Cystic Fibrosis Presenting With Dermatitis

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Background: Patients with cystic fibrosis classically present with evidence of pulmonary disease, exocrine pancreatic insufficiency, and high sweat chloride concentrations. Dermatitis as an initial manifestation of the disease is uncommon and has been attributed to multiple nutritional deficiencies.

Observation: We describe the case of a 3-month-old female infant with cystic fibrosis presenting with dermatitis in the setting of protein-energy malnutrition. A review of the laboratory study results in this case and others showed that a deficiency in zinc, essential fatty acids, and protein likely contributes to the development of the rash seen in cystic fibrosis.

Conclusions: Given the frequent delay in diagnosis, as well as the increased morbidity and mortality associated with protein-energy malnutrition in these patients, it is important to consider cystic fibrosis as a possible diagnosis in any infant presenting with a rash and other signs of malnutrition. The relative contribution of specific nutritional deficiencies and the degree to which they influence and interact with each other in producing the dermatitis remain unclear, although they may all affect a common underlying metabolic pathway.

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Cystic fibrosis is an autosomal recessive disease resulting from mutation of the cystic fibrosis (CF) transmembrane conductance regulator gene (CFTR; OMIM 602421) on chromosome 7, leading to the production of a defective epithelial chloride channel.1 The condition classically manifests as a triad of clinical findings, including chronic pulmonary disease, exocrine pancreatic insufficiency, and abnormally high sweat electrolyte concentrations.2 Less frequently, patients present with protein-energy malnutrition (PEM) characterized by edema, anemia, and hypoproteinemia.3 PEM occurs in 5% to 13% of infants with CF and is associated with increased morbidity and mortality.3,4 Dermatitis as an initial presentation of CF is rare and has been attributed to deficiencies in zinc, protein, and essential fatty acids (EFAs).2,5,6 The rash typically occurs 1 month before the onset of edema and other clinical manifestations.2 Given the increased morbidity and mortality associated with this condition, prompt recognition and initiation of treatment is necessary. We describe the case of a 3-month-old girl with CF presenting with dermatitis and PEM.

A 3-month-old female infant was referred for evaluation of a rash and failure to thrive. She was born at 39 7/7 weeks' gestation (birth weight, 3289 g [50th percentile]; birth length, 50.8 cm [60th percentile]) to nonconsanguineous parents and was exclusively breast-fed until started on a regimen of iron drops and supplemental formula 1 week before presentation. The rash began several days after birth and initially started as a small erythematous macule over the right buttock that subsequently spread to involve the entire buttocks, genitals, and thighs. In the week before admission, the infant developed similar lesions on her trunk, on her proximal upper extremities, and under her chin. The lesions had been treated with a number of medications, including topical corticosteroids, antifungal cream, and pimecrolimus with no resolution. In addition, her parents reported a 4-day history of swelling first noted on her feet, which then affected her legs, arms, and face. She had a lifelong history of green, watery stools, as well as a history of gastroesophageal reflux disease since the age of 3 weeks that was treated with a histamine2 blocker. Her parents noted in-
creased fussiness and hunger in the weeks immediately preceding presentation.

At the time of admission, her body weight, head circumference, and length were 4.11 kg (<3rd percentile), 37 cm (<3rd percentile), and 57 cm (20th percentile), respectively. Physical examination revealed coalescing erythematous plaques with overlying desquamation covering the buttocks and genitourinary region (Figure), with smaller erythematous plaques dispersed diffusely across her anterior torso, arms, hands, and chin. Her face and extremities were markedly edematous. Nails and mucous membranes were normal, and she had no evidence of hepatomegaly or alopecia. Abnormal laboratory values included the following: hemoglobin, 7.6 g/dL (reference range, 10.0-18.0 g/dL); hematocrit, 24.2% (reference range, 31.0%-55.0%); total protein, 3.0 g/dL (reference range, 6.0-8.3 g/dL); albumin, 1.2 g/dL (reference range, 3.5-5.7 g/dL); prealbumin, <7.0 mg/dL (reference range, 18.45 mg/dL); aspartate aminotransferase, 49 U/L (reference range, 13-39 U/L); and increased fecal fat. Her zinc status was not determined until several days after treatment initiation and was 43.6 µg/dL (reference range, 67.0-124.0 µg/dL). The white blood cell count (14,600/µL [reference range, 5000-19,500/µL]), alanine aminotransferase (43 U/L [reference range, 7-52 U/L]), alkaline phosphatase (355 U/L [reference range, 120-450 U/L]), and total bilirubin (0.4 mg/dL [reference range, 0.3-1.2 mg/dL]) were within normal limits. A sweat chloride test was unsuccessful, but a CF polymerase chain reaction test was positive for the F508 mutation, confirming the diagnosis of CF. (To convert alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase to microkatal per liter, multiply by 0.0167; albumin, hemoglobin, and total protein to grams per liter, multiply by 10; total bilirubin to micromoles per liter, multiply by 17.104; hematocrit to a proportion of 1.0, multiply by 0.01; prealbumin to milligrams per liter, multiply by 10; white blood cell count to ×10⁸ per liter, multiply by 0.001; and zinc to micromoles per liter, multiply by 0.153).

The infant was initially treated with an elemental formula via nasogastric tube for her malnutrition but was switched to breast milk, supplemental enzymes, and vitamins after her diagnosis was made. On discharge from the hospital, she exhibited marked improvement with less edema, resolving lesions, and improved nutritional status.

Dermatitis as an initial manifestation of CF is rare and has been previously reported in 24 other known patients.²,⁶-¹⁰ The dermatitis typically presents as erythematous, scaling papules that later progress to extensive coalescing, desquamating plaques. The eruption is usually first noted in the perineum anywhere from several days to 15 months after birth, with subsequent spread to the perioral region, extremities, and trunk. Infants often have a history of several large, loose stools per day occurring at the onset or shortly after development of the lesions. Other findings of PEM, including failure to thrive and pitting edema of the extremities and face, are nearly universal by the time of presentation, whereas alopecia,²,⁵,⁸,⁹,¹³,¹⁶ and hepatomegaly,³,⁵,⁹,¹³,¹⁶ are less consistently observed. Nail and mucous membrane involvement has not been reported, and laboratory values almost always show evidence of anemia and hypoproteinemia.

The cutaneous findings in CF are thought to be caused by a combination of zinc, protein, and EFA deficiencies,²,⁵,⁶ although the exact pathogenesis of the dermatitis is unclear. It is well known that deficits in zinc levels can produce a dermatitis similar to that noted in our case. This is perhaps best seen in acrodermatitis enteropathica, an autosomal recessive disorder associated with decreased intestinal zinc absorption due to mutation of the SLC39A4 gene on chromosome 8q24.³,²⁰ This gene is responsible for producing a transmembrane protein within intestinal enterocytes that facilitates zinc uptake.²⁰ The observed eruption consists of erythematous dry, scaly plaques in a periorificial and acral pattern on the face, scalp, hands, feet, and anogenital regions. Several conditions leading to an acquired zinc deficiency have presented with similar cutaneous findings and include intestinal malabsorption syndromes, prematurity, defects in mammary zinc secretion, prolonged total parenteral nutrition administration, and anorexia.²,⁷

In cases in which zinc was measured, 12 of 16 infants with CF presenting with dermatitis had decreased levels,²,⁵,⁹,¹³,¹⁶,¹⁷ suggesting that deficiency in this nutrient likely contributes to the cutaneous findings. Mild to moderate zinc deficiency in infants with CF who do not have skin lesions has also been described.²¹ Accurate assessment of an individual's zinc status is complicated by the fact that blood levels decrease during states of inflammation and hypoalbuminemia, which are both often present in these infants. When it occurs, low zinc levels in CF may be attributed to decreased release and absorption of zinc from dietary protein secondary to pancreatic insufficiency.²² In addition, steatorrhea may impair reabsorption of endogenously secreted zinc, possibly via the formation of insoluble fat-zinc complexes.²² In support of this hypothesis, Krebs et al²² found that high losses of endogenous zinc associated with fat malabsorption were present in the feces of infants with CF. In children with
the infants in both of those cases were found to have low 24 reported cases of CF presenting with dermatitis, and deficiency. Essential fatty acid status was determined in 2 of 26 observed in patients with CF2,6 and in other studies,26 producing lesions similar to those seen with zinc deficiency. Essential fatty acid status was determined in 2 of 24 reported cases of CF presenting with dermatitis, and the infants in both of those cases were found to have low EFA levels.24 However, given the high prevalence of fatty acid abnormalities in individuals with CF who do not present with lesions (≥85% in those with evidence of malabsorption24 and 47%27 to 67%28 in randomly screened patients with CF), it is likely that other factors also contribute to the dermatitis seen in these patients.

Most cases of CF complicated by malnutrition and dermatitis have had evidence of protein deficiency as manifested by hypoalbuminemia and hypoproteinemia. These findings have led to the comparison of this condition with kwashiorkor, an edematous state of malnutrition that is associated with deficiency in protein and other nutrients. The characteristic skin lesions associated with kwashiorkor may resemble those seen in infants with CF. However, individuals with kwashiorkor may present with additional findings, including softening and thinning of the nails, glossitis, cheilitis, and perlèche.7,29 Similar to CF-associated dermatitis, the dermatologic manifestations seen in kwashiorkor may reflect multiple nutritional deficiencies, including a lack of vitamins and minerals commonly associated with protein-rich foods. Hypozincemia, seen often in kwashiorkor,30 is thought to at least partially contribute to the cutaneous findings, and topical application of zinc has been shown to lead to more rapid healing of kwashiorkor skin lesions.31

In addition to skin changes, kwashiorkor has other clinical features that are similar to those seen in infants with CF and PEM, including edema, anemia, alopecia, elevated liver enzyme levels, and failure to thrive. Indeed, many researchers consider these infants to have a diagnosis of kwashiorkor secondary to malabsorption.5,16 The edema seen in both conditions may have a common underlying cause involving free radical–mediated damage to cell membranes leading to an increased leak of electrolytes and altered fluid homeostasis.32 Anemia is also found in both states and likely arises because of decreased globin synthesis secondary to inadequate protein.13 Hepatic steatosis (fatty liver) may result from a number of malnutrition-related deficits. When reported, hepatic enzyme levels were elevated in nearly all cases of CF dermatitis, and fatty liver was diagnosed in 5 of 6 liver biopsy or autopsy findings.3,7,9,12 One infant had a particularly complicated course that included significant hepatitis and signs of hepatic failure.19

Although it is evident that deficiencies in zinc, EFAs, and protein are associated with the development of dermatitis in infants with CF and in other children and adults as discussed in the preceding paragraphs, the exact pathophysiological mechanism that generates the dermatitis remains to be elucidated. Many studies have investigated the role of prostaglandins in CF, hypothesizing that altered levels of these substances may be the common underlying cause of the skin findings and other clinical manifestations of the disease.33 The metabolism of EFAs such as linoleic acid has been shown to generate bioactive products that may be important in protecting the epidermis from hyperproliferative and inflammatory processes.34 Deficiencies in these EFAs and their metabolites may alter epidermal homeostasis, resulting in the production of proinflammatory leukotrienes, decreased prostaglandin levels, and reduced activity of specific monohydroxy fatty acids that may function to inhibit epidermal hyperproliferation.34 By serving as a cofactor for the Δ6-desaturase enzyme involved in EFA metabolism,31 zinc may also affect this pathway and influence the production of eicosanoids and other biologically active metabolites. Numerous studies have supported the importance of zinc in the metabolism of EFAs, as reviewed by Cunnane et al.35,36 Finally, decreased protein (more specifically, deficiencies in certain amino acids) may alter EFA metabolism.37 PEM is frequently associated with EFA deficiency, and it has been suggested that many of the clinical symptoms—including skin changes—seen in these malnourished individuals may be at least partially attributed to EFA deficiency.38

In conclusion, the dermatitis seen in infants with CF is likely multifactorial, with deficiencies in zinc, EFAs, and protein contributing to its development. However, the relative contribution of each nutrient and the degree to which each influences and interacts with the others in producing the dermatitis are unclear. They all may affect a common underlying pathway such as EFA metabolism, altering the production of eicosanoids and other metabolites. In addition, free radical–mediated damage secondary to suboptimal nutritional status and other oxidative stresses may contribute to the dermatitis and other symptoms seen in these infants.9,32 The same metabolic pathways may be affected in other conditions, such as acrodermatitis enteropathica and kwashiorkor, that often have similar dermatologic findings and overlapping nutritional deficiencies. Given the frequent delay in diagnosis, as well as the increased morbidity and mortality associated with PEM in these patients, it is important to consider CF as a possible diagnosis in any infant presenting with dermatitis and other signs of malnutrition. The differential diagnosis should also include biontin deficiency, immunodeficiency syndromes, and aminoaciduria disorders.

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REFERENCES


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