A Rash on the Face, Anogenital Region, and Extremities of a 3-Month-Old Boy

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A previously healthy 3-month-old boy was brought to the primary care pediatric dermatology clinic by his parents for evaluation of worsening facial, diaper, and extremity rash.

History

The infant was in his usual state of health until 1 month prior to presentation when he began to develop a facial rash, his mother reported. His mother also reported that the initial lesions had been perioral "bumps" that evolved to confluent, erythematous plaques. One week after the perioral rash had appeared, the infant had developed a similar eruption in his diaper region. The patient was seen by his pediatrician at that time, and presumed impetigo was diagnosed and treated. The patient had limited response to topical mupirocin and oral cephalexin.

Upon presentation to our clinic a few weeks later, the patient's mother noted that new lesions had been developing on his upper and lower extremities, in addition to those in the perioral and diaper regions. The infant had recently begun having increased stools, and there was a slowing of his growth curve from the 21st percentile at birth to the 5th percentile at presentation (3 months of age). He was exclusively breast fed, and his mother is a pescatarian.

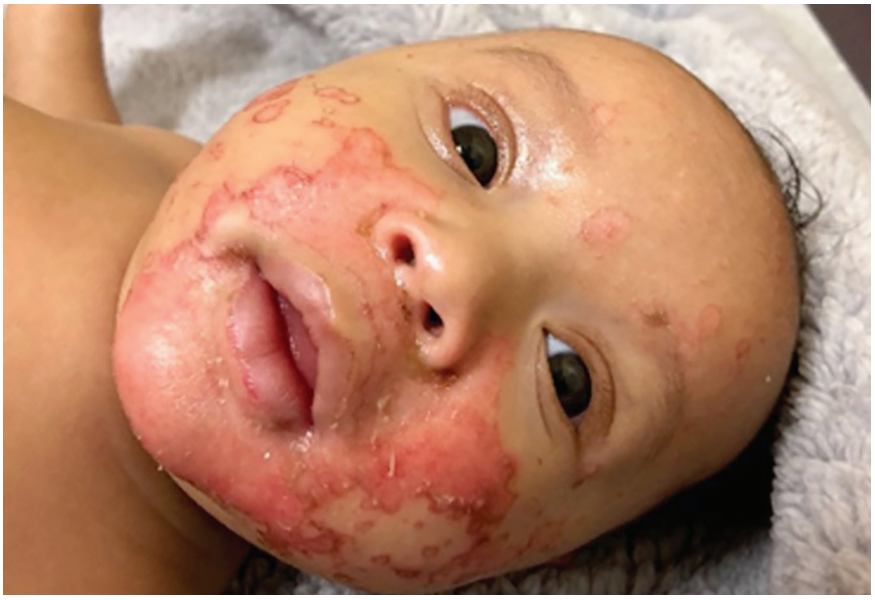

Figure 1. Erythematous, confluent, sharply demarcated, denuded facial plaques were most notable in perioral distribution.

A review of systems showed no history of fevers, irritability, vomiting, feeding difficulty, hair loss, ocular symptoms, or nail changes. The infant was delivered at full-term after an unremarkable pregnancy. He had been born appropriate for gestational age and had an unremarkable newborn nursery course with no subsequent hospitalizations or surgeries.

He had no known allergies, and his family history was only significant for eczema on his father's side. The patient lived with his parents and 8-year-old brother.

Physical examination

The infant was well-appearing and in no apparent distress. Results of a skin examination were remarkable for erythematous, confluent, sharply demarcated, denuded

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facial plaques most notable in perioral distribution. There was a small amount of infranasal crusting as well (Figure 1).

Confluent, erythematous plaques with peripheral prominence were noted in the perianal region, along with mild diffuse erythema in the scrotal region (Figure 2). The inguinal folds were clear, and no xerosis was noted. Smaller, well-demarcated, scaly, erythematous plaques were scattered on the patient's upper and lower extremities (Figures 3 and 4). The rest of the physical examination was unremarkable.

Diagnostic tests

A skin culture of the affected area on the patient's face grew normal skin flora without pathogenic organisms. The patient's serum zinc level was low at 12 µg/dL (reference range, 26-141 µg/dL).

Based on the patient's presentation, what is your diagnosis?

A. Seborrheic dermatitis
B. Acrodermatitis enteropathica
C. Biotinidase deficiency
D. An organic acidemia

Answer: B. Acrodermatitis enteropathica

The presentation of the infant's rash, including distribution and morphology, were suggestive of acrodermatitis enteropathica (AE). While awaiting the results of the patient's serum zinc level, cultures were collected from the crusted areas to rule out bacterial or Candida fungal infections as a causative or contributing factor.

Empirical treatment with topical mupirocin and oral trimethoprim-sulfamethoxazole, 9 mg/kg/d, was initiated to cover for Staphylococcus aureus until results of the cultures returned, which were negative. Elemental zinc sulfate supplementation, 3 mg/kg/d, was then initiated, and the patient's mother resumed taking prenatal vitamins to replete her breast milk.

Discussion

AE is a rare autosomal recessive disease characterized by impaired zinc absorption. The classic triad of clinical findings in patients with AE includes acral and periorificial dermatitis, diarrhea, and alopecia.[1,2] Of note, it is estimated that only about 20% of patients with AE present with all 3 symptoms.[1] Zinc is an essential mineral involved in protein and DNA synthesis, wound healing, cell regulation, and metabolism, as well as a cofactor for many enzymes including digestive enzymes, RNA polymerase, alkaline phosphatase, and alcohol dehydrogenase.[3]

Other symptoms of zinc deficiency may include irritability, growth restriction, immune dysfunction, nail changes, and ocular involvement with photophobia, blepharitis, or conjunctivitis.[4,5] The cutaneous lesions of AE are characterized by erosive erythematous plaques with peripheral scaling and crusting often found distributed in perioral and anogenital areas and on the scalp or distal extremities.[6] The differential diagnosis of AE includes

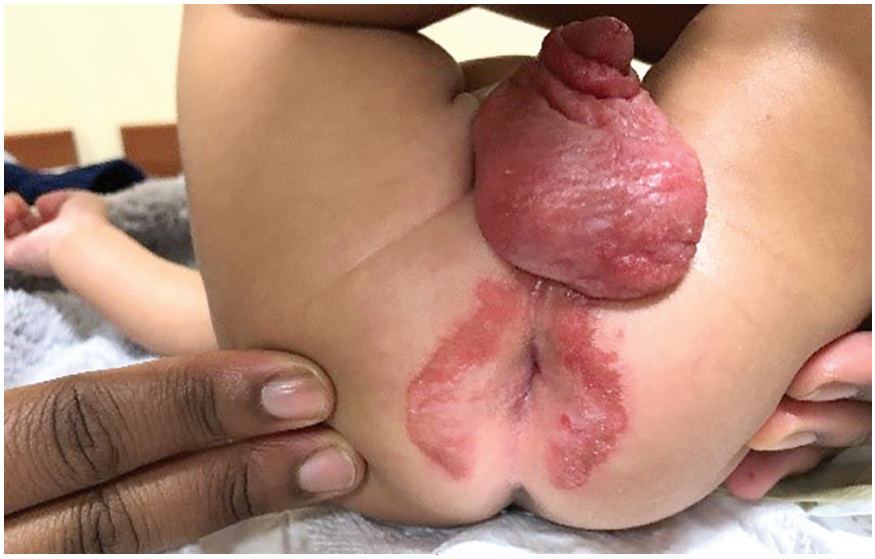

Figure 2. Confluent, erythematous plaques with peripheral prominence were noted in the perianal region, along with mild diffuse erythema on the scrotum.

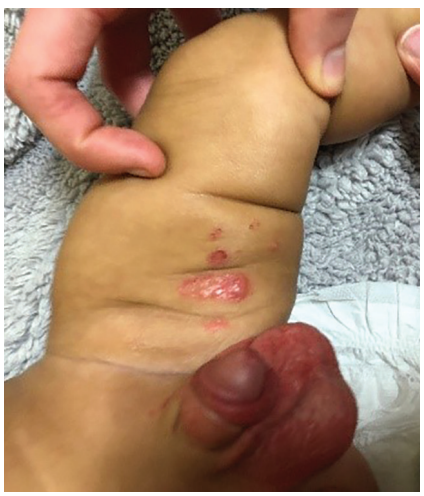

Figure 3. Smaller, well-demarcated, scaly, erythematous plaques were scattered on the patient's lower extremities.

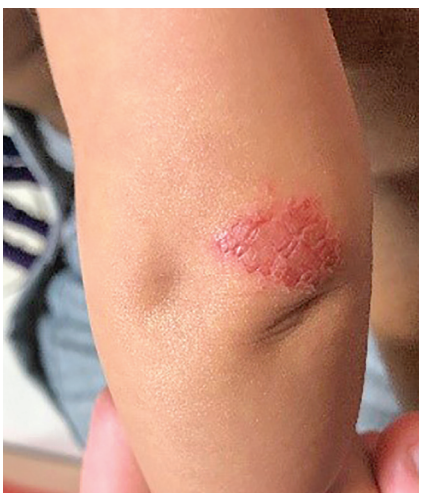

Figure 4. Plaques were also scattered on the patient's upper extremities.

Figure 5. Postinflammatory hypopigmentation was seen in the areas of previous erythema, but near complete resolution of the lesions was noted after 3 weeks of therapy.

severe seborrheic dermatitis, biotinidase deficiency, certain organic acidemias, and other inborn errors of metabolism.

Syndromes of zinc deficiency are classically grouped into 2 types: the congenital form (AE) or acquired form. Acquired forms include malabsorptive syndromes such as Crohn disease or ulcerative colitis, celiac sprue, cystic fibrosis, sickle cell disease, liver or renal disease, systemic malignancies, prematurity, and defects of mammary zinc secretion or insufficient dietary intake.[6]

The etiology of congenital AE is postulated to be from mutations in the *SLC39A4* gene, which encodes the zinc transporter ZIP4.[7] ZIP4 is secreted from the pancreas and plays an integral role in localization of zinc-to-cell membranes and its subsequent uptake from proximal small intestine lumen into the mucosa.[8] ZIP4 is also expressed in human keratinocytes and has been linked to regulation of transcriptional activity of the epidermal zinc-binding protein ΔNp63 and subsequent epidermal differentiation, which may explain the cutaneous manifestations associated with the disease.[9] Mutations in *SLC39A4* are inherited in an autosomal recessive pattern.[7]

The incidence of AE is estimated to be 1 per 500,000 children with no observed predilection for sex or race.[2] Approximately 30% of patients have an affected sibling.[6]

Diagnosis of AE is primarily clinical and may be confirmed by rapid resolution of symptoms in response to zinc supplementation. Serum zinc levels may support the diagnosis, but this clinical test has low sensitivity and specificity. Therefore, the test is not necessary or sufficient for diagnosis because serum zinc levels fluctuate with daily intake and inflammatory states.[10] Of note, patients with normal plasma zinc levels may respond to zinc supplementation.[11] Plasma zinc only composes 0.1% of the body's stores, further complicating accurate clinically significant testing.[3]

Levels of zinc-dependent enzymes, such as alkaline phosphatase, also may be decreased.[12] Genetic testing for *SLC39A4* mutations may be performed but are not necessary for diagnosis. Although biopsy is not required for diagnosis, it may show epidermal hyperplasia with acanthosis, necrotic keratinocytes, crusts, and intraepidermal vacuolization.[3,11] Acquired forms of zinc deficiency often have a more variable presentation and are typically limited with no recurrence after 3 to 4 months of oral zinc replacement therapy.[11] Congenital cases of AE, however, require indefinite oral zinc supplementation to prevent recurrence of clinical symptoms. The minimum recommended dose of supplemental zinc for AE is 3 mg/kg/d, with doses guided by serum zinc measurements taken every 3 to 6 months over the course of a patient's life.[3,5,11] Interestingly, cases of spontaneous remission of AE have been reported around onset of puberty.[13]

Patient outcome

The patient's skin lesions quickly and markedly improved on a diagnostic trial of supplemental zinc therapy, with near complete resolution of the lesions after 3 weeks of therapy. Postinflammatory hypopigmentation was seen in the areas of previous erythema (Figure 5). Genetic testing for mutations in *SLC39A4* was conducted, results of which were negative. However, the clinical presentation and dramatic response to zinc therapy were consistent with the diagnosis of AE. Oral zinc supplementation will be continued indefinitely.

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