inc. (AGMD). http://www.agmd-gimotility.org/lacycip.pdf.
12 Amiot A, Cazals-Hatem D, Joly F, Lavergne-Slove A, Peuchmaur M, Bouhnik Y, Bedossa P, Messing B: The role of immunohistochemistry in idiopathic chronic intestinal pseudoobstruction (CIPO): a case-control study. Am J Surg Pathol 2009;33:749–758.
13 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.
14 Moore SW, Schneider JW, Kaschula RO: Unusual variations of gastrointestinal smooth muscle abnormalities associated with chronic intestinal pseudo-obstruction. Pediatr Surg Int 2002;18:13–20.

S-2. アレルギー疾患とプロバイオティクス

松本健治
国立成育医療研究センター研究所免疫アレルギー研究部

アレルギー疾患児の乳幼児期の腸内細菌叢には乳酸菌群が少なく，好気性菌が多いことが疫学的に報告されている。アレルギー疾患の発症予防を行う事を目的として，新生児期に経口的に乳酸菌を投与する介入研究がこれまでにいくつか行われてきた。最近，これらの報告の meta-analysis の結果が報告され（J Allergy Clin Immunol 2008;121:116），妊娠末期の母胎および新生児に対する乳酸菌の投与はアトピー性皮膚炎の発症を有意に抑制するとされている。しかし，乳酸菌の投与はアレルギー感作や他のアレルギー疾患の発症には全く影響を与えないことも明らかになってきている。そして最も重要な，プロバイオティクスのアレルギー疾患に対する効果の作用機序はほとんど明らかとなっていない。

今回はこれらの現状を概説して問題点を整理し，今後の研究の方向性について話題を提供したい。

S-3. 化学療法後の悪性新生物患児への probiotic 投与の有効性について

永田 智[1)2)]，和田万里子[1)2)]，清水俊明[1)]，山城雄一郎[2)]，朝原 崇[3)]，野本康二[3)]
順天堂大学医学部小児科[1)]，順天堂大学大学院プロバイオティクス研究講座[2)]，ヤクルト本社中央研究所[3)]

【目的】化学療法後の悪性新生物の患児において，probiotics である *Bifidobacterium breve* の感染予防効果と腸内環境是正効果について検討した。

【方法】当科に入院し化学療法を施行された白血病などの悪性新生物患児 42 例をランダムに *B.breve* 投与群とプラセボ群に分け，腸内細菌ならびに便中有機酸の profile，患者の臨床経過，末梢血 NK 細胞活性等について検討した。

【結果】*B.breve* 投与群では，発熱の回数，経静脈的抗菌薬の使用量が，プラセボ群よりともに有意に減少していた。また，プラセボ群では，化学療法後の便中の *Enterobacteriaceae* の菌数が有意に増加していた。さらに，*B.breve* 投与群では，化学療法前後で便中有機酸の産生は低下せず，便 pH も 7.0 以下を保っていた。

【結語】化学療法により低免疫状態に陥った患児に *B.breve* を投与することにより，有機酸産生促進を介して腸内環境が是正され，有毒なグラム陰性桿菌などの腸内増殖を抑制し，感染予防効果を示すことが示唆された。

S-4. Hirschsprung 病類縁疾患に対する synbiotics の投与経験

長谷川泰浩[1)]，清原由起[1)]，中長摩利子[1)]，庄司保子[1)]，位田 忍[1)]，窪田昭男[2)]
大阪府立母子保健総合医療センター消化器・内分泌科[1)]，同　小児外科[2)]

長期的な栄養管理を必要とする Hirschsprung 病類縁疾患などの慢性機能性腸閉塞症の予後は不良である。その理由として腸内細菌叢のコントロールが困難であるために結果として bacterial translocation を発症しやすく容易にカテーテル（CV）感染症，重症敗血症に至る。また一方で繰り返す CV 感染は頻回の CV 入れ替えを必要とするため静脈ルートの減少につながり将来的に小腸移植が困難になることもあり腸内細菌叢のコントロールは極めて重要な課題である。われわれの施設では Hirschsprung 病類縁疾患に対し腸内細菌叢をコントロールする目的で Yakult 中央研究所協力による共通プロトコールに準じて synbiotics を投与している。全例で経腸栄養剤を用い一部症例では中心静脈栄養も併用している。それぞれ便細菌叢の解析，腹部単純 X-p，臨床経過，血液検査を行い評価した。症例によりばらつきを認めるが便総菌数の増加，腹満を含む臨床症状の改善を認め，一方で肝機能異常は認めなかった。今回われわれは比較的長期間に渡り synbiotics を導入し観察できているためその有用性を報告する。

S-5. 乳酸菌投与・非投与症例の血流感染と臨床背景のデータマイニングによる解析

松岡喜美子[1)]，田尻 仁[1)]，横山茂樹[2)]
大阪府立急性期・総合医療センター小児科[1)]，高電工業株式会社インフォメディカルシステム開発部[2)]

血流感染患者の菌検出，乳酸菌製剤投与，患者背景を解析した結果，乳酸菌投与群では，血流感染の軽減や耐性菌感染の抑制の可能性が導出できたので報告する。

【目的】血流感染患者の血中菌検出の有無に対する乳酸菌製剤投与・非投与における感染様相への影響度を解析する。

【対象】2002 年 1 ～ 12 月の血流感染患者の血液培養検体 1,291 件の臨床背景と検出菌。

【方法】医療データマイニングシステム ICONS Miner

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 Otake[1], Mikihiro Inoue[1], Yuhki Koike[1], Kohei Matsushita[1], Toshimitsu Araki[1], Yoshiki Okita[1], Koji Tanaka[1], Katsunori Uchida[2], Noriko Yodoya[3], Shotaro Iwamoto[3], Katsuhiro Arai[4], Masato Kusunoki[1]

[1] *Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Tsu, Mie, Japan;*
[2] *Department of Pathology, Mie University Graduate School of Medicine, Tsu, Mie, Japan;*
[3] *Department of Pediatrics, Mie University Graduate School of Medicine, Tsu, Mie, Japan;*
[4] *Division 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/mm^3) 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.

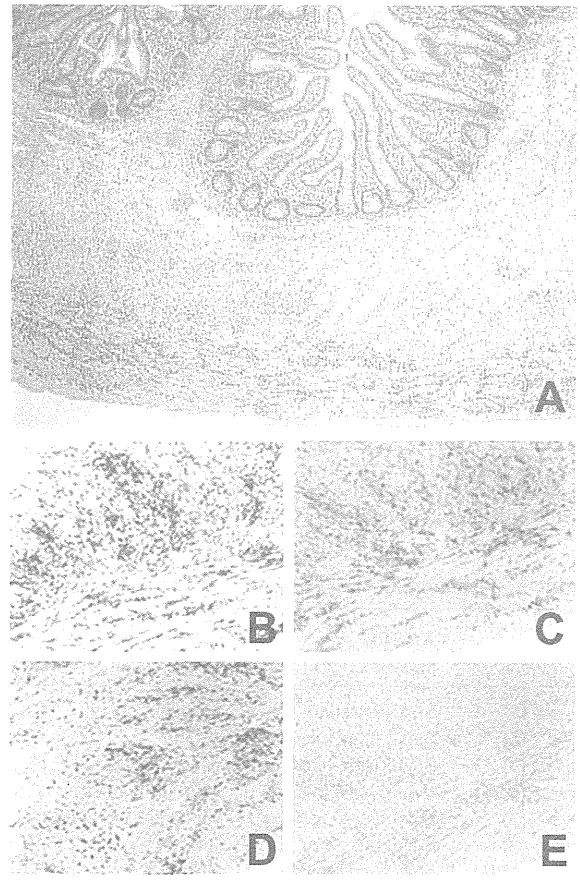


Figure 1. Immunostaining of the biopsy samples. (**A**), Full-thickness biopsy of the small intestine. Histological findings show inflammation in the muscularis propria of the small intestine. Intestinal mucosa and submucosa were mostly normal. Ganglion cells in the submucosal and myenteric plexuses 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×)

3. Discussion

CIPO is a rare, severe, disabling disorder characterized 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-*Yersinia pseudotuberculosis*	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, Ciclosporin, 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

1. Connor FL, Di Lorenzo C. Chronic intestinal pseudo-obstruction: Assessment and management. Gastroenterology. 2006; 130 (2 Suppl 1):S29-36.
2. 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.
3. Mann SD, Debinski HS, Kamm MA. Clinical characteristics of chronic idiopathic intestinal pseudo-obstruction in adults. Gut. 1997; 41:675-681.
4. 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)
5. Smith VV, Milla PJ. Histological phenotypes of enteric smooth muscle disease causing functional intestinal obstruction in childhood. Histopathology. 1997; 31:112-122.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: Virtuous intentions, malign consequences. Liver. 2001; 21:225-232.
13. Tötterman TH, Nisell J, Killander A, Gahrton G, Lönnqvist B. Successful treatment of pure red-cell aplasia with cyclosporin. Lancet. 1984; 22:693.
14. 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.
15. Litwin SD, Zanjani ED. Lymphocytes suppressing both immunoglobulin production and erythroid differentiation in hypogammaglobulinaemia. Nature. 1977; 3:57-58.
16. Nidorf D, Saleem A. Immunosuppressive mechanisms in pure red cell aplasia – A review. Ann Clin Lab Sci. 1990; 20:214-219.
17. 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.
18. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo