Chronic diarrhea associated with high serum level of immunoglobulin A and diffuse infiltration of plasma cell in small intestine

A case report

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Abstract

Rationale: Chronic diarrhea in adult patients due to various causes is very common in clinic, but patient suffering with mal-absorption due to immunoproliferative small intestinal disease was rarely reported in China.

Patient concerns and Diagnoses: A 35-year-old female presented with more than three years history of chronic diarrhea, rickets, high serum value of immunoglobulin A protein, and anemia. Bone marrow aspiration suggested that the patient was in a sideropenic and megaloblastic anemia stage. Duodenal and ileac biopsies revealed atrophy and blunting villi. The bowel lamina propria was infiltrated with slightly increased intraepithelial lymphocytes and mainly with diffuse plasma cells. The following enzyme labeling immunohistochemistry results were strongly positive to alpha-heavy-chain. Computed tomography manifested she had diffuse thickening of small intestine wall. At last a diagnosis of immunoproliferative small intestinal disease was made.

Interventions and Outcomes: On the first month, the patient was treated with vitamin D supplements, calcium, magnesium, potassium, iron, folic acid, mecobalamin replacements and microflora probiotics. The patient frequency of water diarrhea alleviated slightly, but her weight loss, anxiety neurosis and other disorders were still severe. After taking with prednisone (40 mg per day, and gradually reduced to the lowest dose) for another month, the symptoms was gradually subsided.

Lessons: The study shows that immunohistochemical staining for alpha-heavy chain proteins should be completed on small intestine biopsy specimens if the patient is suspected a diagnosis of immunoproliferative small intestinal disease.

Abbreviations: BMI = body mass index, CT = computed tomography, HCD = heavy chain disease, HIV = human immunodeficiency virus, HP = Helicobacter pylori, IPSID = immunoproliferative small intestinal disease, MALT = mucosal-associated lymphoid tissue.

Keywords: chronic diarrhea, immunoglobulin A, immunoproliferative small intestinal disease, mal-absorption

1. Introduction

Chronic diarrhea patients with mal-absorption syndrome due to various causes are very common. The most often related causes are celiac disease, chronic intestinal infection, and so on. But those patients who suffered with immunoproliferative small intestinal disease (IPSID) were only sporadic reported in world population.[1] IPSID defines a diffuse, benign, or malignant lymphoid infiltrate, affecting the mucosa of the small intestine, without any free interval of normal mucosa.[2] This disease primarily affects children and young adults with peak incidence in second and third decades and is mainly observed in developing countries.[3] IPSID known as “Mediterranean” lymphoma or alpha-heavy-chain disease (HCD) which is classified into 3 types according to the anatomical site: digestive, respiratory, and lymphoid. The digestive type is a synonym for IPSID, which can cause severe enteropathy and give rise to malignant lymphoma.[4] A definitive diagnosis of immunoproliferative small intestinal disease is made based on the detection of alpha-heavy-chain proteins in the cytoplasm on immunohistochemistry. The pathologic stages of IPSID have been defined to be the early stage (stage A), intermediate stage (stage B), and late stage (stage C).[5] Stage A involves mature plasma cell infiltration of the mucosal lamina propria in small intestine with variable villous atrophy. Stage B includes atypical plasma cell infiltration associated with the presence of more or less atypical immunoblastic-like cells which extend at least to the submucosa, and subtotal or total villous atrophy can be found. Stage C is characterized by sarcomatous proliferation invading the whole depth of the intestinal wall.[6] We present the case of a 35-year-old female with high level of immunoglobulin A protein in serum and massive dense plasma cell infiltration in intestinal mucosa, who came to us with...
severe chronic water diarrhea and weight loss for more than 3 years.

2. Case report

A 35-year-old female living in a rural area came to our department with more than 3 years history of chronic diarrhea, rickets, high serum value of immunoglobulin A protein, and anemia. She had been diagnosed with suspected celiac disease and chronic bacterial intestinal infection in other hospitals and then been treated with gluten-free diet for more than 6 months, some antibiotics such as tetracycline, metronidazole, and ampicillin for more than 1 month, but with no effect. On physical examination, the patient was pale and nervous, and the body mass index (BMI) was about 15.6 kg/m².

Initial laboratory investigations manifested that she was suffering with severe electrolytic disorder, anemia, but with normal liver and renal functions, no allergic food ingredient, no pathogenic bacteria in stool cultures and parasitological examination of stools, no pathogenic bacteria in stool cultures and parasitological examination of stools, no pathogenic bacteria in stool cultures and parasitological examination of stools, no pathogenic bacteria in stool cultures and parasitological examination of stools. The Helicobacter pylori (HP) hydrogen breath test was negative. But her immunoglobulin A titer in serum was about 22,900 mg/L (the normal value is below 3820 mg/L in our hospital). Because of her high level of immunoglobulin A protein, we completed the bone marrow aspiration and found no evidences to diagnose the patient with lymphoma, plasmoma, multiple myeloma, and so on. The percentage of mature and immature plasma cells in the smear of bone marrow were about 3% and 2.5% (normal ratio) and a lot of megacaryocytes with many small round nuclei were found simultaneously (Fig. 1) which suggested that the patient was in a sideropenic and megaloblastic anemia stage. Protein electrophoresis and immunofixation electrophoresis showed that there were no definitive monoclonal immunoglobulin protein bands in her serum.

Gastrointestinal endoscopy was completed then. Duodenal and ileac biopsies revealed atrophy and blunting villi (Fig. 2). The bowel lamina propria was infiltrated with slightly increased intraepithelial lymphocytes and mainly with diffuse plasma cells (Fig. 3A). The following enzyme labeling immunohistochemistry results were strongly positive to alpha-heavy-chain (Fig. 3B), but negative to lambda and kappa light chain. Computed tomography (CT) manifested she had no hepatosplenomegaly and no lymphadenopathy but had diffuse thickening of small intestine wall (Fig. 4).

We diagnosed this patient with an immunoproliferative small intestinal disease based on upper investigation. She was started on vitamin D supplements, calcium, magnesium, potassium, iron, folic acid, and mecobalamin replacements. At the same time, we treated her with microflora probiotics additionally. One month later, her frequency of water diarrhea alleviated slightly, but her weight loss, anxiety neurosis, and other disorders were still severe. She refused to be treated with anthracycline chemotherapy regimens, and agreed to be treated with prednisone (40 mg per
day, and gradually reduced to the lowest dose). Another 1 month later, she was feeling better, with solid stool (once or twice per day) and had obvious weight restoration (BMI 19.5 kg/m²). The laboratory investigation manifested that the value of immunoglobulin A protein titer in serum decreased to 16,700 mg/L. She would be in a closely outpatient follow-up procedure in our department.

3. Discussion

IPSID is a form of lymphoma which arises in small intestinal mucosal associated lymphoid tissue (MALT), characterized by overproduction of a monoclonal truncated immunoglobulin α-heavy chain without associated light chain. The present patient had suffered with a state of severe malabsorption and a high level of immunoglobulin A protein in serum. Histological investigation showed atrophy villi and diffuse infiltration of mature plasma cells in the small intestine. According to her high level of polyclonal immunoglobulin A in serum and massive infiltration of mature plasma cells in intestine, we diagnosed this patient with an immunoproliferative small intestinal disease. Some searches showed that IPSID was putatively triggered by Campylobacter[7] and antimicrobials had been used in its early stage with consistent, albeit usually temporary, success.[8,9] But the present patient had no clinical remission after being treated with oral antibiotics for more than 1 month.

Celiac disease as an immune-mediated small intestinal enteropathy triggered by gluten has a prevalence about 0.5 to 1% of the population worldwide.[9] Measurements of antitissue transglutaminase and antiendomysial antibodies are the preferred initial screening tests for celiac disease because of its high sensitivity and specificity.[10] These 2 kinds of antibodies in this patient were negative. The patient was put on a gluten-free diet for more than 6 months, but her diarrhea had no remission, gut plasma cell infiltration persisted, and hyper-IgA in serum remained. Plasma cell infiltration in some patient with celiac disease can be found in proximal intestine,[11,12] but never with such intensity, especially in the ileum and colon mucosa. So we ruled out the diagnosis of celiac disease finally. We ruled out chronic infectious diarrhea for negative findings of pathogenic bacteria in stool culture tests.

However, the increase of serum polyclonal IgA is not the feature of IPSID or alpha-chain disease which is characterized by the synthesis of a monotypic truncated immunoglobulin alpha-chain lacking associated light chains.[13,14] We herein reported the case of IPSID patient with severe enteropathy, who was difficult to make a definitive diagnosis because of the lack of detectable M-protein. But several cases lacking of monoclonal alpha-chain protein had been reported previously.[3] The supposed cause is that the truncated alpha-chains have a strong tendency to polymerize and accumulate during the disease progression.[13] We found polyclonal immunoglobulin protein but not M protein band on immunoelectrophoresis, because of the polymerized and accumulated alpha-heavy chain proteins in this patient, who had a normal level of kappa and lambda light chain in the serum. In the present case, the immunohistochemical staining to alpha-heavy chain showed that mature plasma cells infiltration took place only in the mucosal lamina propria, which demonstrated that the patient was in the stage of IPSID, digestive type, stage A.

In conclusion, if a patient based on the clinical characteristics is suspected a diagnosis of IPSID, even when M-proteins are not detected, immunohistochemical staining for alpha-heavy-chain proteins should be completed on biopsy specimens.

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