Short Communication

Cytomegalovirus-Associated Protein-Losing Enteropathy Resulting from Lymphangiectasia in an Immunocompetent Child

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SUMMARY: An immunocompetent 8-year-old boy with cytomegalovirus (CMV)-associated transient protein-losing enteropathy (PLE) is described. Colonoscopic examination revealed lymphoid hyperplasia of the terminal ileum. Histological examination of the biopsied specimens showed marked dilation of the lymphatic vessels. Primary CMV infection was demonstrated by serological test and polymerase chain reaction. The child had complete resolution of the disease without antiviral treatment. The present case suggests the etiologic role of CMV infection in PLE resulting from intestinal lymphangiectasia in childhood.

Protein-losing enteropathy (PLE) is a condition resulting from enhanced mucosal permeability, mucosal desquamation, or lymphatic obstruction. It is often caused by inflammatory bowel disease, infections, celiac disease, intestinal lymphangiectasia, and cardiac disease (1). Many reports have indicated that acute cytomegalovirus (CMV) infection could play a causative role in immunocompetent children who developed PLE. Most of the pediatric cases of CMV-associated PLE have been related to Menetrier’s disease (2). We report a case of an immunocompetent child with CMV-associated PLE resulting from lymphangiectasia at the terminal ileum.

An 8-year-old boy was admitted to our hospital because of edema caused by hypoproteinemia. Two weeks earlier, he had complained of nausea. Subsequently, he developed edema on his eyelids and lower extremities, and was evaluated at a hospital 5 days prior to admission. Serum total protein level was 3.7 g/dl and albumin level was 1.9 g/dl. Serum liver enzyme levels were slightly elevated (aspartate aminotransferase [AST] 107 U/l, alanine aminotransferase [ALT] 71 U/l). Abdominal ultrasonography revealed thickening of the intestinal wall and a small amount of ascites. Chest X-ray showed a substantial amount of bilateral pleural effusion. He was then referred to our hospital for further investigation. The patient’s past history and family history were not remarkable.

On admission, he was afebrile and his body weight was the same as prior to the onset of symptoms. The edema on his eyelids had improved but that on the lower extremities remained. Respiratory sound was weak at the bilateral lower lung field and liver size was slightly enlarged, but neither enlargement of cervical lymph nodes nor splenomegaly was observed. Peripheral blood counts showed leukocyte 8.11 × 10^9/l with 22.5% neutrophils, 55.5% lymphocytes, and 3.0% atypical lymphocytes. Both erythrocyte and platelet counts were normal. Blood chemistries showed total protein of 4.1 g/dl, albumin of 2.5 g/dl, AST of 55 U/l, ALT of 40 U/l, and lactate dehydrogenase of 293 U/l. Serum IgG, IgA, and IgM levels were 458 mg/dl (normal range [NR], 775 - 1,767), 76 mg/dl (NR, 104 - 331), and 94 mg/dl (NR, 55 - 227), respectively. Surface marker analysis of the peripheral blood lymphocytes by flow cytometer showed a reversed CD4/CD8 ratio (36.9/59.5 = 0.62; NR, 1.2 - 2) and an increased proportion of CD3+/HLA-DR+ T cells (33.3%; NR, 0 - 5%). Peripheral blood lymphocyte responsiveness to phytohemagglutinin (PHA) was normal (stimulation index 281; NR, 254 - 388) and natural killer (NK) activity was slightly increased (58.6%; NR, 20.8 - 40.8). Serum CMV IgM and IgG antibodies were both positive by enzyme immunoassay (5.13 and 17.5, cutoff 0.80 and 2.0, respectively). The plasma level of CMV-DNA was positive at 2 × 10^2 copy/ml (NR, < 2 × 10^2 copy/ml) by real-time automated polymerase chain reaction (PCR) detection described previously (3). The bacterial culture of a stool specimen was unremarkable and 13C-urea breath test was negative. Urinalysis was normal. Serum antibody titers against Epstein-Barr virus (EBV) assayed by indirect immunofluorescence method indicated past infection as follows: viral capsid antigen (VCA) IgG, 1:40; VCA IgM, <1:10; EBV-nuclear antigen, 1:40. Bilateral pleural effusion was still present on chest X-ray, but thickening of the intestinal wall and ascites had disappeared on abdominal ultrasonography. Alpha-1-antitrypsin clearance was 21.6 g/day (NR, < 13 g/day), which was consistent with PLE. ⁹⁹ᵐTc human serum albumin scintigraphy revealed abnormal leakage from the terminal ileum. Gastroscopy showed normal gastric and duodenal folds. Colonoscopic examination revealed lymphoid hyperplasia of the terminal ileum (Figure 1). Histological examination of the biopsied specimens taken from the lesion showed marked dilatation of lymphatic vessels (Figure 2). These findings suggested that the patient suffered from PLE resulting from lymphangiectasia at the terminal ileum. No inclusion bodies, CMV antigens, or CMV-DNA were not detected in the intestinal lesion by hematoxylin-eosin staining, immunohistochemical staining with anti-CMV monoclonal antibody (M0864-1; DAKO, Glostrup, Denmark) or PCR, respectively.

A few days after admission, the patient’s edema disappeared completely. Serum total protein and albumin levels continued...
ously healthy child with normal cellular immunity suggested that he had primary CMV infection accompanied by PLE with lymphangiectasia.

A common presentation of CMV-associated PLE in childhood is Menetrier’s disease, which is characterized by gastric foveolar hyperplasia and usually has a benign clinical course in contrast to that in adults (2,6). Although a few pediatric cases of CMV-associated PLE without gastric lesions have been reported, neither colonoscopic nor histological finding was described in these case reports (7,8). Intestinal lymphangiectasia is characterized by obstruction of the intestinal lymphatic vessels and increased lymphatic pressure. Nakase et al. reported an adult case of CMV-associated PLE with intestinal lymphangiectasia (9). In this report, although no intranuclear cytomegalic inclusion bodies were seen, CMV-DNA was detected in the lesion using PCR amplification, indicating direct invasion. Direct viral infection is the most common pathological mechanism of CMV diseases, such as retinitis, hepatitis, and colitis (10), and can be confirmed by identification of CMV or CMV-DNA in the lesion using virus culture, immunohistochemical staining, PCR or in situ hybridization (11). On the other hand, interstitial pneumonitis and vasculitis can be caused by an immunopathological mechanism (12). In this condition, it has been speculated that activation of NK cells and tumor necrosis factor-α released from macrophages stimulated by interferon-γ derived from activated NK cells might be involved in the disease process (12,13). In the present case, no findings indicating direct invasion of CMV were detected in the lesion. As biopsy specimens were taken when the patient was in rapid recovery before admission, it is possible that CMV had already been eliminated from the lesion. Alternatively, intestinal lymphangiectasia might be a presentation of an immunopathological mechanism induced by CMV infection. To examine the latter possibility, accumulation and analysis of similar cases is required.

In summary, we report a pediatric case of CMV-associated PLE resulting from intestinal lymphangiectasia. Our experience suggests that evaluation of intestinal lesions is necessary in children of CMV-associated PLE without findings indicating Menetrier’s disease.

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