

Acquired bullous acrodermatitis enteropathica as a histologic mimic of pemphigus foliaceus in a patient on parenteral nutrition

Davina Wu¹ MD PhD, Maxwell A Fung¹ MD, Maija Kiuru¹ MD PhD, Victoria R Sharon² MD DTMH

Affiliations: ¹Department of Dermatology, University of California, Davis, California, ²Department of Dermatology, Hofstra Northwell School of Medicine, New Hyde Park, New York

Corresponding Author: Victoria R. Sharon, MD, DTMH, 1991 Marcus Ave, Suite 300, New Hyde Park, NY 11040, USA, Email: vsharon@northwell.edu

Abstract

Acquired zinc deficiency can develop as a consequence of poor nutritional intake or from dependence on total parenteral nutrition. Acquired zinc deficiency dermatitis classically manifests with erosions and scaly plaques in a periorificial and acral distribution. We present a case of a woman on parenteral nutrition who presented with bullous acrodermatitis mimicking pemphigus foliaceus histopathologically. This case highlights clinical and histopathologic variants of zinc deficiency that may lead to a delay in diagnosis.

Keywords: zinc deficiency dermatitis, bullae, acantholysis, parenteral nutrition

Introduction

Zinc is an important trace element that plays a role in vital physiologic functions including cellular metabolism, gene expression, and basic enzymatic processing [1]. There is no dedicated store of zinc in the body. Therefore, one must rely on tissue turnover and absorption from exogenous sources. Zinc deficiency can be a result of genetic or acquired causes and clinical features include a distinctive skin rash, diarrhea, failure to thrive, and impaired wound healing.

Cutaneous manifestation of zinc deficiency classically presents with erythematous, often eroded plaques located at periorificial and acral sites. Biopsies of these skin lesions show cytoplasmic pallor of keratinocytes in the upper layer of the epidermis, along with focal spongiosis and overlying parakeratosis [2].

This histologic pattern can also be seen in other conditions associated with nutritional deficiency such as necrolytic acral erythema and pellagra.

Variants in clinical and histopathologic presentation of this dermatitis include vesicular and bullous forms [3-5]. Histopathology associated with bullous, zinc deficiency has been described to demonstrate intra- and subepidermal vesiculation and bullae [4]. We present an underreported histologic variant of zinc deficiency dermatitis with acantholysis mimicking pemphigus foliaceus.

Case Synopsis

A 69-year-old woman was admitted to the hospital for a widespread rash on her face, hands, groin, and feet, present for approximately 2 weeks. The patient was chronically ill owing to recurrent high-grade serous ovarian carcinoma with intra-abdominal metastases. She was status-post multiple surgical resections and cycles of chemoradiation resulting in adhesions leading to multifocal bowel obstruction. Because of her poor prognosis, she was no longer considered a surgical candidate and total parenteral nutrition was recently started in the setting of small bowel obstruction. The patient endorsed discomfort and itching of the rash, which was treated with triamcinolone cream and diphenhydramine without significant improvement. Additionally, she had fatigue, generalized weakness, and abdominal pain.

Her physical examination was notable for sharply demarcated scaly erythematous and hyperpigmented plaques on perioral and periorbital skin. The groin and inner thighs had red hyperpigmented plaques



Figure 1. Sharply demarcated erythematous perioral plaque.



Figure 2. Sharply demarcated scaly plaques of the groin with outer erythematous rim and double edge of peripheral scale.

Figure 3. Acral bullae on an erythematous base.

with an outer erythematous rim and double edge of peripheral scale. There were also multiple scattered unilocular bullae on an erythematous base located on her elbows, fingers, heel, and toes (**Figures 1-4**). Skin biopsies from her left forearm revealed basketweave orthokeratosis, intraepidermal vesiculo-bullous dermatitis with superficial epidermal necrosis, neutrophils, and limited acantholysis (**Figure 5**), with a negative direct immunofluorescence study. A KOH examination of a scraping obtained from the plaque in her groin revealed hyphae, though a PAS-D stain of the biopsy specimen was negative. The differential diagnosis included pemphigus foliaceus, paraneoplastic pemphigus, bullous Sweet syndrome, bullous tinea, and bullous pemphigoid, but there was a strong clinical suspicion for a nutritional deficiency based on the anatomic distribution of her eruption.

Zinc deficiency was confirmed by a low serum zinc level (12 mcg/dL; reference range, 55-150). A borderline low alkaline phosphatase level (38 U/L; reference range 35-115) and low serum albumin (21 g/dL; reference range 3.2-4.6) were also detected.

Owing to her bowel obstruction associated with her recurrent metastatic cancer, along with the precipitous decline in her functional status, she was unable to tolerate the recommended oral zinc supplementation. Based on her overall poor prognosis, the patient was discharged to home with hospice care.

Case Discussion

Zinc deficiency results from either inherited or acquired causes. Inherited zinc deficiency, known



Figure 4. Eroded bullae on forearm.

as acrodermatitis enteropathica, is a rare autosomal recessive condition related to mutations in the SLC39A4 gene leading to defective zinc transport [6]. Acquired zinc deficiency can also result from inadequate zinc in the diet, such as may occur in alcoholics, the malnourished, and vegetarians; gastrointestinal malabsorption syndromes may produce the same result [6].

Patients on parenteral nutrition are particularly vulnerable to acquired zinc deficiency associated with multifactorial causes including: preexisting deficiency from low dietary intake, decreased gastrointestinal absorption, increased gastrointestinal losses, urinary loss, and decreased delivery related to complex formation within the TPN solution [1].

Classic clinical features of zinc deficiency include diarrhea, alopecia, and dermatitis of eczematous plaques of the periorificial and perineal skin. Variations of zinc deficiency dermatitis include vesicular, bullous, pustular, and desquamative forms [3, 5]. Additionally, secondary infections of skin lesions can occur -- such as dermatophyte infection, initially raising a clinical suspicion of bullous tinea in our case -- which can lead to a delay in the diagnosis.

Histopathologic features of zinc deficiency are similar to that seen in other nutritional deficiency dermatoses, with cytoplasmic pallor of keratinocytes in the superficial layers of the epidermis. Unusual patterns of zinc deficiency on histopathology have been rarely reported, including interface dermatitis

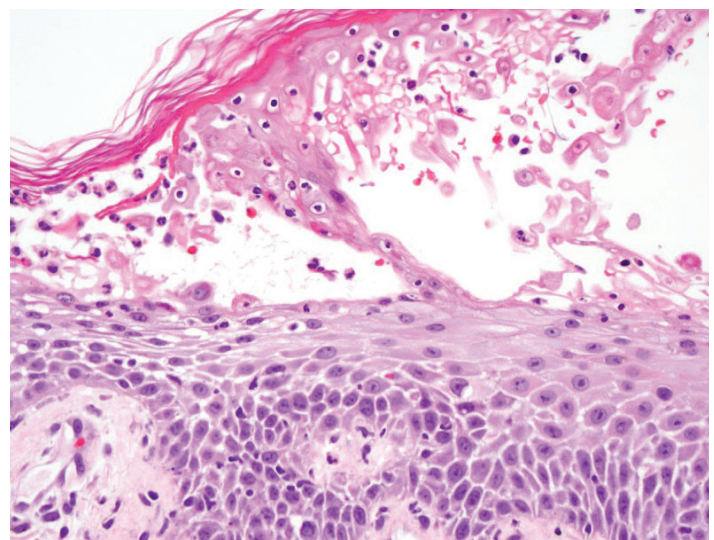
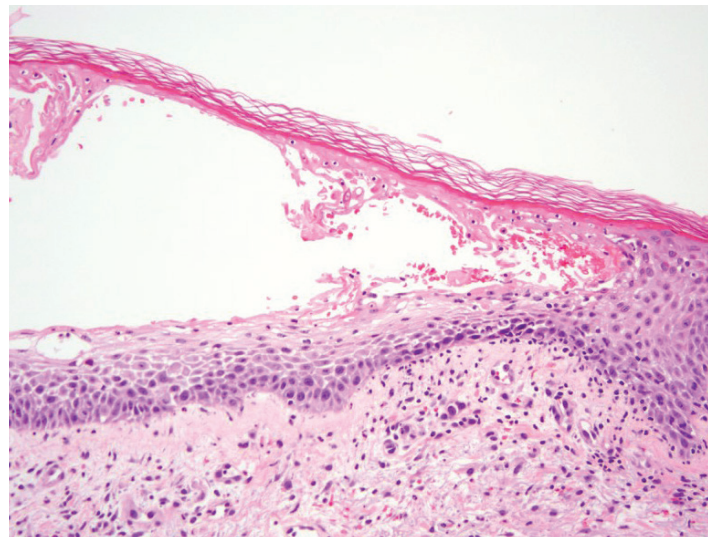


Figure 5. Top) Biopsy from the left forearm demonstrates basketweave orthokeratosis, intraepidermal vesiculo-bullous dermatitis with superficial epidermal necrosis (H&E, 20x). Bottom) Higher power magnification reveals limited acantholysis (H&E, 40x).

in bullous lesions and acantholysis [5, 7-9]. The absence of confluent parakeratosis is also not typical of zinc deficiency. It seems possible that the absence of parakeratosis may suggest an acute, acquired zinc deficiency, since most forms of "deficiency dermatitis" (acrodermatitis enteropathica, pellagra, glucagonoma syndrome), including early lesions, tend to exhibit a subacute or chronic presentation and consistently exhibit confluent parakeratosis [10].

Zinc replacement therapy is the treatment of choice as patients, even those on TPN, can have rapid resolution of the dermatitis and symptoms [11]. Plasma zinc levels can dramatically decrease once TPN is started. Therefore, zinc supplementation ideally

should begin before or at the time TPN is initiated, with a range administration of 2.5 to 5 mg parenteral zinc generally suggested [1]. In cases in which zinc deficiency is detected, the recommended oral zinc supplementation for dietary zinc deficiency in adults ranges from 0.5 to 3 mg/kg/d [6, 12]. For patients on TPN who may have impaired gastrointestinal absorption, parenteral zinc can be considered.

Conclusion

Herein, we present a 69-year-old woman on parenteral nutrition with a two-week history of periorificial and perineal dermatitis, along with acral bullae, clinically consistent with acquired zinc deficiency confirmed by serological testing. A skin biopsy of a bullous lesion revealed acantholysis, a histopathologic underreported finding associated with zinc deficiency. This histologic pattern mimicking pemphigus foliaceus could lead to a delay in diagnosis without clinicopathologic correlation. As acquired zinc deficiency is easily treated with, and rapidly responds to supplementation, a thorough skin exam and strong clinical suspicion is essential.

References

1. Livingstone C. Zinc: physiology, deficiency, and parenteral nutrition. *Nutr Clin Pract*. 2015 Jun. 30(3): 371-82 [PMID: 25681484].
2. Brinster N and Calonje E. "Acrodermatitis Enteropathica" McKee's Pathology of the Skin. Ed. Eduardo Calonje, Ed. Thomas Brenn, Ed. Alexander Lazar, Ed. Phillip H. McKee. Saunders, 2011. 586.
3. Iyengar S, Chambers C, Sharon VR. Bullous acrodermatitis enteropathica: case report of a unique clinical presentation and review of the literature. *Dermatol Online J*. 2015 Apr 16; 21(4) [PMID 25933075].
4. Borroni G, Brazzelli V, Vignati G, Zacccone C, Vignoli GP, Rabbiosi G. Bullous lesions in acrodermatitis enteropathica: histologic findings regarding two patients. *Am J Dermatopathol*. 1992 Aug. 14(4): 304-9 [PMID: 1503203].
5. 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].
6. 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].
7. Juljulan HH and Kurban AK. Acantholysis: a feature of acrodermatitis enteropathica. *Arch Dermatol*. 1971 Jan; 103(1): 105-106 [PMID 5539500].
8. Piper EL. Acrodermatitis enteropathica in an adult. *AMA Arch Derm*. 1957 Aug; 76(2): 221-4 [PMID 13443511].
9. Brazin SA, Johnson WT, Abramson LJ. The acrodermatitis enteropathica-like syndrome. *Arch Dermatol*. 1979 May; 115(5): 597-9 [PMID 109049].
10. Gonzalez JR, Botet MV, Sanchez JL. The histopathology of acrodermatitis enteropathica. *Am J Dermatopathol*. 1982 Aug; 4(4): 303-11 [PMID 7149179].
11. Maskarinec SA and Fowler VG Jr. Persistent rash in a patient

receiving total parenteral nutrition. *JAMA*. 2016 May. 315(20): 2223-4 [PMID: 27218632].

12. Lakdawala N, Grant-Kels JM. Acrodermatitis enteropathica and other nutritional diseases of the folds (intertriginous areas). *Clin Dermatol*. 2015 Jul-Aug; 33(4): 414-9 [PMID: 26051055].