Consideration of Maternal Anti-enterocyte IgA Transfer With Resulting Infantile Alloimmune Enteropathy

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ABSTRACT

Autoimmune enteropathy is a rare cause of infantile diarrhea. Cases typically involve infants with a protracted course of diarrhea found to have underlying autoimmune disease or immune dysfunction, leading to chronic intestinal inflammation. We describe a case of immune-mediated enteropathy in an infant with no identifiable autoimmune disease. The patient was exclusively breastfed by his mother who had Crohn’s disease, and he was found to have circulating anti-enterocyte immunoglobulin A (IgA) antibody. There was no circulating anti-enterocyte immunoglobulin G or immunoglobulin M. The patient’s disease and symptoms resolved with cessation of breastfeeding, and no immunomodulatory medications have been needed in 20 months of follow-up. The case raises suspicion for alloimmune disease, and it is hypothesized that intestinal injury was mediated by maternally transmitted anti-enterocyte IgA antibody.

INTRODUCTION

Autoimmune enteropathy (AIE) is a rare cause of infantile diarrhea. Cases are typically associated with underlying autoimmune disease or immune dysfunction leading to chronic intestinal inflammation necessitating immunosuppressive therapy. We describe a case of immune enteropathy in an infant with circulating anti-enterocyte immunoglobulin A (IgA) which appears to have been maternally transmitted through breast milk. The patient’s disease and symptoms resolved after cessation of breastfeeding.

CASE REPORT

The patient was a male infant born at term to a mother who was diagnosed with Crohn’s disease 16 years ago. She had taken azathioprine and adalimumab from prior to conception until 36 weeks gestation. The patient’s perinatal course was uncomplicated until, at 6 weeks of age, he developed intermittent bloody stool. Cow’s milk protein intolerance was initially suspected, and his mother removed dairy products from her diet. At 8 weeks of age, he presented with decreased oral intake, increasing mixed output (up to 415 mL/kg/d), dehydration, and weight loss. A full septic workup was negative. Stool studies were negative including Norovirus, Rotavirus, Adenovirus, Salmonella, Shigella, Yersinia, Campylobacter, and Escherichia coli O157. He had an elevated white blood count and inflammatory markers. Stool studies demonstrated moderate polymorphonuclear lymphocytes.

Esophagogastroduodenoscopy and sigmoidoscopy were performed 16 days after presentation. These examinations were visually normal (Figure 1). Review of mucosal pathology demonstrated diffuse, severe lymphoplasmacytic inflammation in the stomach, duodenum, and colon without granulomas or apoptosis (Figure 2). Gastric biopsies showed a reactive epithelium with atrophic architecture and focal gland destruction. Duodenal biopsies showed severely flattened and simplified villous architecture with an intact brush border, no tufting, and no evidence of microvillous inclusion disease. Immunocytochemical stains for CD10, CD1a,
CD163, CD3, and CD79a demonstrated increased T cells, scattered B cells, and increased histiocytes without excessive presence of Langerhans cells. Colonic biopsies showed marked chronic inflammatory changes with crypt loss.

The clinical and histologic presentation was concerning for an immune-mediated process. He did not have other clinical features of immune dysregulation, polyendocrinopathy, enteropathy, or X-linked syndrome. Absolute T-regulatory cell count was normal with normal Foxp3 protein expression. His newborn screen was normal and included testing for severe combined immune deficiency and T-cell lymphopenia. His blood glucose levels and thyroid stimulating hormone were normal. Immunoglobulin levels were normal with normal numbers of T, B, and NK cells as well as their subsets. T-cell function to mitogen phytohemagglutinin was normal. Anti-enterocyte immunoglobulin G (IgG), immunoglobulin M (IgM) and IgA levels were obtained which demonstrated the absence of anti-enterocyte IgG and IgM; however, his anti-enterocyte IgA was positive.

Based on these results, it was postulated that maternally produced anti-enterocyte IgA was responsible for the patient’s disease, and breast milk was excluded from his diet. Enteric feedings with a protein hydrolysate formula were introduced, and the patient tolerated this well without recurrence of symptoms. In the following weeks, he was transitioned to a polymeric formula, and a repeat endoscopy and flexible sigmoidoscopy 4 months after the initial presentation was grossly and histologically normal. He remained asymptomatic and off immunomodulatory medications after 20 months of follow-up.

DISCUSSION

AIE has been described by Avery et al in 1968 and Unsworth et al in 1982 and includes a multitude of etiologies relating to autoimmunity or inadequate immune function. There have been reports which have identified patients with AIE and enteric autoantibodies in the absence of immune dysfunction and autoimmunity. In previously described cases, patients have been treated with immunomodulatory medications or persistent removal of enteral feedings to control symptoms. Our patient’s clinical course does not fit any of these previously described cases because his symptoms and histology resolved without the need for immune-suppressive or modulating therapies. Although dietary protein-induced enterocolitis is a common condition of childhood, its clinical and pathologic phenotype is quite different from this patient’s presentation. The patient’s history, laboratory results, and clinical course provide indirect evidence of intestinal

Figure 1. Endoscopic images of the patient’s (A) stomach, (B) duodenum, and (C) colon.

Figure 2. Severe lymphoplasmacytic (A) gastric inflammation, (B) duodenal inflammation, and (C) colonic inflammation (hematoxylin and eosin staining, 200×).
disease resulting from an alloimmune response to transferred maternal anti-enterocyte IgA antibodies.

Immunoglobulin A is the most abundantly transferred immunoglobulin in human breast milk and has been found intact in the stool of infants. Systemic uptake has been demonstrated in breastfed neonates who have an increase of serum IgA of greater than 100% when day 5 serum levels are compared with cord blood samples. A similar mechanism of alloimmune disease in breastfed infants has been proposed by Hauschner et al, describing the occurrence of persistent neonatal thrombocytopenia in infants born to mothers affected by active immune thrombocytopenia. This report of antiplatelet IgA demonstrates maternal antibodies have the ability to be transferred through breast milk past the immediate neonatal period and in high enough levels to cause effects in the infant. Loose intracellular intestinal junctions and increased gut permeability have been proposed as a mechanism by which IgA may cross from the intestine into the serum.

Limitations of this study derive from the fact that our observations were limited to those data obtained as a part of routine clinical care. The patient’s mother had a diagnosis of Crohn’s disease; however, her anti-enterocyte antibody status was not determined as part of her routine care. Although anti-enterocyte antibodies have been reported in various chronic inflammatory conditions of the intestine, there are no large comparative studies indicating the incidence or prevalence of anti-enterocyte antibodies in populations with inflammatory bowel disease or other immune enteropathies. It is also possible that an unidentified infectious trigger or idiopathic immune-mediated process leads to this unusual, prolonged immune response.

This report presents indirect evidence of a newly described disease wherein maternal anti-enterocyte alloantibodies may be responsible for a form of infantile enteropathy. Although much remains unknown about the immunologic pathways of immune enteropathy, this case report suggests that alloimmune triggers may need to be considered when evaluating breastfeeding infants with evidence of immune-mediated enteropathy.

DISCLOSURES
Author contributions: JB Luginbill and MJ Giefer drafted the manuscript and approved the final revision. JC Rutledge approved the final version. MJ Giefer is the article guarantor.

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