Cytomegalovirus infection-associated protein-losing gastroenteropathy in children: a case report and review of the literature

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ABSTRACT

Although protein-losing gastroenteropathy (PLG) is a rare entity in childhood, the recent observations describe that the cytomegalovirus (CMV) infection-associated PLG may develop in the previously healthy children. While most CMV infections are asymptomatic or cause mild diseases, some children with CMV infection have been reported to be complicated by PLG. Here we present a case of PLG caused by CMV infection associated with transient eosinophilia in a previously healthy 2-year-old boy. The diagnosis of CMV infection-associated PLG was made based on the findings of the protein leak from the jejunum confirmed by the functional imaging with Tc-99m human serum albumin (Tc-99m HSA) and the presence of the CMV antigen-positive blood leukocytes. He also demonstrated the transient eosinophilia. No immunological defects or allergies were identified. He achieved complete resolution within several weeks without specific therapy for CMV and steroids. In such case, functional imaging using Tc-99m HAS should be performed as it is useful for diagnosis and monitoring the conditions.

Introduction

Protein-losing gastroenteropathy (PLG) is characterized by an excessive loss of serum proteins into the gastrointestinal tract, resulting in hypoproteinemia, hypoalbuminemia, and edema (Braamskamp et al., 2010). Though the precise incidence and prevalence are unknown, it is considered to be rare in children. Hypoproteinemia might be complicated by edema, ascites, pleural, and cardial effusions. It can be caused by different disorders, with protein leakage through either mucosal injury, for example in inflammatory bowel diseases and neoplasms, or through abnormalities of the lymphatic system, as in primary intestinal
lymphangiectasia, congestive heart failure, or after Fontan procedure (Braamskamp et al., 2010). Unlike the disease in adults, PLG is usually benign and self-limited in children (Megged and Schlesinger, 2008).

While most cytomegalovirus (CMV) infections are asymptomatic or cause mild diseases, some children with CMV infection have been reported to be complicated by PLG (Leonidas et al., 1973; Hochman et al., 1996; Iwanaga et al., 2004; Takeyama et al., 2007; Tokuhara et al., 2007; Megged and Schlesinger, 2008; Hoshina et al., 2009; Russo et al., 2012). Here we present a case of PLG caused by CMV infection associated with transient eosinophilia in a previously healthy 2-year-old boy, in whom the functional imaging with Tc-99m human serum albumin (Tc-99m HSA) was useful not only for making the diagnosis but also for monitoring the progress of the PLG.

Case Report

A previously healthy 2-year-old Japanese boy was admitted to our hospital with evaluation of edema. One week prior to admission, he had a fever that lasted two days. He also had a cough during the two days prior to admission, and his edema then became apparent. He had no symptoms of vomiting or diarrhea.

On admission, his physical examination revealed periorbital and pretibial edema and swelling of his scrotum. He had normal vital signs. His weight was 12.5 kg [ +0.8 standard deviation (SD)], and his height was 83.5 cm(-0.6 SD). He had no allergic history. Laboratory tests on admission showed hemoglobin level, 11.4 g/dL; hematocrit, 43 %; peripheral leukocyte, 13,200 /μL with eosinophil count of 1,580 /μL (12 %); serum total protein, 3.0 g/dL; albumin, 1.5 g/dL; and C-reactive protein, 0.24 mg/dL. Serum IgE level was within normal level (43 IU/mL) and radioallergosorbent tests for specific IgE antibodies against food antigens, such as flour, egg, milk and soy were negative. A urinalysis was normal without proteinuria. Functional imaging with Tc-99m HSA on day 5 after admission detected a protein leak from the jejunum (Figure 1a). Alpha-1 anti-trypsin excretion in the stool was elevated to 174 mg/dL (normal, <54 mg/dL (Braamskamp et al., 2010)). The alpha-1 antitrypsin clearance was 65 mg/24h (normal, <20 mg/24h (Braamskamp et al., 2010)). We diagnosed the patient as having PLG. Enzyme immunoassay titer for CMV VCA-IgG and IgM were elevated (IgG, 6.2; IgM, 5.6), and CMV antigen-positive blood leukocytes was detected (18 cells per 50,000 white blood cells) while the antigen of Helicobacter pylori (H.pylori), a known infectious agent to cause PLG (Braamskamp et al., 2010) was negative in the stool.

Figure 1. Tc-99m HSA scintigraphy on day 5 after and day 26 after admission. (a) On the 5th day after admission, the protein leak from the jejunum (square) and ileocecum (circle) was demonstrated. (b) On the 26th day admission, the protein leak from the upper part of the small intestine was reduced (circle).
**Table 1.** Reported cases of cytomegalovirus-associated protein-losing gastroenteropathy in childhood in the literature

<table>
<thead>
<tr>
<th>No. (Ref.)</th>
<th>Age</th>
<th>Gender</th>
<th>Chief complaints</th>
<th>Diagnosis</th>
<th>CMV</th>
<th>GCV</th>
<th>Course (weeks)</th>
<th>Remarks/Concomitant disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2)</td>
<td>12m</td>
<td>female</td>
<td>Fever, Vomiting</td>
<td>ND, ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2 (2)</td>
<td>3.5y</td>
<td>female</td>
<td>Edema, Jaundice</td>
<td>ND, ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3 (2)</td>
<td>24m</td>
<td>male</td>
<td>Vomiting, Diarrhea, Edema</td>
<td>ND, ND</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>4 (2)</td>
<td>3y</td>
<td>female</td>
<td>Abdominal pain, Diarrhea, Edema</td>
<td>ND, ND</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>5 (2)</td>
<td>3.5y</td>
<td>male</td>
<td>Anemia, Vomiting</td>
<td>ND, ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6 (2)</td>
<td>4y</td>
<td>male</td>
<td>Edema</td>
<td>ND, ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7 (2)</td>
<td>4.5y</td>
<td>female</td>
<td>Diarrhea, Edema</td>
<td>ND, ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>8 (2)</td>
<td>2.5y</td>
<td>male</td>
<td>Fever, Edema</td>
<td>ND, ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>9 (4)</td>
<td>1m</td>
<td>female</td>
<td>Diarrhea</td>
<td>yes, yes (twice)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10 (6)</td>
<td>8y</td>
<td>male</td>
<td>Edema</td>
<td>yes, yes (twice)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>11 (7)</td>
<td>7y</td>
<td>male</td>
<td>Abdominal pain, Distension, Edema</td>
<td>no, no</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>12 (8)</td>
<td>2.5y</td>
<td>male</td>
<td>Edema</td>
<td>no, yes</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>13 (9)</td>
<td>3y</td>
<td>male</td>
<td>Diarrhea, Edema</td>
<td>yes, no</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>14 (Present case)</td>
<td>2y</td>
<td>male</td>
<td>Edema</td>
<td>yes, yes (twice)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
</tbody>
</table>

No., number; Ref, reference number; α1-AT, α1 antitrypsin clearance study; FI, Functional nuclear imaging; Ab, virus titers of antibodies; Ag, viral antigen testing; GCV, ganciclovir administration, ND, not done
Based on the increased titers of antibodies against CMV and the CMV antigen-positive blood leukocytes, his diagnosis of CMV associated PLG was made. The patient exhibited pitting edema, increasing body weight (from 12.5 to 13 kg) and decreased urine output developed on the following 3 days after admission. On the 3rd day and the 10th day after admission, intravenous administration of human serum albumin (1 g per kg of body weight) and immunoglobulins (200 mg per kg of body weight) was performed for hypoalbuminemia (albumin, 1.4 g/dL) and hypogammaglobulinemia (IgG, 270 mg/dL), respectively, while treatment with corticosteroid for PLG or that with ganciclovir for CMV were not commenced. His edema disappeared on the 15th day after admission and body weight returned from 13 to 11.7 kg on the 23rd day after admission. While peripheral eosinophil count rose to 4,896 /μL (25.5 %) on the 15th day after admission, functional imaging with Tc-99m HSA repeated on the 26th day of admission revealed that the protein leak from the upper part of the small intestine was reduced (Figure 1b). Six months after onset of illness, he was symptom free and had normal laboratory test results including serum albumin level and peripheral eosinophil count.

Discussion

We present a rare case of CMV infection complicated by PLG in a healthy young boy. Although the pathogenesis of CMV infection-associated PLG remains unknown, the possibilities include chemical irritants, toxins, dietary factors, neuro-emotional factors, endocrinological, or immunological abnormalities, an allergic process, and autoimmune disorders. In the literature, there are only 13 reported cases of CMV-associated PLG in childhood, which are summarized in Table 1 with the present case [2, 4, 6-9]; the median age of patients was 36 months (range: 6-week-old to 7 year-old) with male to female ratio of 1.8 with male predominance; edema was the most common clinical feature, found in 75% of the patients; the diagnosis of PLG was made by the detection of alpha-1-antitrypsin in a stool sample, or with the use of functional imaging in all cases; treatment was supportive including the intravenous albumin transfusions and a high protein diet in most cases, while two patients received ganciclovir administration; the median duration of the disease was 4 weeks (range: 0.5 week to 8 weeks); in regard to the concomitant conditions, H.pylori coinfection was reported in the two patients, liver transplantation in one, Crohn’s disease in one, retinitis in one, lymphangiectasia in one, eosinophilic gastroenteritis in one, and eosinophilia in the current case. Thus, eosinophilia is a distinctive feature in comparison with the previously reported cases of childhood CMV infection-associated PLG. It has been postulated that CMV infection in the gastrointestinal tract might be locally cytopathogenic, passively allowing the mucosal penetration of allergens, and then stimulate the allergic reaction (Takeyama et al., 2007). Therefore, transient eosinophilia in the present case may suggest the pathogenic mechanisms of CMV infection-associated PLG in which an aberrant mucosal immunity due to local damage of gastrointestinal cells caused by CMV infection is involved.

The diagnosis of PLG will be derived from history, physical examination, and clinical manifestations (Braamskamp et al., 2010). However, if necessary, it can be established by the detection of alpha-1-antitrypsin in a stool sample, or with the use of functional imaging (Braamskamp et al., 2010). An important advantage of functional imaging is to enable us to identify the site of the protein loss. In fact, several studies have reported that Tc-
99m HSA is the best tracer to diagnose PLG (Chiu et al., 2001). In this regard, it is also noteworthy that our patient received functional imaging using Tc-99m HSA twice, i.e., in the early stage and again in the convalescent stage to diagnose PLG and to confirm the recovery of PLG. As a result, it proved the remarkably reduced protein leak in the convalescent stage compared to that in the early stage. These findings suggest that the functional imaging of Tc-99m HSA for PLG is useful for not only the diagnosis but also for monitoring the disease activity.

In conclusion, we should have high index of suspicion for the CMV infection-associated PLG even in a previously healthy child who presents edema without proteinuria and transient eosinophilia. In such case, functional imaging using Tc-99m HAS should be performed as it is useful for diagnosis.

Authors’ Contribution

YT performed the literature search and drafted the manuscript. YT and EK were also treating physicians for the patient. KY was the consultant physician during hospitalization. ST and KK conceived of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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References


