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CASE REPORT

Protein-losing enteropathy associated with rotavirus infection in an infant

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Abstract

Rotavirus is an acute enteric pathogen in infants and children. We reported a rare case of a 6-mo-old infant with protein-losing enteropathy (PLE) caused by rotavirus gastroenteritis, and evaluated the immunological profile in peripheral blood lymphocytes. Laboratory examinations showed lymphopenia, hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia, and elevation of alpha-1-antitrypsin (α1-AT) clearance. Lymphocytes subpopulation study revealed the reversal of CD4+/CD8+ ratio with the selective decrease of CD4-positive lymphocytes. Moreover, the excessive increase of T cells producing IFN-gamma (IFN-γ) was found, which plays an important role in the protection against viral infection. The primary or secondary activation of immune system by rotavirus may influence structural integrity and vascular permeability, which may play a triggering role in protein-losing enteropathy.

Key words: Protein-losing enteropathy; Rotavirus; Lymphocytes producing IFN-γ; Alpha-1-antitrypsin; Reversal of CD4+/CD8+ ratio

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INTRODUCTION

Rotavirus is the most important acute enteric pathogen in children. Rotavirus infection sometimes causes severe dehydration that is characterized by vomiting and diarrhea. Unusual complications by rotavirus infection are pneumonia, aseptic meningitis, acute myositis, encephalopathy and pancreatitis[1-3]. There are several causes of protein-losing enteropathy (PLE) in children, involving allergic enteropathy, congenital heart disease[4-6], and gastroenteritis, lymphangiectasia. We reported a case of an infant with PLE following rotavirus gastroenteritis and investigated the phenotypic profile in this patient.

CASE REPORT

A 6-mo-old boy presented with vomiting and diarrhea for 2 d prior to admission. Subsequently, he was hospitalized because of dehydration. The physical examinations revealed normal body weight (6755 g), pretibial pitting edema, abdominal distention and hypoactive bowel sounds. Laboratory examinations showed white blood count 9500/μL with 12% lymphocytes, decreased protein (27 g/L)/albumin (14 g/L) with low IgG levels (< 1.9 g/L) and hypocalcemia (0.068 g/L). C-reactive protein (CRP) was normal. A stool examination on the day of admission demonstrated positive rotavirus antigen (rapid immunochromatographic test) and no eosinophils, but rotavirus antigen was not detected on d 5 of disease. No bacteria was detected in the stool culture. Alpha-1-antitrypsin (A-1-AT) clearance was elevated to 638 mL/d (normal value < 30 mL/d). A urinalysis demonstrated neither proteinuria nor hematuria. Abdominal ultrasound and computed tomography showed bowel expansion and intestinal wall thickening with a small amount of ascites. Therefore, the diagnosis of PLE associated with rotavirus gastroenteritis was made. However, Tc99m-labeled albumin scintigraphy and intestinal biopsy could not be performed due to poor state of the patient. Although we started treatment with intravenous hyperalimentation for caloric intake and extensive replacement of albumin and gamma globulin, it was difficult to keep the normal serum level of these proteins. Although vomiting stopped, white-watery diarrhea developed more than ten times per day. Periorbital edema and abdominal distention were increased, and body weight increased to 7215 g (460 g/wk). The patient was treated with intravenous dexamethasone. After the improvement of diarrhea, we initiated the

medium-chain triglycerides (MCT) milk and the symptom did not recur. About one month later, A-1-AT clearance was decreased to 43.9 mL/d, yet abdominal CT partially showed persistent intestinal wall thickening. Lymphocytes, serum protein and albumin were normalized. In the acute phase, immunophenotyping of peripheral blood lymphocytes revealed selectively decreased percentage of CD4+ cells (15.71%) with normal percentage of CD8+ cells (38.76%) and reversal of CD4/CD8 ratio (0.41). IFN-gamma (IFN-γ) producing CD4+ and CD8+ lymphocytes were markedly elevated to 14.85% and 77.58%. CD19+, CD16+ and CD56+ were within normal range. One month later, immunophenotyping still revealed selectively decreased percentage of CD4+ cells (14.55%) and reversal of CD4+/CD8+ ratio (0.42), but IFN-γ producing CD4+ and CD8+ lymphocytes were decreased to 3.46% and 0.19%. Three months later, in the convalescent phase, the proportion of CD4+ lymphocytes was normalized with CD4/CD8 ratio almost 1.0. The rotavirus antibody titer determined using complement-fixation (CF) antibody was negative (1:4) at the time of admission. Five weeks later, the antibody titer increased to 1:128. Both IgM and IgG antibodies for cytomegalovirus were negative in serological test. In clinical course, no elevation of CRP occurred.

DISCUSSION

PLE is a disease characterized by a leakage of protein loss from the gastrointestine, which results in hypoproteinemia. PLE is associated with many disorders. Although PLE is etiologically diverse, the mechanism of protein loss was classified into two groups: (a) an abnormality of the lymph system; (b) enhancement of vascular permeability and/or an abnormality of intestinal mucosal membrane. In this patient, we believed that rotavirus gastroenteritis was involved in the pathogenesis of PLE. Because rotavirus antigen was detected on the day of admission, this is not nosocomial infection. We speculated that the mechanism of protein and lymphocyte leakage resulted from enhancement of vascular permeability, which was triggered by rotavirus infection damaging intestinal mucosa. Immunological studies showed markedly increased percentage of IFN-γ producing CD4+ and CD8+ lymphocytes. IFN-γ plays a major role in the host defense against rotavirus and the development of Th1 response. Gao *et al*[7] reported that serum and stool levels of IL-18 and IFN-γ were increased in children with rotavirus enteritis. These cytokines might have protective effects against acute rotavirus infection at the early stage. Xu *et al*[8] suggested that multiple toll-like receptors might modulate the immune response in the acute phase with rotavirus infection and play a role in the activation of IFN-γ. In other reports, determination of serum cytokines (interleukin-6, interleukin-8, tumor necrosis factor-alpha and CRP) might be a useful in differentiating viral from bacterial gastroenteritis[9-11]. These cytokines in patients with bacterial gastroenteritis were significantly higher than those in patients with viral gastroenteritis, especially in combination with interleukin-6 and CRP. Although we tested only CRP, it has never been elevated in clinical course. Therefore, we diagnosed our case as viral infection and gave no treatment of antibiotics, but more studies for other cytokines will be needed. Recently, it has been reported that a high frequency of rotavirus infections may increase the risk of celiac disease autoimmunity[12-14]. Unfortunately, we could not exclude the possibility of this disease because of no examinations for autoantibodies, including antigliadin antibodies (AGA), antitransglutaminase antibodies (TGA) and antiendomysium antibodies (EMA). Wang *et al*[15] described rotavirus infection induced strong inflammation and immune responses. Although treatment with steroid in PLE patients is controversial, we treated this patient with dexamethasone to control inflammation, achieving some improvement.

Previous phenotypic studies have demonstrated that the percentages of CD4+ and CD8+ cells was reduced in acute phase of rotavirus infection with diarrhea, and subsequently this proportion of T lymphocytes recovered to almost normal levels in convalescent phase[15]. In PLE associated with cytomegalovirus, lymphocytes subpopulation showed normal percentage of T cells, B cells and NK cells. Furthermore, the CD4/CD8 ratio was normal[16]. It is not clear why the CD4+ lymphocytes were selectively reduced in the peripheral blood in this case. In patients with PLE, Garty *et al* described two hypotheses for selective CD4+ cells loss after Fontan procedure[5]. The first is that CD4+ cells may have a longer half-life, leading to faster depletion from the circulation. A slower replenishment of the cells may result in fewer availability. Another hypothesis may be the selective transport of CD4+ cells. Our immunological studies of rotavirus induced PLE revealed the selective CD4+ lymphocyte reduction and the excessive inflammation. Some immune-mediated process induced by rotavirus gastroenteritis may play a triggering role in the pathogenesis of PLE, but further investigations are needed.

In summary, we reported a rare case of severe transient rotavirus gastroenteritis accompanied with PLE. Interestingly, although the reason is not clear, the immunophenotyping of peripheral blood lymphocytes in acute phase showed a markedly decreased percentage of CD4+ cells. Rotavirus infection should be considered in patients with acute and symptomatic protein loss of gastrointestinal origin.

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