

Severe Infant Rash Resistant to Therapy Due to Zinc Deficiency

A Case Report

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Abstract: Pediatric skin diseases are a common presenting complaint to emergency medicine physicians but often pose a significant diagnostic challenge. Skin eruptions that are unusually severe for the diagnosis in question, lasting beyond the typical time of resolution, or not responding to conventional therapy should raise concern of a misdiagnosis. We present the case of a severe rash not responding to conventional atopic dermatitis therapy that led to a diagnosis of transient neonatal zinc deficiency. Clinicians caring for children should be aware of zinc deficiency and its corresponding clinical presentation, because it is readily treatable and may lead to the avoidance of unnecessary treatments and prevention of serious complications.

Key Words: dermatology, skin rash, zinc deficiency

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Pediatric skin diseases are a common presenting complaint to emergency medicine physicians but often pose a significant diagnostic challenge. In a recent review of outpatient pediatric clinic visits, 24% of the presenting complaints related to the skin. Conditions commonly seen and managed were as follows: 37% were due to some form of dermatitis (most commonly atopic dermatitis), 17% were due to bacterial infections, 6.5% were viral skin infections, and 14.5% were fungal infections.¹ Skin eruptions that are unusually severe for the diagnosis in question, lasting beyond the typical time of resolution, or not responding to conventional therapy should raise concern of a misdiagnosis. We present the case of a severe rash not responding to conventional atopic dermatitis therapy that led to an alternate diagnosis.

CASE

A previously healthy 3-month-old male infant presented to the emergency department with a 3-week history of erythematous plaques of his cheeks, which subsequently spread to involve his neck, perianal area, and extremities. One week after the onset of the rash, he developed loose stools followed by increasing fussiness. The infant was born at term, via an uncomplicated pregnancy and delivery. He had been breast fed exclusively and was feeding and gaining weight well. There was no relevant family history. Treatments for the rash included fucidin cream, cephalixin, and 1% hydrocortisone cream with no improvement.

On examination, the patient's vital signs were within normal limits. General physical examination revealed no abnormalities apart from the skin. Examination of the skin revealed symmetrically distributed, well-demarcated erythematous erosive plaques with a periphery of red/brown scale, located on the perioral, periorcular,

perinasal, and perianal areas as well as dorsum of the hands, neck, and large folds of the extremities (Figs. 1, 2). He also had partial alopecia and a few pustules on the chin.

Given the unclear diagnosis and poor response to treatment, he was referred to pediatric dermatology. Blood tests undertaken included a complete blood count and serum electrolytes, which were normal. Liver function tests were relevant only for a mildly elevated aspartate aminotransferase (65 U/L; normal range, ≤ 40 U/L) and a serum alkaline phosphatase (130 IU/L; normal range, < 449 IU/L). Because of clinical suspicion, serum zinc (Zn) level was obtained and found to be significantly reduced (342 $\mu\text{g/L}$; normal range, 647–1301 $\mu\text{g/L}$). Swabs of the pustules on the chin were positive for methicillin-sensitive *Staphylococcus aureus*.

The rash, clinical features, and blood tests were consistent with a diagnosis of transient neonatal zinc deficiency (TNZD) due to low breast milk Zn. Zinc supplementation was initiated with Zn gluconate 30 mg by mouth once daily (0.6 mg/kg per day of elemental Zn). He was also given fucidin cream to be applied to the pustules on the chin.

OUTCOME

After only 3 days, the rash was significantly improved, and at the 14th day, the rash was completely resolved, leaving only postinflammatory hyperpigmentation (Figs. 3, 4). The previous pustules were also resolved. With introduction of solid foods, Zn supplementation was stopped and there has been no recurrence with normal Zn levels.

DISCUSSION

Zinc is the second most abundant trace element in humans.² It acts as an integral component of numerous metalloenzymes and is essential for growth, wound healing, antioxidant function, and normal immune function.^{3,4}

Given its multiple and important functions, deficiency of Zn can result in various clinical manifestations and is responsible for approximately 4% of the worldwide morbidity and mortality burdens of young children.⁵ For this reason, the World Health Organization has highlighted Zn deficiency as an important public health issue.⁶ However, Zn deficiency remains relatively uncommon in developed countries, likely relating to the higher consumptions of Zn-rich foods.^{4,6}

Infants are particularly vulnerable to Zn deficiency because they rely on a high source of Zn from breast milk especially during the first several months of life while other dietary sources are lacking.^{7–9} This is even more important in preterm infants who lack significant hepatic Zn stores present in term infant.¹⁰ If these needs are not met, clinical sequelae of Zn deficiency develop, including a characteristic skin rash, alopecia, and diarrhea as well as significant impairment in growth and development if early treatment is not implemented.⁴

The etiology of Zn deficiency can be categorized into those resulting from inadequate intake, excessive loss, malabsorption, increased demand, or other diseases with no known pathological mechanism.⁴ In infants, inadequate intake is a common mechanism,

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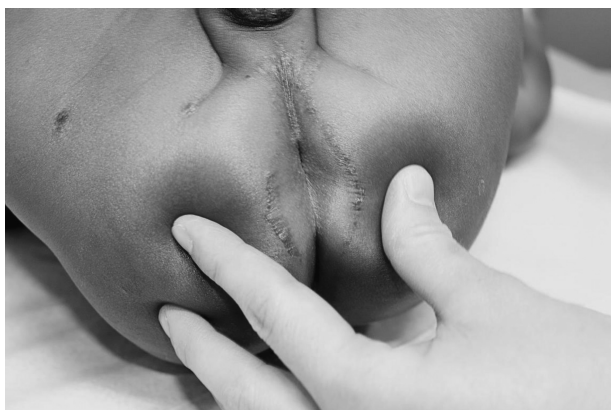


FIGURE 1. Perianal area before treatment.

and can result from TNZD, secondary to low breast milk Zn. The clinical features in the present case were consistent with this diagnosis. Other common etiologies include prematurity, absent Zn supplementation during total parenteral nutrition, and maternal serum Zn deficiency.⁴ Transient neonatal Zn deficiency due to low breast milk Zn is characterized by a low serum Zn in exclusively breastfed infants.¹¹ It results from *SLC30A2* gene mutations, leading to ZnT-2 protein dysfunction, which is a transporter protein responsible for secreting Zn into human breast milk.¹² Three different mutations in the *SLC30A2* gene that code for the ZnT-2 protein have been described, thus far including H54R, G87R, and 663delC.^{13,14}

Acrodermatitis enteropathica is a rare autosomal recessive disorder that can also lead to Zn deficiency in the neonate/infantile period. It is caused by a mutation in the *SLC39A4* gene that encodes the Zip4 transporter, resulting in inadequate intestinal absorption of Zn.¹⁵ These patients present with indistinguishable clinical characteristics to other types of Zn deficiency but require lifelong Zn supplementation.⁴



FIGURE 2. Face before treatment.



FIGURE 3. Perianal area after treatment.

Skin involvement is usually the first and most characteristic clinical manifestation of TNZD. Erythematous scaly or erosive plaques located periorificially, around the mouth, eyes, nose, and genital area are the most characteristic findings, whereas the neck, acral sites, and large skin folds of the extremities can also be affected.^{16–19} This is in contrast to atopic dermatitis, which is very pruritic, spares the diaper area and is generally not well demarcated. Diarrhea, alopecia, and irritability are commonly associated findings with TNZD.^{4,14} Knowledge of the skin lesions that are suggestive of Zn deficiency and the chronology in appearance of the lesions are useful features to establish a diagnosis of Zn deficiency so that treatment can be initiated as early as possible, thereby avoiding significant morbidity and mortality.

If Zn deficiency is suspected, a low alkaline phosphatase is a quick and sensitive test readily available in the acute care setting that can support the clinical suspicion.^{12,17} Alkaline phosphatase is a Zn-dependent enzyme and, as a result, is low with Zn deficiency as was noted in our patient.^{4,18} Normal ranges for alkaline phosphatase vary by age, sex, and variations within individual laboratories.¹⁹ Patients who are of the male sex and who are younger have higher baseline alkaline phosphatase.²⁰ One study looking at normative data for different ages and sexes in pediatrics found male infants aged 0 to 6 months to have a mean alkaline phosphatase of 746 IU/L.²⁰

The diagnosis is confirmed by measuring the serum Zn level in the affected patient, collected in a plastic tube to avoid Zn

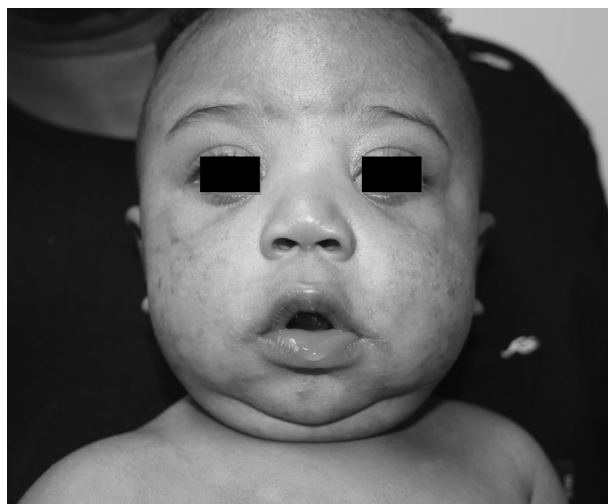


FIGURE 4. Face after treatment.

contamination. Ideally, this should be performed fasting and off any supplements.⁴ Measurement of the mother's serum Zn, as well as in the breast milk, will help establish the diagnosis of transient neonatal Zn deficiency due to inadequate breast milk Zn. However, in many centers, measuring Zn levels in breast milk may not be available. Although breast milk Zn was not measured in the current case, the clinical presentation, timing of symptoms, response to treatment, and lack of recurrence with solids confirmed the diagnosis. In addition, the mother did not have any risk factors for serum Zn deficiency.

Treatment should be established as early as possible with 0.5 to 1 mg/kg per day of elemental Zn.⁴ The skin rash can often be complicated by secondary staphylococcal and/or candida infections because of abnormal immune function.²¹ A high index of suspicion is required to diagnose these infections and antimicrobial treatment implemented if clinically present. With Zn supplementation, symptoms typically resolve rapidly and are generally continued for approximately 3 to 4 months until complementary nutrition is introduced in the diet.

In summary, skin diseases are a common and important presenting complaint to the emergency department. Although clinicians accurately diagnose many important conditions such as infections and eczema, it is equally important to be aware of conditions, which can mimic these rashes. Clinicians caring for children should be aware of Zn deficiency and its corresponding clinical presentation, because it is readily treatable and may lead to the avoidance of unnecessary treatments and prevention of serious complications such as growth retardation, infection, and cognitive delay.

REFERENCES

- Lampell MS. "Childhood rashes that present to the ED Part I: viral and bacterial issues." *Pediatr Emerg Med Pract.* 2007.
- MacDonald RS. The role of zinc in growth and cell proliferation. *J Nutr.* 2000;130:1500S–1508S.
- Eckhart CD, Sloan MV, Duncan JR, et al. Zinc binding: a difference between human and bovine milk. *Science.* 1977;195:789–790.
- Corbo MD, Lam J. Zinc deficiency and its management in the pediatric population: a literature review and proposed etiologic classification. *J Am Acad Dermatol.* 2013;69:616–624.e1.
- Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet.* 2008;371:243–260.
- World Health Organization. Workshop to review the results of the studies evaluating the impact of zinc supplement on childhood mortality and severe morbidity. *WHO Web site.* Available at: http://www.who.int/maternal_child_adolescent/documents/zinc_mortality/en/. Accessed June 6, 2013.
- Miletta MC, Bieri A, Kernland K, et al. Transient neonatal zinc deficiency caused by a heterozygous G87R mutation in the zinc transporter ZnT-2 (SLC30A2) gene in the mother highlighting the importance of Zn (2+) for normal growth and development. *Int J Endocrinol.* 2013;2013:259189.
- Hambidge KM, Krebs NF. Zinc deficiency: a special challenge. *J Nutr.* 2007;137:1101–1105.
- Zlotkin SH, Cherian MG. Hepatic metallothionein as a source of zinc and cysteine during the first year of life. *Pediatr Res.* 1988;24:326–329.
- Ackland ML, Michalczyk A. Zinc deficiency and its inherited disorders – a review. *Genes Nutr.* 2006;1:41–49.
- Chowanadisai W, Lönnerdal B, Kelleher SL. Identification of a mutation in SLC30A2 (ZnT-2) in women with low milk zinc concentration that results in transient neonatal zinc deficiency. *J Biol Chem.* 2006;281:39699–39707.
- Lova Navarro M, Vera Casaño A, Benito López C, et al. Transient neonatal zinc deficiency due to a new autosomal dominant mutation in gene SLC30A2 (ZnT-2). *Pediatr Dermatol.* 2014;31:251–252. Epub January 23, 2014.
- Lasry I, Seo YA, Ityel H, et al. A dominant negative heterozygous G87R mutation in the zinc transporter, ZnT-2 (SLC30A2), results in transient neonatal zinc deficiency. *J Biol Chem.* 2012;287:29348–29361. Epub June 25, 2012.
- Murthy SC, Udagani MM, Badakali AV, et al. Symptomatic zinc deficiency in a full-term breast-fed infant. *Dermatol Online J.* 2010;16:3.
- Dufner-Beattie J, Wang F, Kuo YM, et al. The acrodermatitis enteropathica gene ZIP4 encodes a tissue-specific, zinc-regulated zinc transporter in mice. *J Biol Chem.* 2003;278:33474–33481.
- Kumar P, Lal NR, Mondal AK, et al. Zinc and skin: a brief summary. *Dermatol Online J.* 2012;18:1.
- Glover MT, Atherton DJ. Transient zinc deficiency in two full-term breast-fed siblings associated with low maternal breast milk zinc concentration. *Pediatr Dermatol.* 1988;5:10–13.
- Maverakis E, Fung MA, Lynch PJ, et al. Acrodermatitis enteropathica and an overview of zinc metabolism. *J Am Acad Dermatol.* 2007;56:116–124. Epub October 30, 2006.
- Turan S, Topcu B, Gökçe I, et al. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. *J Clin Res Pediatr Endocrinol.* 2011;3:7–11. Epub February 23, 2011.
- Corathers SD. Focus on diagnosis: the alkaline phosphatase level: nuances of a familiar test. *Pediatr Rev.* 2006;27:382–384.
- El Fékih N, Monia K, Schmitt S, et al. Transient symptomatic zinc deficiency in a breast-fed infant: relevance of a genetic study. *Nutrition.* 2011;27:1087–1089.
- Prasad AS. Zinc deficiency. *BMJ.* 2003;326:409.