Acquired acrodermatitis enteropathica as a presenting sign of celiac disease

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INTRODUCTION

Cutaneous manifestations can occur in association with various gastrointestinal diseases.[1] When dermatitides present in the setting of unintentional weight loss before a gastrointestinal disease is diagnosed, early recognition can aid in the diagnosis of nutritional deficiency secondary to malabsorption.[2] A case of acquired acrodermatitis enteropathica (AE) is reported in the setting of zinc deficiency as a presenting sign of celiac disease (CD).

Abbreviations used:

AE: acrodermatitis enteropathica
CD: celiac disease
GFD: gluten-free diet

CASE REPORT

A 40-year-old African-American woman with a history of chronic eczema, previous alcohol abuse, gout, and hypothyroidism presented with a worsening eruption and intermittent diarrhea to the emergency department. The cutaneous eruption began 2 months prior with desquamation of the hands, feet, perioral and perineal skin with associated pain and swelling and concurrent hair loss. Over the previous 8 months, the patient experienced increasing weakness, fatigue, intermittent diarrhea, and 70 pounds of unintentional weight loss. Psychosocial habits included 1 to 2 glasses of wine a day along with smoking. No significant family history was elicited, and the patient was not on any medications.

Dermatologic examination found erythematous desquamative patches, erosions, and crusted lesions involving the distal fingers of both hands, left dorsal arm, sacrum, perineum, left medial leg, and bilateral distal feet with a predilection for acral interdigital web spaces (Fig 1). Diffuse nonscarring alopecia of the scalp and scaling patches on the vermillion lips were also noted. A punch biopsy of the left medial thigh showed psoriasiform epidermal spongiosis with a slight superficial perivascular lymphohistiocytic infiltrate (Fig 2). Diffuse hypogranulosis and broad overlying parakeratosis were present in the overlying epidermis along with ballooning degeneration of the spinous layer. These findings were consistent with nutritional deficiency dermatitis.

The patient also had methicillin-resistant *Staphylococcus aureus* and *Escherichia coli* sepsis secondary to pneumonia and was admitted to the intensive care unit for a few days where she required ventilator respiratory support and systemic antibiotics.

Laboratory and imaging studies ruled out necrolytic acral erythema, pellagra, and biotin deficiency. Zinc levels were low (28 μg/dL; normal, 60−130 μg/dL) and antitransglutaminase and antiendomysium antibodies were positive, supporting the diagnosis of CD with zinc deficiency. Although the patient denied current alcohol abuse, her history of excessive alcohol intake may have also contributed to chronic low zinc levels and, therefore, her deficiency dermatitis.[3] One distal duodenal biopsy found focal villi blunting and Brunner's gland hyperplasia without significant intraepithelial lymphocytes. The patient was treated with a gluten-free diet (GFD) and zinc sulfate, 220-mg oral capsule twice daily, resulting in resolution of her gastrointestinal and cutaneous symptoms within 4 weeks.

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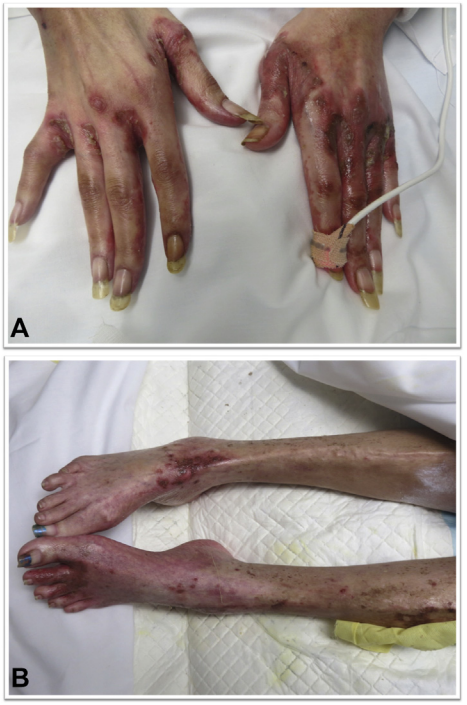

Fig 1. Acquired acrodermatitis enteropathica. Erythematous desquamative patches, erosions, and crusted lesions involving the distal fingers of bilateral dorsal hands (**A**) and lower extremities (**B**).

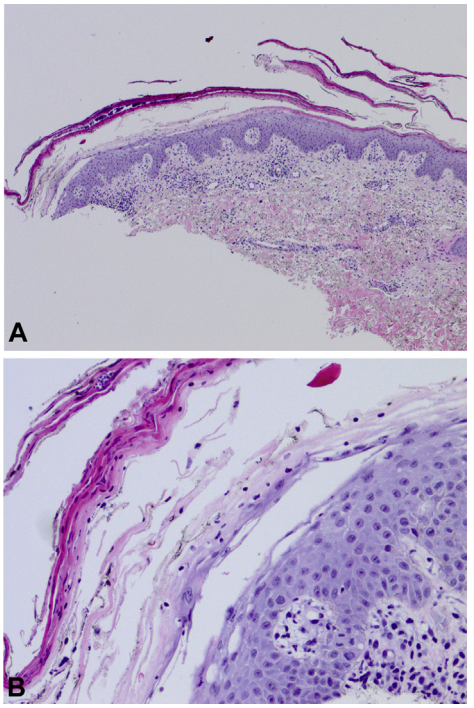

Fig 2. Acquired acrodermatitis enteropathica. Hematoxylin-eosin–stained tissue from left medial thigh shows psoriasiform epidermal spongiosis with a slight superficial perivascular lymphohistiocytic infiltrate at low (**A**) and high (**B**) power. (Hematoxylin-eosin stain; original magnifications: **A**, ×100; **B**, ×400.)

DISCUSSION

The rare autosomal recessive metabolic disorder AE results from a zinc transporter protein (ZIP4) loss of function mutation encoded by the SLC39A4 gene on chromosome 9.[4] As part of the regulatory system for zinc homeostasis, ZIP4 enables intracellular zinc transport from the lumen of the small intestine and, when absent, leads to systemic zinc deficiency.[4] Periorificial and acral dermatitis, alopecia, and diarrhea in association with epidermal necrosis on histology point to the diagnosis.[5] Although most literature on zinc deficiency dermatitis focuses on this heritable variant and its presentation in young children, a variety of scenarios producing acquired zinc deficiency in adulthood manifest similar clinicopathologic findings.[2,5-8] Anorexia nervosa, alcoholism, intestinal malabsorption, and diets high in mineral binding phytate are the most common causes of acquired acrodermatitis enteropathica.[5] Low zinc intake also results in zinc deficiency; however, the recommended daily intake of 8 mg for women and 11 mg for men is easily attained in developed countries.[9] Dietary zinc deficiency must not be completely overlooked, as the extensive use of proton-pump inhibitors, decreased consumption of meat and fish, and diets abundant in phytate-rich foods are not uncommon.

As zinc interacts with a multitude of molecular structures, it is not surprising that cellular and systemic zinc levels are tightly regulated. Of the anatomic sites involved in zinc homeostasis, including the kidneys, skin, and sites of tissue repair, the small intestine is thought to be the central avenue for homeostasis.[5] Thus, acrodermatitis enteropathica may develop when gastrointestinal pathologies decrease the absorption of zinc across the luminal membrane of the small intestine.[6-8]

Celiac disease is a chronic gastrointestinal condition characterized by the inability to tolerate gliadin, the alcohol-soluble fraction of gluten. This results in an immunologically mediated inflammatory response to the ingestion of gluten and ultimately leads to damage of the intestinal mucosa with comorbid malabsorption. Common symptoms include diarrhea, abdominal cramps, flatulence, weight loss, growth delay in children, and fatigue. Diagnosis is determined with positive immunoglobulin A antitissue transglutaminase and antiendomysial antibodies—both of which were positive in our patient. Although small bowel biopsies are the gold standard to confirm gluten-sensitive enteropathy, classic findings are frequently patchy when taken from the distal duodenum. In contrast, literature

supports the superior reliability of duodenal biopsies from the bulb, which were unfortunately not obtained in our patient.[10]

As expected with any acute to subacute malabsorptive process, electrolyte and micronutrient abnormalities are highly prevalent in newly diagnosed CD cases. Wierdsma and colleagues[2] found zinc deficiency most prevalent among a comprehensive list of vitamins and minerals with 66.7% of CD patients deficient at the time of diagnosis. The role of zinc deficiency may be bidirectional and self-perpetuating in such cases. Zinc deficiency compromises gastrointestinal epithelial barrier function and may trigger pathologic conditions such as celiac disease, gastrointestinal cancer, inflammatory bowel disease, malabsorption, and food allergies in predisposed individuals.[11] Inversely, when luminal epithelial cells are damaged, compromised regulation of zinc homeostasis can lead to deficiency. Notably, AE secondary to zinc deficiency is a rare cutaneous manifestation of CD compared with dermatitis herpetiformis seen in 15% to 25% of CD patients, and even urticaria/atopic dermatitis (~5%), psoriasis (~4%), and alopecia areata (~1%).[12] Less is known about the incidence of AE in CD patients, and to our best knowledge it has not yet been documented as the presenting sign of CD.

Zinc replacement therapy is recommended when serum or plasma levels are less than 50 mg/dL or in patients with acquired acrodermatitis enteropathica starting at 3 mg/kg/d of elemental zinc. Zinc replacement, in addition to adopting a GFD, achieved complete resolution within 4 weeks in the case presented. Experts debate over the necessity of zinc replacement in addition to a GFD in patients with deficiency presumed to be secondary to CD and epithelial barrier dysfunction. In a randomized controlled trial, plasma zinc levels increased irrespective of zinc replacement when CD patients with zinc deficiency adopted a GFD.[13] Regardless, more data are required before we would support abstaining from zinc replacement when obvious deficiency is apparent.

When presented with atypical or refractive dermatitis in the setting of unintentional weight loss, one must consider underlying celiac disease.

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