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The diagnostic value of capsule endoscopy in children with intestinal lymphangiectasia

Jie Wu1, Zhiheng Huang1, Min Ji2, Zhinong Jiang3, Yuhuan Wang1, Zifei Tang1, Ying Huang1

1Gastroenterology Department/Endoscopy Center, and 2Department of Radiology. Children’s Hospital. Fudan University. Shanghai, China. 3Department of Pathology. Sir Run Run Shaw Hospital. Zhejiang University School of Medicine. Hangzhou, Zhejiang. China

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Correspondence: Ying Huang, MD, PhD. Department of Gastroenterology. Children’s Hospital of Fudan University. 399 Wanyuan Rd. Minhang District. Shanghai, China
e-mail: yhuang815@163.com

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List of abbreviations: CT: computed tomography; IL: intestinal lymphangiectasia; MRI: magnetic resonance imaging; VCE: video capsule endoscopy.

ABSTRACT
Background: intestinal lymphangiectasia is an unusual cause of protein-losing enteropathy due to either congenital malformation or obstruction of the intestinal lymphatics. However, few reports have investigated the use of video capsule endoscopy in children with intestinal lymphangiectasia. This study was performed to evaluate the diagnostic value of video capsule endoscopy for pediatric intestinal
lymphangiectasia.

**Methods**: in this retrospective study, all patients who underwent video capsule endoscopy between January 2014 and July 2020 were included. Clinical information and video capsule endoscopy data were analyzed.

**Results**: twelve children were enrolled, 7 males and 5 females, with an age at disease onset of 4.5 (range: 3.2-9.3) years and a disease duration of 12.0 (range: 1.3-30.0) months. The most common symptoms were hypoproteinemia (10, 83.3 %), diarrhea (7, 58.3 %), edema (6, 50.0 %), and abdominal pain (3, 25.0 %). Eight patients had low lymphocyte counts, whereas 10 had reduced serum albumin levels (23.2 ± 5.8 g/L). Video capsule endoscopy revealed an overall white snowy appearance due to the presence of whitish, swollen villi in all patients. Regarding the macroscopic lesions of lymphangiectasia, 7 cases involved the entire small bowel from the duodenum to the ileocecal valve, while 5 cases involved part of the small bowel. All patients were treated with medium-chain triglyceride diets, and albumin infusions were administered to 10 patients; sirolimus treatment was administered to 3 patients. At the last follow-up, 5 patients still had hypoalbuminemia and one patient had died of intestinal lymphoma.

**Conclusion**: video capsule endoscopy is useful for the diagnosis of intestinal lymphangiectasia and should be applied as a valuable and less invasive examination to confirm or establish a diagnosis.

**Keywords**: video capsule endoscopy. Children. Intestinal lymphangiectasia. Hypoalbuminemia.

**INTRODUCTION**

Intestinal lymphangiectasia (IL) is a rare disease characterized by dilatation and rupture of intestinal lymphatic channels, leading to protein-losing enteropathy (1). IL is defined as the dilation of existing mucosal, submucosal or subserosal lymphatics within the gastrointestinal tract. Furthermore, IL causes the loss of lymph fluid into the
gastrointestinal tract, resulting in the development of hypoproteinaemia, edema, lymphocytopenia, hypogammaglobinemia, and immunologic anomalies (2). IL is easily diagnosed by upper gastrointestinal endoscopy and confirmed by pathology if the lesions involve the duodenum. However, the presence of patchy areas of lymphangiectasia in the jejunum and ileum cannot be detected because of the length limitation on upper gastrointestinal endoscopy. Thus, it is necessary to explore the entire small bowel to determine the extent of lymphangiectasia.

The development of video capsule endoscopy (VCE) was a milestone in gastroenterological endoscopy. The United States Food and Drug Administration approved the use of CE for the evaluation of small-bowel diseases in adults in 2001 (3). In 2004, VCE was approved for children aged 10 years or older. Overall, VCE is an important diagnostic tool for signs of small-bowel diseases, such as patchy areas of lymphangiectasia in the jejunum and ileum (4,5).

The diagnosis of IL via VCE in pediatric patients has been documented in only a few case series (6). In general, data are lacking, especially for Chinese children. This study was performed to analyze the clinical features and describe the feasibility and value of the use of VCE for the diagnosis of IL, shedding new light on the clinical application of VCE.

MATERIALS AND METHODS

This retrospective study was approved by the Ethics Committee of the Children’s Hospital of Fudan University. An informed consent for participation was obtained from the parents or legal guardians of the patients. In this study, all patients who were diagnosed with IL who underwent VCE between January 2014 and July 2020 were included.

The OMOM capsule endoscopy system was used in this study, with a diameter of 11.0 mm and a length of 25.4 mm, purchased from Jinshan Science & Technology (Chongqing, China). The intestinal preparation procedure was described previously (7). The diagnosis of IL was made via upper gastrointestinal endoscopy, VCE, and histological pathology. Clinical information, VCE data, and follow-up data were analyzed.
RESULTS

Patient characteristics
From January 2014 to July 2020, 12 children were diagnosed with IL by VCE at the Children’s Hospital of the Fudan University; 7 were male and 5 were female. Among these patients, the age at disease onset was 4.5 (range: 3.2-9.3) years, and disease duration was 12.0 (range: 1.3-30.0) months. No patients had a family history of IL.

Clinical and laboratory data
The clinical features of the patients varied. The most common symptoms were hypoproteinemia (10, 83.3 %), diarrhea (7, 58.3 %), edema (6, 50.0 %), and abdominal pain (3, 25.0 %) (Table 1). Ascites and pleural effusion were detected by ultrasound in 4 patients.

According to laboratory tests, 8 patients had low lymphocyte levels and 10 had reduced levels of serum albumin (23.2 ± 5.8 g/L) (Table 2). Furthermore, 5 patients had anemia, with hemoglobin levels ranging from 98 g/L to 110 g/L.

Additional investigations were performed to detect a possible infectious etiology of IL. However, tests for human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), herpes simplex, rubella virus, and parasites were negative, while case 3 was positive for Epstein-Barr virus (EBV) DNA.

VCE and imaging data
Gastroscopic assistance for capsule introduction was needed in 9 out of the 12 children. In all children, the capsule was expelled in the stool and no adverse effects occurred. The average small-bowel transit time was 331.6 ± 184.8 min.

VCE showed an overall white, snowy appearance due to the presence of whitish, swollen villi in all cases. Seven children had macroscopic lesions of lymphangiectasia involving the entire small bowel from the duodenum to the ileocecal valve (Fig. 1A-C); only part of the small bowel was affected in five patients (Fig. 1D-F). All patients underwent upper gastrointestinal endoscopy before VCE, and 7 were suspected of
having IL based on the presence of macroscopic lesions of lymphangiectasia (Fig. 1G-H). Seven patients underwent enteroscopy and 3 were suspected of having IL based on the presence of macroscopic lesions of lymphangiectasia (Fig. 1I). IL was confirmed by the histologic analysis of duodenal and jejunal biopsy specimens, which showed dilated intestinal lymphatics (Fig. 2). Six patients were diagnosed with IL by duodenal biopsy after gastrointestinal endoscopy. Five patients with a normal duodenum underwent enteroscopy to obtain jejunal biopsies. Moreover, magnetic resonance imaging (MRI) and computed tomography (CT) showed thickening of the walls of the jejunum and ileum (Fig. 3).

**Treatment and follow-up**

All patients were treated with a medium-chain triglyceride (MCT) diet; albumin infusions were administered to 10 patients because of severe hypoproteinemia. Ten patients underwent follow-up and 2 were lost to follow-up. Case 3 died of intestinal T-cell lymphoma. Case 12 was diagnosed with mesenteric lymphangioma. Cases 9, 10 and 12 were administered sirolimus treatment. At the last follow-up, 5 patients still had hypoproteinemia and needed hospital follow-up and albumin infusions regularly.

**DISCUSSION**

This study reports the characteristics of 12 children with IL who underwent small-bowel examination by VCE. IL may be characterized as a disorder involving dilated intestinal lacteals causing a loss of lymph into the lumen of the small intestine, and resulting in hypoproteinemia, hypogammaglobulinemia, hypoalbuminemia, and reduced numbers of circulating lymphocytes or lymphopenia (8). Mucosal lesions can be detected in the duodenum of children during gastroscopic examination if IL is suspected. However, enteroscopy and VCE are needed for lesions below the horizontal part of the duodenum, jejunum, and ileum (9). Overall, VCE can aid in achieving a diagnosis when patients have distal disease of the small bowel.

We performed a literature review of IL patients diagnosed by VCE. In 2006, the study by P. Chamouard diagnosed two authentic adult cases with protein-losing enteropathy via VCE. Thus showing that the technique is useful in cases of protein-losing
enteropathy to enable the identification of intestinal lymphangiectasia, and to specify
the location after ruling out other disorders liable to induce protein-losing
gastrointestinal syndromes (4). We have found several articles regarding the
usefulness of VCE in children with IL (6,10,11). The first series was published by
Christine Rivet et al., and included 4 children aged 6, 10, 15 and 17 years. Our study
involved 12 children diagnosed with IL by VCE, including 5 with partial small-bowel
involvement and 7 with complete small-bowel involvement.

The diagnosis of IL is confirmed if diffuse snow-white dots, villous prominence, and
chyle are observed in the small-bowel mucosa (12). A high-fat meal challenge before
endoscopy can improve the diagnostic yield. Pathology shows the dilation of existing
mucosal, submucosal, or subserosal lymphatics within the gastrointestinal tract (1,13).
For the diagnosis of primary IL, secondary factors such as autoimmune disease, tumor
and infectious diseases (tuberculosis, parasites) should be excluded (14-16).

Endoscopic examination and duodenal biopsy are standard criteria for the diagnosis of
intestinal lymphangiectasia.

For patients with hypoproteinemia, it is reasonable to begin the evaluation with upper
endoscopy or colonoscopy. Furthermore, VCE should be performed if the underlying
etiology remains uncertain or a small-bowel etiology is suspected. VCE offers a
relatively easy way to view the mucosa of the entire small bowel, to make an educated
guess based on the gross appearance, and to exclude other disorders possibly
responsible for protein loss (13).

IL is often associated with diarrhea and abnormal laboratory findings. The main
laboratory findings in IL are reduced lymphocyte counts and low calcium ion, serum
albumin, and gamma globulin (IgA, IgG, IgM) levels. Clinical history, physical
examination, and laboratory data are important clues to the diagnosis of IL (17).
Moreover, nutritional treatment is very important and a low-fat diet with
supplementary MCT is the cornerstone of the medical management of primary IL (18).

Our study had limitations. VCE could not be used in more IL patients due to difficulty
swallowing the device. Lymphoscintigraphy is another efficient way to detect intestinal
lymphangiectasia. Unfortunately, there are no lymphoscintigraphy instruments in our
hospital because of the limited resources. Therefore, lymphoscintigraphy could not be
performed.

CONCLUSIONS
Both primary and secondary causes of IL should be evaluated to determine the appropriate management of affected patients. VCE may be useful for diagnosing IL and determining both the extent of the lesions and appropriate follow-up.
REFERENCES


Table 1. Clinical features of IL patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 12</th>
</tr>
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<tbody>
<tr>
<td>Sex (male : female)</td>
<td>7 : 5</td>
</tr>
<tr>
<td>Age at admission (years)</td>
<td>7.1 ± 3.8</td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
<td>4.5 [3.2-9.3]</td>
</tr>
<tr>
<td>Duration time (months)</td>
<td>12.0 [1.3-30.0]</td>
</tr>
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</table>

**Symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>8</td>
</tr>
<tr>
<td>Edema</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
</tr>
<tr>
<td>Ascites and pleural effusion</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2. Laboratory findings in IL patients

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Value</th>
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<tbody>
<tr>
<td>Lymphocyte (× 10^9/L)</td>
<td>1.77 ± 0.97 (1.2-4)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>23.50 ± 5.66 (40-55)</td>
</tr>
<tr>
<td>Prealbumin (mg/L)</td>
<td>216.58 ± 63.30 (200-400)</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td>2.01 ± 0.23 (2.2-2.6)</td>
</tr>
<tr>
<td>IgG (g/L)</td>
<td>4.41 ± 2.28 (6.98-14.26)</td>
</tr>
<tr>
<td>IgA (g/L)</td>
<td>0.59 ± 0.38 (0.92-2.5)</td>
</tr>
<tr>
<td>IgM (g/L)</td>
<td>0.72 ± 0.40 (0.56-2.16)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.07 ± 0.49 (0-1.7)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>3.54 ± 1.10 (0-5.18)</td>
</tr>
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</table>
Fig. 1. VCE image. Whitish, swollen villi were seen in the duodenum (A), jejunum (B), and ileal mucosa (C) of case 11. Images of mild (D) and moderate-severe (E, F) lymphangiectasis in cases 2, 9 and 12, respectively. No whitish patches in the duodenum of case 4 (G). Image of the duodenum (H) and terminal ileum (I) after gastrointestinal endoscopy and enteroscopy examinations in case 11.
Fig. 2. Duodenal biopsy showing a markedly dilated lymphatic duct in case 12.
Fig. 3. MRI and CT images showing thickening of the walls of the jejunum and ileum in cases 12 (A, B) and 10 (C, D), respectively.