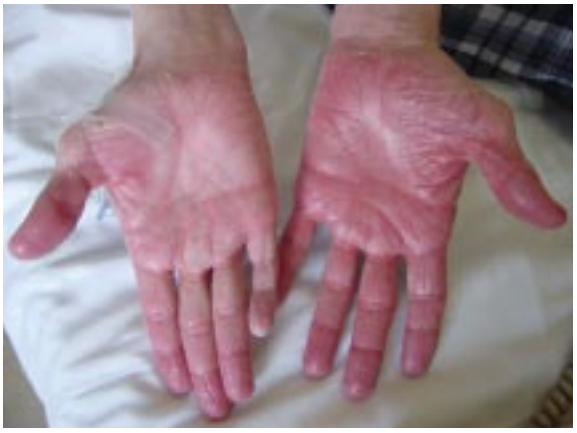
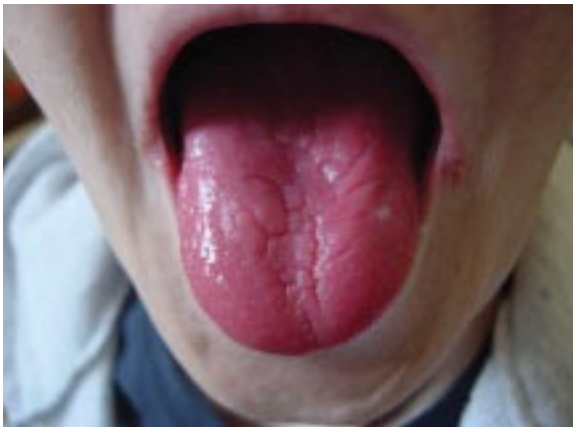
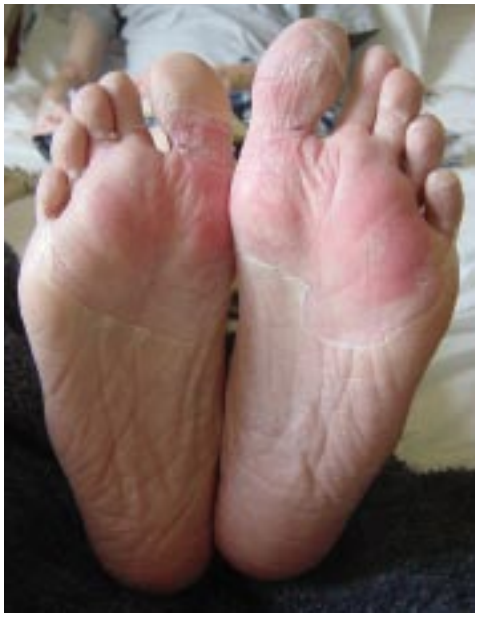
What Is Your Diagnosis?







A 40-year-old man presented with a 25-year history of recurrent idiopathic pancreatitis with malabsorptive diarrhea, hypothyroidism, ascites, and mental status changes. The patient was admitted for workup of cirrhosis and management of hepatic encephalopathy. In addition to his diarrhea, he also noted intolerance to many foods, with a subsequent shift in his diet to increased consumption of grain products. The patient also was found to have oligospermia with hypotestosteronism. On physical examination, he had symmetric well-defined areas of erythematous desquamation of his palms and soles. The patient's forearms had bilateral ill-defined erythematous scaly patches and plaques with bilateral koilonychia of several fingernails. Additionally, he had fine gray hair and eyelash and eyebrow alopecia. His tongue showed loss of papillae and he had angular cheilitis.

PLEASE TURN TO PAGE 324 FOR DISCUSSION

Vanessa A. Richlin, MS, Case Western Reserve University School of Medicine, Cleveland, Ohio.
Jorge A. Garcia-Zuazaga, MD, Department of Dermatology, University Hospitals of Cleveland.
Michael J. Beck, MD, Internal Medicine and Pediatrics, Milton S. Hershey Medical Center, Hershey, Pennsylvania, and Penn State Children's Hospital, Hershey.
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The Diagnosis: Acquired Acrodermatitis Enteropathica

Acrodermatitis enteropathica (AE) was first recognized by Brandt[1] in 1936, and Danbolt and Closs[2] named the group of symptoms AE in 1942.[3] Moynahan[4] was the first to emphasize the role of zinc deficiency and hypothesized that the absence of an oligopeptidase from the intestine was responsible for the hypozincemia.[5]

AE is a rare autosomal recessive disorder caused by a mutation in a zinc transporter protein. Specifically, mutations in the solute carrier family 39 (zinc transporter) member 4 gene, *SLC39A4*, located at band 8q24.3, are likely responsible. This zinc transporter is expressed in the duodenum and jejunum (the main sites of zinc absorption), kidneys, and colon, and is secreted in breast milk.[6-8] Several acquired forms of zinc deficiency have been described, which lead to conditions similar to AE, and thus are commonly discussed with AE. Additionally, there are several AE-like eruptions unrelated to zinc deficiency.[5]

The classic presentation of all forms of AE is the triad of dermatitis, alopecia, and diarrhea, though this triad is only recorded in 20% of cases.[9] The classic cutaneous findings include a symmetric, erythematous, scaly, eczematous, or vesicobullous eruption over periorificial and acral surfaces.[3,5,10] Facial involvement may be perioral, especially perlèche (angular cheilitis), or periorbital, and acral involvement can include parenchymal tissue swelling, paronychia, and nail dystrophy.[3] Examples of facial and acral involvement exhibited by our patient can be seen in Figure 1. Hair loss resulting in alopecia is common. Less commonly seen are ophthalmic changes, which include conjunctivitis, blepharitis, and decreased visual acuity. Gastrointestinal complaints most commonly include diarrhea with irregular exacerbations, abdominal pain, and foul-smelling stools. Psychological disturbances may accompany this condition, manifested by mood changes, anorexia, and behavioral alterations. Low zinc levels also have been associated with high blood ammonia levels, likely secondary to effects on ornithine transcarbamoylase (in the urea cycle) and adenosine monophosphate deaminases (in skeletal muscle).[11] Hypozincemia has been correlated with hypogonadism and growth retardation.[12,13] Finally, the most serious complication is associated immunodeficiency, which seems to be related to the

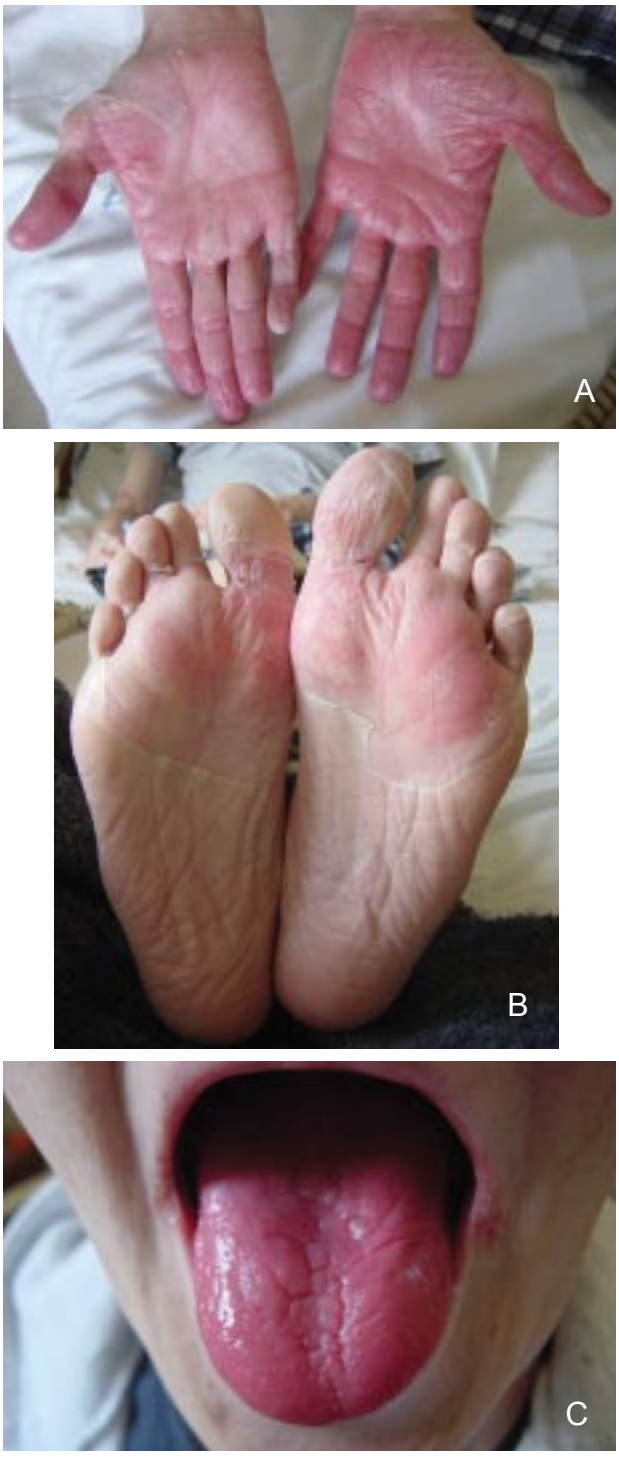

Figure 1. Erythematous and eczematous desquamation of the left palm (A) and bilateral soles of the feet (B). The tongue is smooth, with loss of papillae, and there also is angular cheilitis (C).

decreased number of T cells and reduced activity of macrophages.[3] Secondary infections are most commonly caused by *Candida albicans*, but *Pseudomonas aeruginosa* and *Klebsiella* species also have been reported.[3,9]

The diagnosis of AE is clinical but is supported by a low zinc level of serum, hair, erythrocyte, or urine, with serum levels being the most widely used for diagnosis. Because interpretation of these laboratory values is prone to a number of errors, including overlap with the reference range, diurnal variations, and alteration by albumin level,[5] it may be beneficial to perform a biopsy for confirmation.

Supportive histologic features are similar to glucagonoma syndrome. There is focal parakeratosis overlying areas of unaffected basket weave stratum corneum, mild spongiosis, and acanthosis, with absence of the granular layer. The keratinocytes appear pale in the upper layers of the epidermis. Subcorneal or intraepidermal clefts also have been associated with AE.[5] Interestingly, forms of AE without hypozincemia have been reported; therefore, measurement of metalloenzymes containing zinc may be indicators of zinc deficiency. There are approximately 300 metalloenzymes containing zinc, including alkaline phosphatase, carbonic anhydrase, RNA and DNA polymerase, and carboxypeptidases A and B.[12] Physicians most commonly test for alkaline phosphatase and the level is decreased in patients with zinc deficiency.[3] Finally, jejunal biopsies have been performed and the findings of electron-dense filamentous inclusions in Paneth granular cells are considered pathognomonic. This procedure is not routinely performed nor considered necessary in most cases.[14]

Hereditary AE is a disease of infancy and usually manifests at the end of breast-feeding as perioral and acral dermatitis. Maternal breast milk has much higher zinc content than cow's milk.[5] AE-like conditions can be seen at all ages and are secondary to a number of different physiologic and pathologic states, including malnutrition, malabsorption, or increased metabolism of zinc. Malnutritive states include total parenteral nutrition, anorexia, and diets high in phytates and calcium. Malabsorptive states include inflammatory bowel disease, short bowel syndrome, celiac disease, cystic fibrosis, and pancreatic insufficiency. High metabolic states include prematurity, adolescence, pregnancy, extensive burns, surgery, sickle cell anemia, and systemic malignancies.[3,10] Other causes of AE are defects of mammary zinc secretion, termed *lactogenic acrodermatitis*[5]; diabetes; and renal tubule dysfunction.[3] Conversely, there are several metabolic disorders that cause cutaneous eruptions similar to AE and are not associated with zinc deficiency, including methylmalonic aciduria, multiple carboxylase deficiency, essential fatty acid deficiency, organic acidemia and other aminoacidopathies.[3]

The differential diagnosis is broad, including epidermolysis bullosa, cystic fibrosis, glucagonoma syndrome, widespread candidiasis, pellagra, seborrheic dermatitis, hypovitaminosis, atopic dermatitis, and celiac disease. In children, biotinidase deficiency, phenylketonuria, Hartnup disease, Leiner disease, Wiskott-Aldrich syndrome, severe combined immunodeficiency, congenital periorificial, and palmoplantar keratoderma also should be considered.[3,10,14]

For more than 3 decades, the preferred treatment for AE and acquired zinc deficiency conditions had been clioquinol (5-chloro-7-iodo-8-hydroxyquinoline). However, this treatment has been linked to subacute myelo-optico-neuropathy characterized by peripheral neuropathy and blindness, and thus its use has been abandoned. Since Barnes and Moynahan[13] discovered the etiology of AE to be zinc deficiency, oral zinc has been the mainstay of treatment. Zinc can be administered as acetates, amino acid chelates, gluconates, or sulfates. The latter seems to be the best tolerated and is most commonly used. Current recommendations are dosages of 1 to 2 mg/kg daily for children and 220 mg 3 times daily for adults, usually for a prolonged course.[5] Because of the chronic nature of treatment, one must continue to be watchful for adverse effects. Nausea and vomiting are the most common adverse effects, and there also is the potential for hemorrhage and hypocupremia to occur. Therefore, serum copper levels should be monitored. A rapid clinical response can be expected in 24 to 48 hours, with resolution of cutaneous lesions and hair regrowth beginning within 2 to 4 weeks.[3,15]

Acquired AE was diagnosed in our patient because of a decreased serum zinc level of 46 μg/dL (reference range, 70–150 μg/dL). His serum copper and serum selenium levels were within reference range at 71 μg/dL and 41 μg/dL, respectively (reference ranges, 70–140 μg/dL and 23–190 μg/L, respectively). Sweat chloride was within reference range at 29 mmol/L (reference range, 0–40 mmol/L) and ceruloplasmin was 25 mg/dL (reference range, 20–40 mg/dL). Antinuclear, antimitochondrial, anti–smooth muscle, antigliadin, anti-endomysial, and anticardiolipin antibodies were negative. The patient was discharged with oral zinc sulfate 220 mg

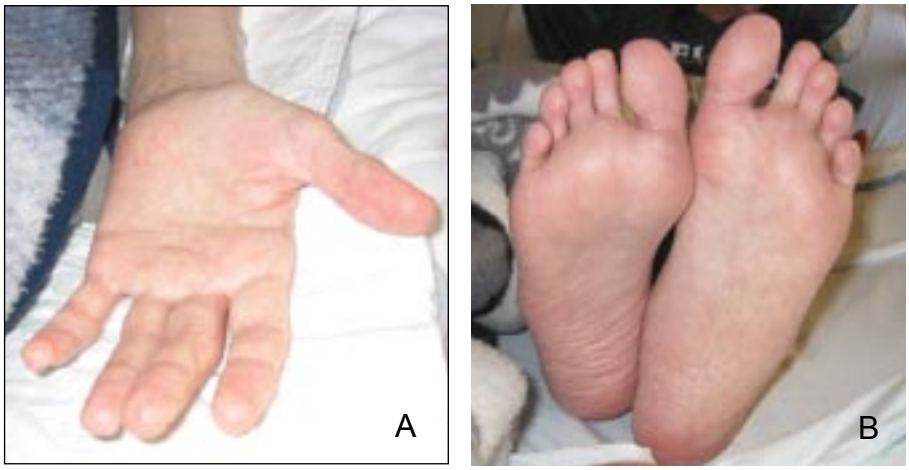

Figure 2. Resolution of lesions on the palm (A) and soles of the feet (B) 6 weeks after initiation of oral zinc sulfate.

twice daily, which led to resolution of his skin lesions and some hair regrowth at 6 weeks (Figure 2).

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