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Intestinal Lymphangiectasia – A Report of Three Chinese Children in Malaysia

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ABSTRACT

This is a report of 3 Chinese children with intestinal lymphangiectasia in Malaysia. Two children responded to a low fat diet and medium-chain triglyceride supplement. The third child has recurrent chylous ascites. None of the children has recurrent infections despite low CD4+ cells and low levels of IgG and IgA.

Intestinal lymphangiectasia is a rare congenital disorder of the mesenteric lymphatic that leads to the obstruction of the lymphatics of the intestine and protein losing enteropathy. Restriction of dietary fat intake will usually result in remission. Recurrent chylous ascites is a problem and management can be difficult.

Keywords: intestinal lymphangiectasia, children, chronic diarrhoea, Malaysia

INTRODUCTION

Protein losing enteropathy can occur in association with a wide variety of gastrointestinal and non-gastrointestinal diseases in paediatric patients[1]. Its causes are varied and can be divided according to the mechanisms of protein loss: abnormal gut permeability or obstruction to lymphatic flow[1]. Causes of altered gut permeability include Crohn's disease, ulcerative colitis, coeliac disease, autoimmune enteropathy, and allergic gastroenteropathies. Intestinal lymphangiectasia is a rare malformation of the mesenteric lymphatics that leads to obstruction of lymphatic flow and protein losing enteropathy. It may be congenital or acquired[2,3] and was first described by Waldmann et al in 1961[4].

We report three cases of intestinal lymphangiectasia that were seen in the University Hospital, Kuala Lumpur. They were young Chinese children who presented with chronic diarrhoea, abdominal distension, hypoalbuminaemia and lymphopenia. It is an important condition to be considered in the differential diagnosis of chronic diarrhoea in children.

Case 1

A 10-month-old Chinese girl was referred with a 4-month history of chronic diarrhoea and progressive abdominal distension since the age of 2 months. Substitution of feeds to a protein hydrolysate (Pregestimil®, Mead Johnson) failed to improve her symptoms. Clinically, there was lymphoedema involving the hands, ankles and feet. The abdomen was grossly distended with ascites. Dipstick analysis of urine for protein was negative. Other investigation results are shown in Table I. Her serum IgG and IgA levels were low but IgM was normal. Barium meal and follow through showed that there were coarse mucosal folds and flocculation in the small intestine. Histological examination of a proximal jejunal biopsy was consistent with intestinal lymphangiectasia, showing grossly dilated lymphatics. The child was started on medium chain triglyceride (MCT) based formula (Portagen®, Bristol-Myers). Over time, the diarrhoea subsided and the oedema improved. Now at 9 years of age, the child has no ascites or lymphoedema of the limbs, and has normal growth parameters. She is on a low fat diet supplemented with MCT and fat-soluble vitamins. A slight increase in the intake of fat containing foods will cause relapse of her symptoms with diarrhoea lasting for two to three days. Her albumin levels range between 19 and 21 g/L. She still has persistent lymphopenia (absolute lymphocyte counts ranging between 2.68 and 1.06 x 10^9/L) but does not suffer from severe infections.

Case 2

A 14-month-old Chinese girl presented with diarrhoea of three weeks' duration and progressive abdominal distension of one week's duration. She had intermittent abdominal distension and occasional diarrhoea since 3 months old. On examination, she had generalised pitting oedema of the hands and feet and gross ascites. There was obvious wasting of her buttock and thigh muscles. Dipstick analysis for urinary protein was negative. Other investigation results are shown in Table I. Barium meal of the upper gastrointestinal tract revealed thickening of the bowel wall and vulvulae conniventer involving the jejunum and ileum. CT-scan of the abdomen showed thickened small intestinal wall of the small intestine with ascites. An upper gastrointestinal endoscopy showed numerous tiny white spots scattered with clear-cut margin in the duodenum. Histological examination of the biopsied materials was normal. A peroral jejunal biopsy with a Crosby capsule was performed. The typical appearance of intestinal lymphangiectasia was not apparent as the lesion was probably patchy. However, the diagnosis of intestinal lymphangiectasia was based on strong circumstantial evidence such as chronic diarrhoea, presence of ascites, hypoalbuminaemia and lymphopenia. The child was

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Table I – Results of laboratory investigations in the 3 cases of intestinal lymphangiectasia

Results of investigations	Case 1	Case 2	Case 3
Haemoglobin (g/L)	131	151	108
Total white cells (x 10^9/L)	6.7	15.7	7.4
Neutrophils (%)	76	77	75
Lymphocytes (%)	15	8	23
Eosinophils (%)	5	4	-
Monocytes (%)	4	11	2
Lymphocyte count (x 10^9/K)	1.005	1.256	1.702
Platelets (x 10^9/L)	413	176	405
Serum albumin (g/L)	27	12	24
IgG (mg/dl) (Normal: 931 – 1916)	267	314	210
IgA (mg/dl) (Normal: 70 – 473)	45	< 7	42
IgM (mg/dL) (Normal: 34 – 265)	113	27	42

Table II – T and B cells enumeration of Case 2 and Case 3

Description	Case 2 Cells x 10^9/L (%)	Case 3 Cells x 10^9/L (%)	Reference range Cells x 10^9/L (%)
Peripheral T lymphocytes	0.752 (34)	0.453 (49)	1.7 – 5.5 (53 – 71)
CD4+ T cells	0.221 (10)	0.231 (25)	1.2 – 3.7 (28 – 52)
CD8+ T cells	0.509 (23)	0.203 (22)	0.6 – 2.0 (13 – 31)
NK cells	0.088 (4)	0.046 (5)	0.2 – 0.7 (2 – 12)
Total B lymphocytes	0.885 (40)	0.111 (12)	0.8 – 2.7 (19 – 38)
CD4/CD8 ratio (T cells)	0.43	1.14	1.1 – 3.6

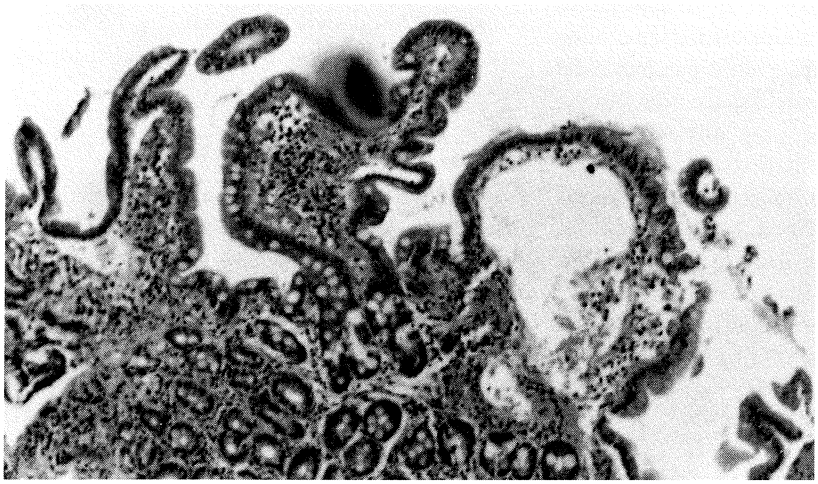

Fig 1 – Photomicrograph of small bowel biopsy of Case No. 3 showing dilated lymphatics within submucosa that is characteristic of intestinal lymphangiectasia.

started on Portagen. She was also given intravenous human albumin infusion to relieve the ascites. Presently at two years, she is free of diarrhoea while on a low fat diet with lipid-soluble vitamin supplementation. Her abdomen was still distended at the last follow-up, but no limb oedema was noted. Her latest serum albumin level was 21 g/L; absolute lymphocyte count 2.1 x 10^9/L. T and B cells enumeration are shown in Table II. The absolute lymphocyte count was low with a markedly reduced number of CD4+ T helper cells and a marginally low CD8+ T suppressor cells. The natural killer cells were reduced and the total B lymphocytes were normal.

Case 3

A 6-month-old Chinese boy was referred to us due to progressive abdominal distension causing respiratory distress. Abdominal distension and non-pitting oedema of the left hand and mid-forearm were noted from birth. The child was tachypnoeic, with gross ascites and was small for his age. Urinalysis for protein was negative. Other investigation results are shown in Table I. Several abdominal paracenteses had to be performed to relieve the tense ascites. Chylous fluid was also obtained. Supplemental parenteral nutrition was started because of poor oral intake. A laparotomy revealed extensive dilated and leaking blebs of lymphatics on the right paracolic gutter around the abdominal aorta and superior mesenteric artery as well as the serosal surface of the small intestine, confirming the diagnosis of intestinal lymphangiectasia. In an attempt to relieve the child of ascites which had caused respiratory embarrassment, a peritoneo-venous shunt was created. Post-operatively, his ascites improved but he had persistent soft stool while on ordinary infant formula and soft diet. The ascites and lymphoedema worsened again 6 months after the first admission. Around this time, he began to have diarrhoea. A small bowel biopsy was performed to exclude other small bowel enteropathy. Histological examination showed typical dilatation of lymphatics in the intestinal mucosa (Fig 1) with a normal villous height. T and B cells enumeration showed low CD4+, CD8+ T cells and B cells (Table II). He was started on Portagen with albumin infusion to reduce his ascites. A second laparotomy revealed a blocked peritoneo-venous shunt. The shunt was clear of proteinaceous clots and flushed with heparinised saline. Post-operatively, his diarrhoea was put under control and his nutritional status improved. The ascites was markedly reduced but lymphoedema of limbs remained. He is currently free of respiratory distress and is able to tolerate a low fat diet with porridge and rice. No severe infections were noted.

DISCUSSION

Intestinal lymphangiectasia as a cause of protein losing enteropathy was first described by Waldmann et al in 1961[4]. It may be congenital or acquired. Primary intestinal lymphangiectasia has been more frequently described in children and young adults[5,6]. Our cases are very much similar to the two Chinese children reported by Quak et al from Singapore[7]. All of them had chronic diarrhoea and ascites. Other features included failure to thrive, generalised oedema, and limb oedema which may be asymmetrical. Chronic diarrhoea is not a universal feature[5,6]. The mechanism of diarrhoea and multiple absorptive defects are related to an anatomical block of the intestinal lymphatic system, causing intense intercellular oedema of the mucosal cells lining the lumen of the intestines[8]. Similar blockade of the lymphatic system of the

limbs cause lymphoedema of the peripheries which is seen in this condition. Lymphangiographic studies of the lymphatic system of the affected limbs with contrast medium had shown abnormally dilated lymphatics with enlarged lymph glands found along the course of these channels[8,9].

Diagnosis of intestinal lymphangiectasia can be confirmed by biopsy of the duodenum, jejunum or ileum. The hallmark of the lesion of this disorder is gross dilatation of the lymphatics of the lamina propria of the small bowel[9]. This frequently distorts and enlarges individual villi. There is, however, no villous atrophy. The nature of the involvement of the small intestine may be patchy[8,10]. Upper gastrointestinal endoscopy may show bleb-like white pebbly nodules or cystic nodules[4,11]. These are cavities of dilated lymphatics filled with chylomicrons and precipitated lymph proteins[7]. This was seen in Case 2. Although histological examination of the biopsied materials did not reveal typical dilated lymphatics, however, strong circumstantial evidence such as history of chronic diarrhoea, presence of ascites, failure to thrive and the demonstration of hypoalbuminaemia and lymphopenia are sufficient to make a firm diagnosis of intestinal lymphangiectasia, even if typical histological appearance was absent.

Radiological examination of the intestinal tract, namely barium meal, and follow through in intestinal lymphangiectasia has been well described[6].Typical radiological appearances include thickened mucosal folds, distal dilution of barium, dilatation of the lumen and smooth nodular protusions into intestinal lumen[9,12]. This appearances were seen in the first 2 cases.

The immunological abnormalities of intestinal lymphangiectasia are a deficiency in cell-mediated immunity and hypogammaglobulinaemia. The commonest immunological abnormalities seen are reduced concentrations of immunoglobulins IgG, IgA, and IgM and lymphopenia; as seen in all three cases. Other abnormalities include skin allergy, impaired homograft rejection and poor *in vitro* lymphocyte proliferative responses[13-15]. The lymphopenia is due to the loss of recirculating, long-lived CD4+ T helper cells into the lumen of the intestine[14,16]. This results in a marked reduction of the percentage and absolute numbers of CD4+ T helper but normal CD8+ T suppresser cells[17]. In cases 2 and 3, the absolute numbers of CD4+ T helper cells were markedly reduced. The CD8+ T suppresser cells and total B lymphocytes in case 3 were similarly reduced. Recurrent bacterial infections and infections with atypical mycobacteria, warts and cellulitis had been reported. Of the 18 patients studied by Strober et al, two died after prolonged periods of debilitation associated with many bacterial infections[13]. One of six patients described by Tift and Lloyd developed serious infections[5]. We noticed that despite the immunological abnormalities shown in all our 3 cases, none of them had increased incidence of infection to date.

Medical treatment of intestinal lymphangiectasia is life-long, since the abnormality is rarely sufficiently localised to permit cure by excision of the abnormal bowel. Fat intake should be restricted, and the diet supplemented with medium chain triglycerides and lipid soluble vitamin. The rationale for the use of MCT (C6:0 to C12:0) is that it bypasses the intestinal lymphatic system and thoracic duct and enters the portal venous system directly[18]. Supplementation with MCT has been shown to result in marked improvement in general well-being, rapid and sustained improvement in oedema, cessation of diarrhoea and improvement in growth[5,19]. In infancy, therapy can be achieved by the use of ready-made formula, such as Portagen which is exclusively based on MCT. In older children, a strictly fat-free diet is often unpalatable and usually unenforceable. MCT supplementation will improve the palatibility of the diet and enhance compliance. In some patients, additional supplementation with calcium salts and water-soluble forms of fat soluble vitamins are necessary[20].

Other forms of medical therapy were described recently. High dose daily corticosteroids had been used in three patients in another study; the youngest was 12 years old, with evidence of inflammatory process causing protein-losing enteropathy[21]. Oedema and hypoalbuminaemia disappeared in all three patients. Two patients remained in remission after discontinuation of steroids. Octreotide had been reported to maintain remission in a patient with intestinal lymphangiectasia and protein-losing enteropathy secondary to inflammatory process after remission was achieved by corticosteroids[22]. Antiplasmin therapy was reported to be effective in a patient with lymphangiectasia and increased plasma fibrinolytic activity, who did not respond to dietary therapy[23]. The subjects in these reports were mainly older patients with underlying inflammatory process, unlike our patients who were young infants with primary intestinal lymphangiectasia. It is likely that the mainstay of treatment for primary intestinal lymphangiectasia is the use of low fat, high protein, MCT diet[24].

Extravasation of chyle into the peritoneal cavity from ruptured blebs of the dilated intestinal lymphatics at the serosal surface can cause troublesome chylous ascites[25]. Its management is aimed at controlling the ascites and treating the underlying cause. Total parenteral nutrition, oral alimentation with low fat, high protein diets have been the traditional treatment of such children. However, this management approach has not been found to be very successful[26]. Repetitive abdominal parancentesis is sometimes necessary. Surgical anastomosis between dilated lymphatics and the long saphenous vein has been reported[27]. In a review of 58 children with chylous ascites, Unger et al[26] noted that cure was significantly more likely when the procedure was of a definitive nature than just exploration and drainage. Patients in whom chylous ascites recurs upon resumption of regular oral diet should undergo surgical exploration in search of the source of leak. If all these

fail, a peritoneo-venous shunt (Levine shunt) should be inserted to divert the ascitic fluid to the systemic circulation. In Case 3, the extensive nature of the dilated lymphatics within the peritoneal cavity precluded a definitive procedure such as total excision of the dilated lymphatics. Therefore a peritoneo-venous shunt was performed. Although this resulted in some improvement, the shunt was found to be blocked six months post-operatively and a revision was therefore necessary.

In conclusion, intestinal lymphangiectasia is a rare cause of chronic diarrhoea in childhood. It is due to an abnormal lymphatic system which can involve the gut and the limbs, causing non-pitting oedema of the limbs, chronic diarrhoea with steatorrhoea, lymphopenia, hypoalbuminaemia and low circulating immunoglobulin levels. This disorder can be a primary disorder of the mesenteric lymphatics, or secondary to cardiovascular anomalies or involvement of mesenteric lymphatics in certain disease conditions. Intestinal lymphangiectasia in infants and children is usually a primary disorder. Diagnosis can be confirmed by demonstration of the typical dilated lymphatics of small bowel biopsy. Dietary restriction on fat intake is the mainstay of treatment and a life-long commitment. Most of these children are free of severe infections and enjoy relative good health.

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