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Thymoma-associated chronic diarrhea: A case of autoimmune enteropathy

Patricio Riquelme[a,1], Alison H. Tisch[b,2], Ying Liang[b,3], Anson W. Lowe[a,4], Alexander D. Colevas[b,2], Heather A. Wakelee[b,*,2]

[a]*Department of Medicine, Stanford University, Stanford, CA, United States*
[b]*Department of Medicine, Division of Oncology, Stanford University, Stanford, CA, United States*

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Abstract
Thymomas are tumors arising from thymic epithelial cells that are frequently associated with autoimmune conditions. One such disorder, autoimmune enteropathy, is an uncommon autoimmune process found in patients with thymoma that is characterized by chronic diarrhea (>6 weeks duration), malabsorption, and characteristic small intestinal histopathology. The presence of anti-enterocyte or anti-goblet cell antibodies supports the diagnosis of autoimmune. As this is a relatively uncommon disorder, treatment options have not been well studied. We report the case of a 35-year-old Caucasian male with recurrent thymoma that subsequently developed autoimmune enteropathy as confirmed by symptoms, biopsy and serologies. Prednisone and octreotide, which have previously been shown to treat recurrent thymoma, were used to successfully treat his autoimmune enteropathy and recurrent thymoma, leading to resolution of diarrhea, subsequent weight gain, and radiographic confirmation of regression of metastatic thymoma. Autoimmune enteropathy should be considered in the differential diagnosis of patients with thymoma presenting with intractable diarrhea and weight loss. The use of prednisone and octreotide may be helpful in treating both conditions.

*Correspondence to: Stanford University 875 Blake Wilbur Drive, MC 5826 Stanford, CA 94305.
E-mail address: hwakelee@stanford.edu (H.A. Wakelee).
[1]Present address: Department of Hospital Medicine, Oregon Health & Sciences University, Portland, OR 97239, United States.
[2]Present address: Stanford Cancer Center, 875 Blake Wilbur Drive, Stanford, CA 94305, United States.
[3]Present address: Department of Medical Oncology, Cancer Center, Sun Yat-sen University, Guangzhou 510060, China.
[4]Present address: Stanford Gastroenterology, 900 Blake Wilbur Drive, Stanford, CA 94304, United States.

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1. Introduction

Up to 40% of patients with thymomas will develop an autoimmune process, with half developing myasthenia gravis [1], while others may develop pure red-cell aplasia, systemic lupus erythematosus, autoimmune thyroid disorders, and syndrome of inappropriate antidiuretic hormone secretion among others [2]. Thymoma-associated autoimmune conditions that are known to affect the gastrointestinal tract include acquired hypogammaglobulinemia or Good's syndrome [3,4], thymoma-associated multiorgan autoimmunity [5,6], and autoimmune enteropathy [7-9]. Autoimmune enteropathy (AE) is a rare disorder, more frequently seen in children then adults, and is caused by immune-mediated damage to intestinal mucosa leading to chronic diarrhea and malabsorption. Much of what we know about AE in adults is based on a case series published by investigators at the Mayo Clinic [9], which proposed diagnostic criteria and offered insight into treatment options, which consisted predominantly of corticosteroids. Similarly, corticosteroids along with octreotide, a somatostatin analog that has been used to treat diarrhea, have been shown to treat thymoma [10] and associated autoimmune conditions [11,12]. Herein, we describe a case of recurrent thymoma complicated by AE successfully treated with prednisone and octreotide.

2. Case report

A 35-year-old man with a history of metastatic thymoma developed profuse, watery non-bloody diarrhea occurring 5-10 times per day without associated abdominal pain, ultimately leading to a 20-lb weight loss over a two month period. Four years prior, the patient was diagnosed with metastatic thymoma and was initially treated with neoadjuvant chemotherapy (four cycles of cyclophosphamide, doxorubicin, and cisplatin), followed by surgical resection of a mediastinal mass and multiple, pleural based lesions. He subsequently developed new pleural lesions in the right thorax, which were treated with external beam radiation rather then surgical resection. Following radiation therapy, the patient was found to have very slow growth of his right pleural lesions but remained clinically stable off therapy for 17 months until he developed diarrhea.

Prior to his hospitalization, the patient underwent an extensive outpatient workup of his diarrhea and weight loss, including testing for infectious etiologies and celiac disease, with all laboratory tests unremarkable. Serum immunoglobulins (IgG, IgM, IgA) were within normal range. A colonoscopy was unrevealing, but an esophagogastroduodenoscopy (EGD) exam showed duodenal villous blunting with up to 20 lymphocytes per 100 enterocytes. An octreotide scan showed uptake in the right hemithorax corresponding to an area of known thymoma recurrence, as well as in the duodenum. Treatment with loperamide, diphenoxylate/atropine, tincture of opium, metronidazole, and importantly adherence to a gluten-free diet, as well as a lactose-free diet, did not provide relief for his diarrhea.

On admission, the patient was afebrile and hemodynamically stable. He did not drink alcohol or use illicit drugs. His exam was remarkable for dry mucus membranes, flat neck veins, and no lymphadenopathy. He did not have any abdominal tenderness, bloating, or palpable masses on exam. Admission labs were notable for a non-anion gap, hyperchloremic metabolic acidosis that was ascribed to his diarrhea. Celiac serologies and an infectious workup were repeated which again were normal. He underwent another EGD exam, which showed flattened mucosal folds in the duodenum, and duodenal biopsies demonstrating prominent villous blunting, goblet cell loss, focal apoptosis, and increased intraepithelial lymphocytes. Duodenal biopsies revealed a few, scattered CD30+ reactive cells, suggesting that enteropathy-associated lymphoma was not the cause. Anti-enterocyte antibodies, however, showed strong, linear staining along the apical border of enterocytes (Fig. 1).

Given this patient's thymoma recurrence and the development of an autoimmune process, he was started on prednisone 0.6 mg/kg per day and octreotide 400 mcg subcutaneous injection three times a day. His diarrhea quickly resolved on this regimen and he was discharged home on total parenteral nutrition. Three months later the patient had only gained one pound, but reported having one regular bowel movement per day and had stopped using total parenteral nutrition as he was tolerating a regular diet. CT scans done at this time showed interval improvement in his pleural-based metastatic lesions (Fig. 2) and thus he was continued on octreotide and prednisone. On his most recent follow-up visit nine months after discharge, he had gained five pounds, had returned to work, and on repeat CT scan his pleural lesions remained stable in size. He is currently on a prolonged prednisone taper and receives monthly octreotide intramuscular injections, with plans to continue this regimen for one year as per the protocol by Loehrer et al. [10] with plans for further reassessment at the one-year mark.

3. Discussion

Autoimmune enteropathy is a rare disorder caused by immune system-mediated damage to the gastrointestinal mucosa leading to chronic, intractable diarrhea and ultimately malabsorption and weight loss. To date, AE has been reported in the literature for 4 patients with thymoma [7-9]. The largest case series of adult patients with AE (one of which had thymoma) was reported by investigators at the Mayo Clinic, which led to the following diagnostic criteria based on symptoms and histopathology: adult-onset chronic diarrhea (>6 weeks duration), malabsorption, partial to complete villous blunting of the small intestine, deep crypt lymphocytosis, increased crypt apoptotic bodies, minimal intraepithelial lymphocytosis, and the exclusion of other causes of villous atrophy including celiac disease, refractory sprue, and intestinal lymphoma [9]. Circulating anti-enterocyte or anti-goblet antibodies support the diagnosis of AE, but are themselves not diagnostic as they may be found in asymptomatic, first-degree relatives or with other inflammatory diseases [9]. The patient described herein met the above criteria and was found to have elevated titers of anti-enterocyte antibodies further arguing for AE as the underlying etiology for his symptoms.

Other thymoma-associated autoimmune conditions known to cause diarrhea and malabsorption include acquired