Thymoma-Associated Autoimmune Enteropathy

A Report of Two Cases

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Abstract

Autoimmune enteropathy is an increasingly recognized cause of severe protracted diarrhea, usually affecting infants and children predisposed to autoimmune phenomena. Although this may be a common cause of diarrheal illness, it is scarcely recognized in the American literature. In association with thymoma, a case of so-called graft-vs-host-like colitis and 2 cases of chronic diarrhea associated with thymoma were reported, but, to our knowledge, no cases of autoimmune enteropathy have been reported as such. We describe 2 adults with autoimmune enteropathy found in association with a thymoma.

Autoimmune enteropathy is an increasingly recognized cause of severe protracted diarrhea, usually affecting infants and children predisposed to autoimmune phenomena. The preponderance of previous reports relate to children and were found in association with congenital immunodeficiencies or with other autoimmune disorders, such as type 1 diabetes mellitus, eczema, and hypothyroidism.1-5 Furthermore, these reports have originated predominantly within European, Japanese, and Australian institutions. In fact, 1 study found this to be the most common cause of intractable diarrhea in Italian infants.6 In North America, a single case of so-called graft-vs-host-like colitis7 and 2 cases of chronic diarrhea associated with thymoma were reported,8,9 but to our knowledge no cases of autoimmune enteropathy have been reported as such.

The defining features of autoimmune enteropathy include chronic diarrhea, failure to respond to dietary restriction, predisposition to autoimmunity, and the presence of serum anti-goblet cell antibodies.10 In patients with an unexplained, recalcitrant, diarrheal illness, the diagnosis of autoimmune enteropathy should be considered. We report 2 cases of autoimmune enteropathy arising in previously immunocompetent patients with thymomas.

Methods

To demonstrate the presence of antienterocyte antibodies in the patient’s serum, indirect immunofluorescence was performed using patient serum and normal human colon samples. Cross-sections of normal human colon were placed in Michel Transport Medium (Newcomer Supply, Middleton, WI) and stored at 4°C. Samples were then
washed 3 times for 10 minutes in Michel Buffered Wash Solution (Newcomer Supply) at room temperature.

The specimens were then snap-frozen in -50°C isopentane (2-methylbutane). The frozen samples were stored at -80°C. Five-micrometer tissue samples were cut with a cryostat after embedding the tissue in optimum cutting temperature embedding compound (Sakura Finetek, Torrance, CA). The sections were cut onto silane-coated slides. The sections were air-dried for 20 minutes at room temperature, post-fixed in 4°C acetone for 10 minutes, and air-dried again for 20 minutes at room temperature. The slides were then transferred to room temperature tris(hydroxymethyl)aminomethane (Tris)-buffered saline, pH 7.6, with 0.05% polysorbate (Tween 20) (Dako, Carpinteria, CA).

The suspected positive human serum was frozen and stored at -80°C. Before use, the serum was spun for 30 minutes at 4,500 rpm and then diluted to 1:5, 1:10, 1:20, and 1:40 dilutions in Tris hydrochloride-buffered saline (Dako). The sections were incubated with the suspected positive human serum at the aforementioned dilutions for 20 minutes at room temperature. This was followed by incubation with 1:40 fluorescein-labeled anti-human IgG (Dako) or 1:20 fluorescein-labeled anti-human IgM (Dako) for 60 minutes at room temperature (both were diluted in Tris hydrochloride-buffered saline).

The sections were mounted in Aqua-Mount (Lerner Laboratories, Pittsburgh, PA) aqueous mountant.

The following negative controls were run: to control for tissue autofluorescence, 1 section of colon was incubated with Tris-buffered saline, pH 7.6, with 0.05% Tween 20 to replace the fluorescein isothiocyanate-labeled antibody; to control for nonspecific staining, 1 section of colon was treated with the most concentrated dilution of the serum, 1:5, and then incubated with Tris-buffered saline, pH 7.6, with 0.05% Tween 20 to replace the fluorescein isothiocyanate-labeled antibody; to control for serum cross-reactivity, 1 section of colon was treated with 2 control patient serum samples.

**Case Reports**

**Case 1**

A 52-year old man with a 4-year history of bulbar and proximal muscle weakness sought care with a chief complaint of diarrhea. He reported a 40-pound (18-kg) weight loss during a 4-month diarrheal illness. He denied abdominal pain, nausea, vomiting, or melena. Other than cachexia, the physical examination findings were unremarkable. The initial evaluation included normal CBC count, chemistry panel, and liver function test results. Stool cultures and examination for ova and parasites were negative. Colonoscopy was endoscopically normal to the cecum, and multiple step biopsies were taken. Esophagogastroduodenoscopy demonstrated candidal esophagitis, atrophic gastritis, and atrophic-appearing duodenal folds. Multiple biopsy specimens of the esophagus, stomach, and duodenum were obtained. While awaiting the results of histopathologic examination, the patient was placed on a gluten-free diet without improvement, and he was admitted to the hospital several days later because of intractable watery diarrhea. A D-xylose test was performed that showed no evidence of absorption. Biopsies of the small and large bowel revealed increased chronic inflammation involving the lamina propria and epithelium, scarce goblet cells, and increased

![Image 11](Patient 1) Small bowel mucosa with increased mononuclear cells and absent goblet cells (H&E, x200).

![Image 21](Patient 1) Colonic mucosa with increased mononuclear cells and absent goblet cells (H&E, x200).
apoptotic bodies [Image 11, Image 21, and Image 31]. Neither viral inclusions nor other infectious agents were seen. No evidence of architectural distortion was identified. An antral biopsy was performed simultaneously that showed mild chronic gastritis.

A chest radiograph demonstrated a mediastinal mass that was confirmed on computed tomography scan. At the same time, results of the neurologic evaluation were suggestive of myasthenia gravis. This suspicion was confirmed with Tensilon testing. Surgery was undertaken to remove the anterior mediastinal mass, which proved to be a cortical thymoma with local invasion into the lung and left phrenic nerve (invasive, polygonal cell type in the Shimosato-Mukai1 classification), necessitating resection of the latter.

Repeated biopsies of the small and large bowel performed 3 weeks after thymectomy revealed essentially normal histologic features [Image 41 and Image 51]. Although a mildly increased infiltrate of chronic inflammatory cells remained, apoptotic bodies were rare, and goblet cells were abundantly present. An indirect immunofluorescence test (method described previously) demonstrated the presence of anti-enterocyte antibodies in the patient’s serum.

The patient’s diarrheal illness did not return. However, he experienced progressive respiratory insufficiency due to the myasthenia gravis and died 2 years after resection.

Case 2

A 48-year-old Filipino woman with a history of myasthenia gravis and thymoma was admitted to the hospital with refractory diarrhea. The thymoma was diagnosed 10 years earlier and treated with surgery and radiation. Histologically, it was a cortical thymoma with invasion into adjacent lung (invasive, polygonal cell type in the Shimosato-Mukai11 classification). It recurred 5 years before manifestation in the apex of her left lung. This was treated with another course of radiation therapy.

The myasthenia gravis initially was controlled with medications alone, but in recent years, it had progressively worsened, punctuated by multiple myasthenic crises. Once she required intubation, and intravenous immunoglobulin and plasmapheresis were administered on multiple occasions.

She had various infectious diseases, including tuberculosis and Mycobacterium avium-intracellulare infections, both of which were treated with full courses of antibiotics several years before admission. In addition, she had an episode of Escherichia coli septicemia 1 year before admission.

She initially was evaluated for diarrhea 2 years before admission. Stools were repeatedly guaiac-negative and negative for Clostridium difficile toxin, and diarrhea persisted after discontinuation of multiple medications. The diarrhea did not respond to the addition of pancreatic enzymes and responded only transiently to bulk-forming and antimotility agents. The results of a small bowel follow-through and a computed tomography scan were normal. A trial of intravenous immunoglobulin was without effect. During this admission, total parenteral nutrition was begun, and biopsy specimens from the small bowel were obtained endoscopically. Following discharge she became progressively cachectic, despite outpatient total parenteral nutrition, and was readmitted 3 months later with pneumonia due to Klebsiella pneumoniae.
Despite aggressive interventions, adult respiratory distress syndrome developed, and the patient died of disseminated intravascular coagulation.

Biopsies of the small bowel revealed villus blunting and increased mononuclear infiltration of the lamina propria and intestinal epithelium. Goblet cells were not identified in the biopsy specimens, and increased apoptotic bodies were noted Image 61 and Image 71. There were scattered neutrophils within the lamina propria and focal acute cryptitis. Neither infectious agents nor architectural distortion were identified.

Discussion

These patients developed severe intractable diarrhea in association with their thymomas. In the first case, the diarrheal illness resolved after resection of the tumor, and histologic resolution was documented. In the second case, the diarrhea began after resection of a thymoma. In both cases, the most arresting feature of the colonic histology was the paucity of goblet cells, but a histologic resemblance to the lesion of graft-vs-host disease (GVHD) also was observed.

The defining features of autoimmune enteropathy include chronic diarrhea, failure to respond to dietary restriction, predisposition to autoimmunity, and the presence of serum anti-goblet cell antibodies. It typically occurs in persons predisposed to autoimmunity. Specifically, patients tend to have underlying congenital immunodeficiencies, such as IgA deficiency and common variable immunodeficiency, or have a constellation of autoimmune phenomena, such as type I diabetes mellitus. Biopsy specimens, in earlier reports, have been described consistently as showing increased acute and chronic inflammation involving the lamina propria and intestinal epithelium. Many reports have mentioned goblet cell depletion, acute cryptitis, mild villus blunting, and numerous apoptotic bodies. None showed crypt architectural distortion, granulomas, parasites, or viral inclusions. In our 2 cases, the most arresting feature was the complete absence of goblet cells.

If the clinical and histologic features are known, it is relatively easy to distinguish autoimmune enteropathy from celiac disease. Patients with autoimmune enteropathy are
unresponsive to dietary restriction, and the history may include one of the aforementioned known predisposing factors. Furthermore, the entire intestinal tract is affected in autoimmune enteropathy, and in the small bowel, the villi are not completely flattened.

Distinction from lymphocytic colitis presents a slightly more challenging problem. The usual case of lymphocytic colitis is confined to the large bowel and tends to be patchy, favoring the ascending colon, although some patients seem to have pathology in the small bowel. As described, autoimmune enteropathy involves the entire length of the intestine. While the two disorders share the finding of increased mononuclear infiltration in the lamina propria and epithelium, increased subepithelial collagen is not a feature in autoimmune enteropathy. In addition, the striking loss of goblet cells and increased apoptotic bodies have not been observed in lymphocytic colitis. Last, acute cryptitis seems to be a fairly consistent feature in autoimmune enteropathy that is not commonly seen in lymphocytic colitis.

Thymomas have been associated with a long list of autoimmune conditions, most commonly myasthenia gravis, which both of these patients also had. This is believed to be due to loss of self-tolerance due in some way to abnormal thymic architecture. We believe that the 3 cases described in the literature are examples of autoimmune enteropathy occurring in patients with thymoma. These and our 2 cases illustrate an association between the two, but the incidence of autoimmune enteropathy in thymoma is unknown.

The pathogenesis of autoimmune enteropathy seems to involve the stimulation of CD4+ T cells by enterocytes that aberrantly express class II major histocompatibility complex antigens. Superficially located mature enterocytes normally express class II major histocompatibility complex antigens. In the unusual scenario in which immature enterocytes located within the crypts display these antigens, they become capable of stimulating a T-cell response to self-antigens. Stimulated CD4+ T cells then can orchestrate an immune response, including the paracrine stimulation of B cells to produce anti-goblet cell antibodies. Antienterocyte antibodies, which have been variously referred to as anti-gut antibodies and anti-goblet cell antibodies, have unknown sensitivity and specificity in this disorder. Their presence was demonstrated in patient 1, while the test was not performed on specimens from patient 2. The initial underlying defect that initiates these events has not been determined. Similarities between these immunopathologic findings and those noted in Crohn disease have been noted.

An intriguing feature, and one that may provide a unifying explanation for the disorder, is the histologic resemblance to GVHD. GVHD is the triad of enteropathy, dermatitis, and hepatitis. It is typically seen in the setting of bone marrow transplantation but has been described in other settings, including transfusion. The histologic findings consist of mucosal thinning and ulceration, intraepithelial lymphocytes and neutrophils, architectural abnormalities, and edema of the lamina propria. The enteric histology in GVHD is perhaps most remarkable for the presence of increased apoptotic bodies, the histologic representation of the type of cell death known as apoptosis. This appearance also has been described in radiation exposure, chemotherapy, and, previously, in thymoma-associated autoimmune enteropathy.

The treatment for autoimmune enteropathy has not been elucidated. Theoretically, the underlying disorder should be addressed, but, except in cases associated with thymoma, this may be fruitless. In fact, case 1 may represent the first example of successful treatment of autoimmune enteropathy. Some response has been reported with immunosuppression.

The patients described, with no risk factors for GVHD and no history of radiation or chemotherapy exposure, represent 2 further examples of the association between thymoma and autoimmune enteropathy. We believe that the autoimmune enteropathy is a direct consequence of the thymoma, as supported especially by the complete clinicopathologic resolution documented in case 1. However, as illustrated in case 2, thymic resection may be followed by the onset of autoimmune enteropathy. This course of events is not infrequently seen in thymoma-associated myasthenia gravis.

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References


