Title
Bullous acrodermatitis enteropathica: case report of a unique clinical presentation and review of the literature

Journal
Dermatology Online Journal, 21(4)

Authors
Iyengar, Sanjana
Chambers, Cindy
Sharon, Victoria R

Publication Date
2015

DOI
10.5070/D3214026272

Volume 21 Number 4
April 2015

Case Presentation

Bullous acrodermatitis enteropathica: case report of a unique clinical presentation and review of the literature

Sanjana Iyengar BA[1], Cindy Chambers MD MAS MPH[2], Victoria R. Sharon MD DTMH[2]

Dermatology Online Journal 21 (4): 6

[1]Department of Medicine, Florida State University College of Medicine, Tallahassee, FL

[2]Department of Dermatology, University of California, Davis, Sacramento, CA

Correspondence:

Victoria R. Sharon, MD, DTMH
3301 C Street, Suite 1400
Sacramento, CA 95816, USA
Email: vrs2001@gmail.com

Abstract

Acrodermatitis enteropathica is a rare autosomal recessive disease characterized by pink scaly plaques and erosions in the periorificial and acral regions. A mutation in a gene responsible for zinc transport results in significant zinc deficiency in individuals lacking oral supplementation. We present a female infant with acrodermatitis enteropathica with crusting of the periorificial regions along with perineal plaques. A delay in diagnosis and treatment led to the development of pronounced painful acral bullae. Although plaques and erosions in the periorificial and acral regions are most commonly observed, bullae should also be considered in the spectrum of clinical manifestations of acrodermatitis enteropathica. The rare bullous variant of acrodermatitis enteropathica can be distinguished histologically.

Keywords: Acrodermatitis enteropathica, bullae, zinc deficiency

Introduction

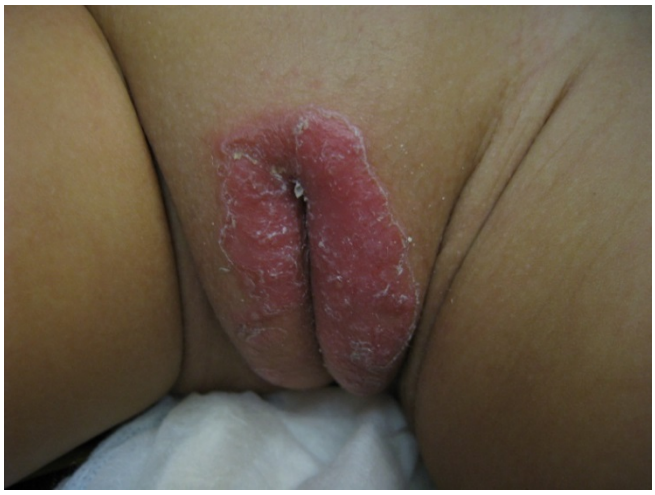
Zinc is a vital trace element found in nuts, whole grains, leafy vegetables, and shellfish[1]. Deficiency of zinc results from acquired or genetic causes. Acquired zinc deficiency develops from lack of zinc in the diet or decreased uptake of zinc in the duodenum or jejunum. Genetic zinc deficiency, called acrodermatitis enteropathica, can be traced to a mutation in the gene responsible for zinc transportation, resulting in poor zinc absorption. Acrodermatitis enteropathica is a rare disorder associated with cutaneous eruptions, diarrhea, and alopecia[2]. Skin changes mainly consist of erythematous plaques but can also include vesicles, bullae, and erosions[1]. The rare bullous variant of acrodermatitis enteropathica often presents with acral bullae and has characteristic histologic features, which serve to distinguish it from its other counterparts.

Case synopsis

A 15-month-old previously healthy girl presented with a two-month history of periorificial and perianal dermatitis with progressive painful acral blistering causing decreased mobility. The patient had been treated unsuccessfully for presumed atopic dermatitis, dermatophyte infection, impetigo, and viral infection with topical corticosteroids, antifungals, systemic antibiotics, and antiviral medications, respectively.

Physical examination revealed crusting of the lateral canthi, alar creases, and oral commissures as well as sharply-demarcated scaly pink plaques on the labia majora accompanied by bullae of the distal extremities (figures 1 and 2). Skin biopsies from the

foot and shin revealed prominent intracytoplasmic vesiculation, keratinocyte pallor and necrosis, and interface dermatitis (figure 3a, 3b). These findings were histopathologically unusual, but consistent with nutritional deficiency based upon clinical suspicion. A diagnosis of acrodermatitis enteropathica was confirmed by a markedly reduced serum zinc level (0.18 µg/mL: normal range, 0.6-1.2 µg/mL). A reduced albumin level (3.7 g/dL; normal range, 3.8-5.4 g/dL) and alkaline phosphatase level (55 U/L; normal range 70-160 U/L) were also noted.



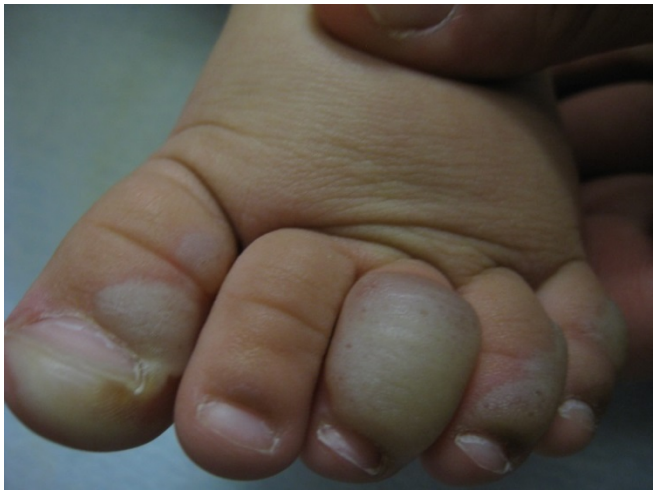
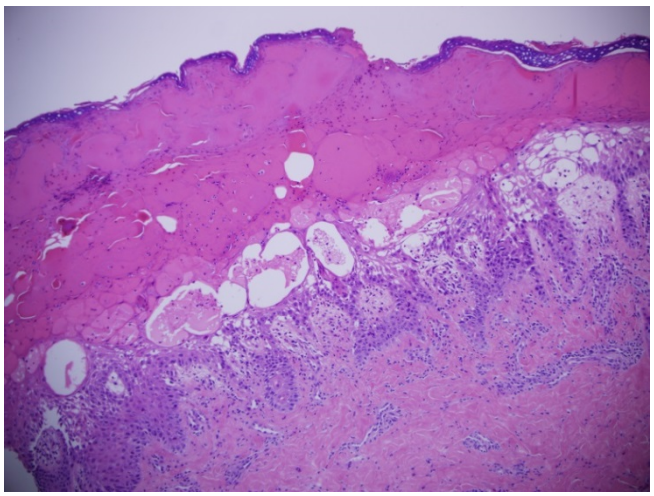


Figure 1. Pre-zinc therapy: sharply-demarcated scaly pink thin plaques on the labia majora. **Figure 2.** Pre-zinc therapy: acral bullae.



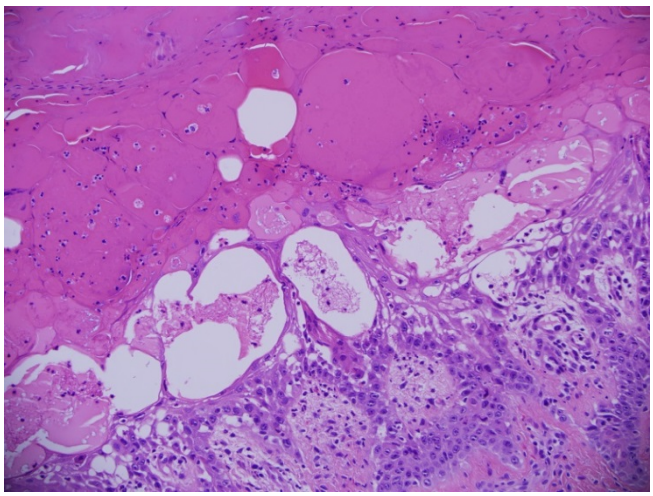
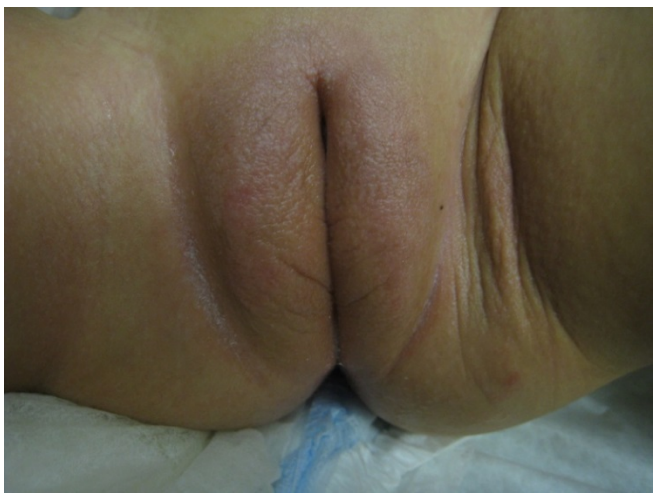


Figure 3 a, b (a) Scanning magnification of a biopsy from the foot reveals cytoplasmic pallor and prominent intraepidermal vesiculation (hematoxylin & eosin stain, 10X). (b) Higher power H&E magnification demonstrates keratinocyte pallor, keratinocyte necrosis, intraepidermal vesiculation, and interface changes (hematoxylin & eosin stain, 20X).

The patient was treated with oral zinc sulfate (1 mg/kg three times daily) with significant improvement within three days and near-complete resolution of her lesions at two weeks (figures 4 and 5). She has been maintained on 2mg/kg of zinc sulfate once daily without recurrence during 3 years of available follow-up.



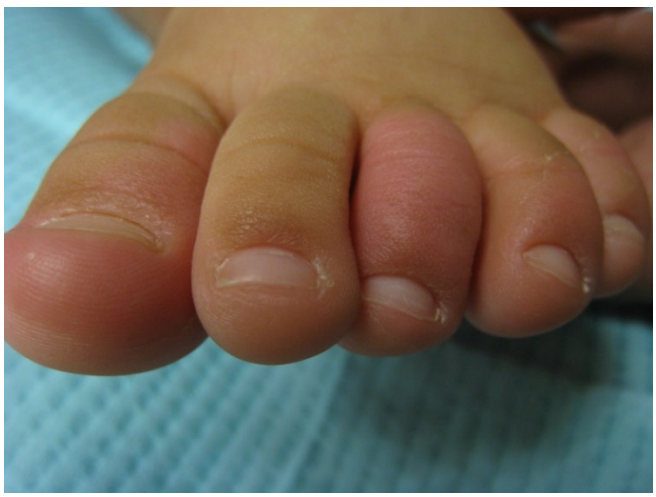


Figure 4. Post-zinc therapy: complete resolution of labial plaques two weeks later. **Figure 5.** Post-zinc therapy: complete resolution of acral bullae two weeks later

Discussion

First described in 1936, acrodermatitis enteropathica is a rare autosomal recessive disease of disordered zinc transport leading to severe zinc deficiency[3]. Mutations of the *SLC39A4* gene (Zip4 transporter) on chromosome 8q24.3 can be traced to the condition. Acrodermatitis enteropathica occurs at an estimated incidence of 1 per 500,000 children worldwide with no preference for race or gender[3]. In developing countries such as Southeast Asia and sub-Saharan Africa, zinc deficiency can be seen in a third of the population. In developed countries such as the United States, inadequate zinc intake can be seen in vegetarians, alcoholics, malnourished, and premature infants.

Early clinical findings of acrodermatitis enteropathica typically include perioral, perianal, and acral dermatitis, with more advanced disease often manifesting with alopecia, diarrhea, and failure to thrive[3]. Cutaneous lesions classically present with well-demarcated pink, scaly, and variably eroded plaques. Pustules, blisters, or bullae may develop, mimicking infectious, inflammatory, or autoimmune skin diseases. Hypogonadism, delayed puberty, and changes in mentation may also be seen in cases of severe zinc deficiency[4].

The diagnosis of acrodermatitis enteropathica can be difficult because fungal and bacterial superinfections commonly result from zinc deficiency[5]. However, biopsy reveals findings consistent with nutritional deficiency including cytoplasmic pallor, vacuolization, and keratinocyte necrosis[3]. Subcorneal and intraepidermal clefts may develop secondary to balloon degeneration[4]. Bullous acrodermatitis enteropathica characteristically has intra-epidermal vesiculation with absent to scant spongiosis in the presence of keratinocyte eosinophilia and/or necrosis[1].

Early treatment of acrodermatitis enteropathica skin lesions is vital as this condition left untreated can be fatal[4]. Treatment for acrodermatitis enteropathica includes supplemental zinc sulfate of 1 to 2 mg/kg/day in children or 220 mg three times a day in adults[6]. Plasma or serum zinc levels should be monitored every 3 to 6 months[3]. In addition, copper levels should be evaluated because zinc administration leads to a decrease in copper absorption. Clinical improvement may be seen within days to weeks of systemic therapy.

To our knowledge, there have been few cases of bullous acrodermatitis enteropathica reported in the literature. In 1992, two infants with bullous lesions affecting the paronychial areas and distal extremities were noted by Borroni et al[7]. Prior to the appearance of scaly, erythematous patches on the perioral, perianal, and buttock regions, both patients experienced repeated episodes of diarrhea. Oral zinc supplementation of 100 to 200 mg daily aided in resolution of cutaneous lesions in a few days. Similarly, in 2008 an 8 month-old infant was diagnosed with acrodermatitis enteropathica after being misdiagnosed with bullous impetigo and irritant dermatitis[1]. Clinical features such as growth retardation, psychomotor delay, and failure to thrive were noted and rapidly resolved status-post zinc supplementation. Table 1 summarizes key features of reported patients with bullous acrodermatitis enteropathica.

Table 1. Summary of key features of reported patients with bullous acrodermatitis enteropathica

	Age	Gender	Key features	Histopathology	Successful resolution status post-zinc supplementation	Zinc dosage
Patient 1 [7]	7 mo	F	Diarrhea preceding skin rash; diffuse non-scarring alopecia; bullae noted on hands and feet; exclusively bottlefed	Intraepidermal vesiculation; keratinocyte pallor; perivascular lymphocytic infiltrate	Yes	200 mg daily initially; 100 mg daily maintenance indefinitely
Patient 2 [1]	8 mo	F	Formula fed, anorexic, failure to thrive, growth retardation, psychomotor delay; small aphthae on buccal mucosa; scaly, crusted plaques noted on acral areas bilaterally	Mild spongiosis; epidermal necrosis; intra-epidermal vesiculation; lymphocytic and neutrophilic inflammatory infiltrate; superficial and perivascular infiltrate	Yes	40mg twice daily indefinitely

Patient 3 (current case)	15 mo	F	Previously healthy; decreased mobility; acral bullae; pink plaques on labia majora; crusting of the lateral canthi, alar creases, and oral commissures	Intracytoplasmic vesiculation, keratinocyte pallor and necrosis, and interface dermatitis	Yes	1mg/kg three times daily. Maintenance 2mg/kg daily indefinitely
Patient 4 [1]	1 yr	F	Premature; discontinued formula 2-3 weeks earlier; vesiculobullous lesions on hands, knees, and feet	Intra-epidermal vesicles; eosinophilic keratinocytes; necrotic keratinocytes; superficial lymphocytic infiltrate with prominent vasculature	Yes	Not specified; indefinite treatment
Patient 5 [7]	5 mo	M	Diarrhea preceding skin rash; premature; bullae noted on hands and feet; discontinued breastfeeding soon prior to eruption	Intra- and subepidermal vesiculation; epidermal necrosis; neutrophils and eosinophils; superficial lymphohistiocytic inflammatory infiltrate	Yes	100 mg twice daily indefinitely
Patient 6 [2]	23 yr	M	History of Crohn's disease; multiple vesiculobullous lesions on feet; red patches around fingernails; currently on total parenteral nutrition	Intraepidermal vesiculation; epidermal necrosis; ballooning of keratinocytes; lymphohistiocytic infiltrate	Yes	Not specified; indefinite treatment

Abbreviation/Acronym List: M, male; F, female; yr, year; mo, month

Conclusion

Herein, we present a 15-month-old previously healthy female with a two-month history of periorificial and perianal dermatitis with progressive painful acral blistering. A markedly reduced serum zinc level was noted and a diagnosis of bullous acrodermatitis enteropathica was rendered following histopathologic examination. This case highlights the diversity of the cutaneous clinical and histologic spectrum of acrodermatitis enteropathica and the importance of having a high clinical suspicion of zinc deficiency in atypical cases. It also highlights potential diagnostic and therapeutic delays and complications which can ensue if acrodermatitis enteropathica persists unrecognized and untreated.

References

1. Jensen SL, McCuaig C, Zembowicz A, Hurt MA. Bullous lesions in acrodermatitis enteropathica delaying diagnosis of zinc deficiency: a report of two cases and review of the literature. J Cutan Pathol. 2008 Oct. 35 (Suppl 1): 1-13 [PMID: 18537855]
2. Lee WJ, Kim CH, Won CH, Chang SE, Lee MW, Choi JH, Moon KC. Bullous acrodermatitis enteropathica with interface dermatitis. J Cutan Pathol. 2010 Sep. 37(9): 1013-5 [PMID: 19615039]
3. Maverakis E, Fung MA, Lynch PJ, Draznin M, Michael DJ, Ruben B, Fazel N. Acrodermatitis enteropathica and an overview of zinc metabolism. J Am Acad Dermatol. 2007 Jan. 56(1): 116-24 [PMID: 17190629]
4. Lakdawala N, Babalola O 3rd, Fedeles F, McCusker M, Ricketts J, Whitaker-Worth D, Grant-Kels JM. The role of nutrition in dermatologic diseases: facts and controversies. Clin Dermatol. 2013 Nov-Dec. 31(6): 677-700 [PMID: 24160272]
5. Jung AG, Mathony UA, Behre B, Küry S, Schmitt S, Zouboulis CC, Lippert U. Acrodermatitis enteropathica: an uncommon differential diagnosis in childhood - first description of a new sequence variant. J Dtsch Dermatol Ges. 2011 Dec. 9(12): 999-1002 [PMID: 21762381]
6. Sehgal VN, Jain S. Acrodermatitis enteropathica. Clinics in Dermatology. 2000 Nov-Dec. 18(6): 745-748 [PMID: 11173209]
7. Borroni G, Brazzelli V, Vignati G, Zaccone C, Vignoli GP, Rabbiosi G. Bullous lesions in acrodermatitis enteropathica. Histopathologic findings regarding two patients. Am J Dermatopathol. 1992 Aug. 14(4): 304-9 [PMID: 1503203]