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Bullous lesions in acrodermatitis enteropathica delaying diagnosis of zinc deficiency: a report of two cases and review of the literature

Acrodermatitis enteropathica (AE) is a rare disorder associated with poor absorption of zinc. A variety of clinical and histological findings have been reported in the literature, described mainly in isolated case reports. Because of the varied nature of these cases, the histological features of AE are described often as non-specific. We describe lesions of AE in two patients who presented with vesiculobullous and erosive skin lesions, both showing intra-epidermal, inflammatory vesiculation with surrounding eosinophilic epidermis and necrotic keratinocytes. The lack of clinical suspicion of AE led to their misdiagnosis. We present these two patients to further characterize the bullous variant of AE, and we review the previously reported clinical and histopathological findings.

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Deficiency of zinc occurs in a genetic and acquired form. The condition presents as dermatitis, classically located in the periorificial, intertriginous and acral areas. The lesions range from scaly, 'eczematous' lesions to erosive lesions and may present as a vesicular or bullous eruption. Nail, mucosal and ocular findings are associated in some cases. Severe complications include failure to thrive, impaired immune function and propensity for secondary infection.

Clinical and histopathological findings of acrodermatitis enteropathica (AE) described in the literature are diverse and mimic common dermatoses, particularly atopic dermatitis and, therefore, often lead to a delay in diagnosis and treatment. Because of the varied nature of the findings described in reports, the clinical and histopathological findings are often reported as non-specific. Yet AE, particularly in its bullous form, exhibits characteristic histological features, which, in the appropriate clinical setting, allow for accurate diagnosis. Presented with a patient with periorificial vesicles and/or bullae, certain histological features may help to narrow the differential and establish a diagnosis of zinc deficiency.

Bullous AE has characteristic histopathological findings including intra-epidermal vesiculation, among absent to scant spongiosis. In place of epidermal spongiosis, AE exhibits vesiculation among a background of eosinophilic epidermis with keratinocyte necrosis (personal observation). The combination of periorificial and acral bullae with histopathological

features of vesiculation in the presence of keratinocyte eosinophilia and/or necrosis should clue physicians to consider AE in their differential diagnosis.

Presentation of patients

Patient 1

A 1-year-old white girl presented with a 2-week history of a skin eruption. Arising initially on her left knee, the condition soon spread bilaterally over her hands and feet, then onto her face. She was treated with topical steroids, cefadroxil and topical antifungals with no benefit.

She was premature, delivered at 34 weeks, because of preeclampsia but was otherwise healthy and eating a broad diet. She was breast-fed for 1 week, then began on formula for approximately 1 year, during which solid foods were introduced gradually. Two to 3 weeks after discontinuing her formula, the skin eruption developed.

Physical examination revealed bright red, eroded plaques periorificially, as well as vesiculobullous lesions on her hands, knees and feet (Fig. 1A,B). The differential diagnosis included immunoglobulin A (IgA) linear dermatosis, Sweet's syndrome, epidermolysis bullosa simplex and infection.

Histological examination of a skin biopsy from the left knee revealed multiple intra-epidermal vesicles. The dermis contained a superficial, perivascular predominantly lymphocytic and macrophagic infiltrate (Fig. 2A,B). Direct immunofluorescence and tissue cultures were negative.

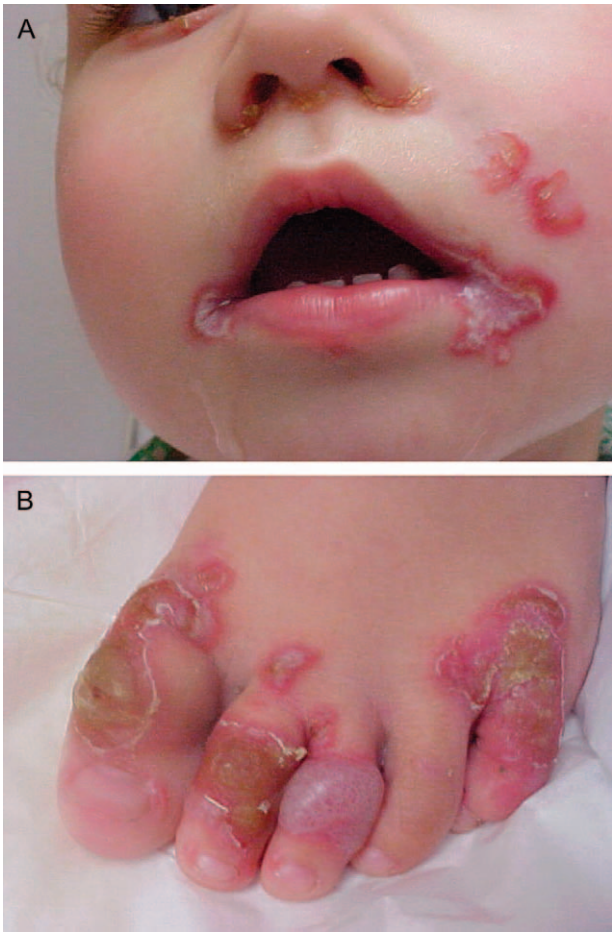

Fig. 1. A) Periorificial pink, erosive plaques of patient 1. B) Acral bullae and pink plaques of patient 1.

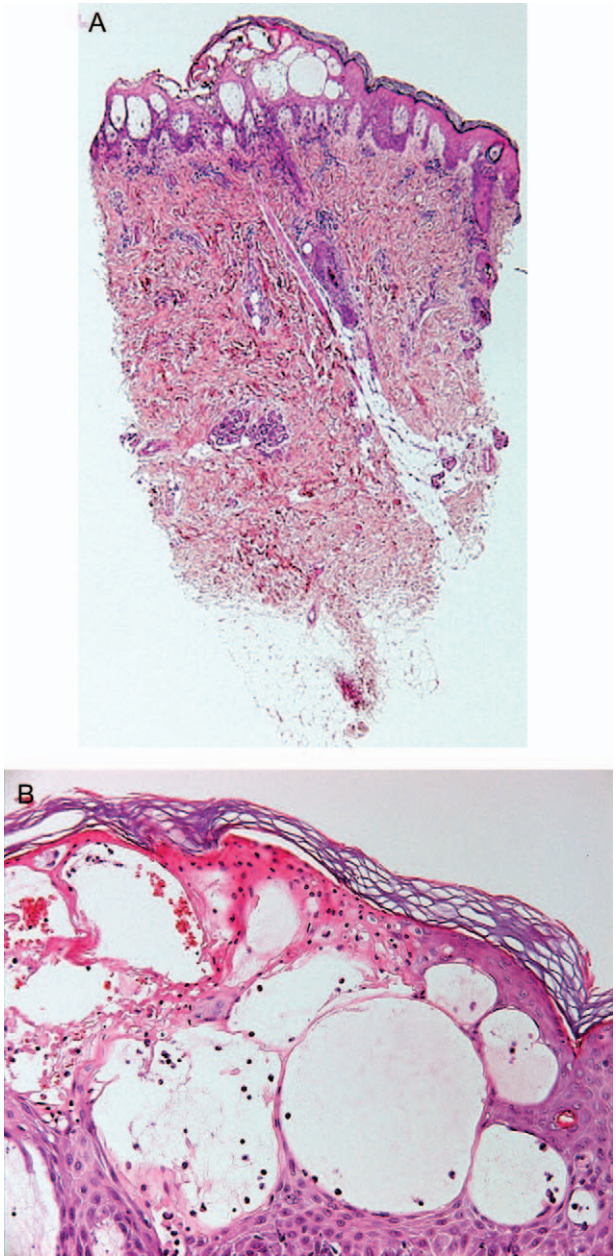

Fig. 2. A) Hematoxylin and eosin-stained (H&E) scanning magnification of initial biopsy of patient 1 showing prominent intra-epidermal vesiculation. B) H&E higher power of initial biopsy of patient 1 with necrotic, eosinophilic keratocytes and intra-epidermal vesicles.

Based on the clinical and pathological findings, the differential diagnoses considered included viral eruption and allergic contact dermatitis.

A recommendation was made for the patient to avoid irritants and potential allergens. However, she continued to flare within 2 weeks of the initial evaluation.

A second biopsy from the left dorsal hand was obtained. This specimen exhibited orthokeratosis and small intra-epidermal vesicles surrounded by eosinophilic keratocytes. The vesicles were separated by strands of necrotic keratocytes and contained a moderate number of neutrophils and lymphocytes. The dermis contained a superficial infiltrate of lymphocytes within a prominent vasculature (Fig. 3).

Given the clinical findings of prominent acral and periorificial lesions and her lack of response to allergen avoidance, the findings were consistent with AE. The diagnosis was confirmed by serological studies revealing reduced zinc levels at 14 mcg/dl (reference range 60–130 mcg/dl). The patient began oral zinc supplementation, her skin eruption improved within a few days and the lesions resolved over the following 2 weeks. She remains healthy on zinc therapy.

Patient 2

A term 8-month-old black female was hospitalized for an impetiginized 'eczematous' eruption. The eruption was primarily on the face and diaper areas, progressing since she was 2 months old. It was worsening in spite of moderate treatment with corticosteroids. She was formula fed, but anorexic with failure to thrive. During her hospitalization, she was diagnosed with buccal candidiasis and allergies to bovine milk and soy products.

Three months later, she was rehospitalized for suspected bullous impetigo and irritant dermatitis and treated with intravenous cloxacillin and topical 1% hydrocortisone cream. Child abuse and parental negligence were suspected, and the patient was placed in foster care.

Her skin lesions improved initially, yet later recurred. At 13 months of age and suffering from retarded growth, she was readmitted under child protection. Her height and weight were below the third percentile, and she was suffering from psychomotor delay. Nasogastric supplementation was required because of profound anorexia.

A dermatology consult was obtained during this admission. On physical examination, she had multiple hypopigmented, scaling and crusted plaques with a peripheral collarette (Fig. 4A,B). These were located around the mouth, vulva and buttock. Similar patches were observed on acral areas bilaterally, specifically the interdigital webs of the fingers, toes, elbows and knees. Small aphthae were present on the buccal mucosa. Her tongue was bright pink and denuded. She exhibited diffuse alopecia.

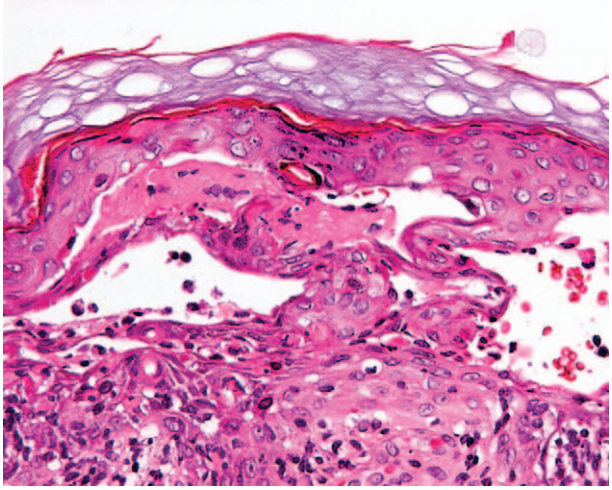

Fig. 3. Hematoxylin and eosin-stained biopsy of patient 1 showing eosinophilic, necrotic epidermis with intra-epidermal bullae.

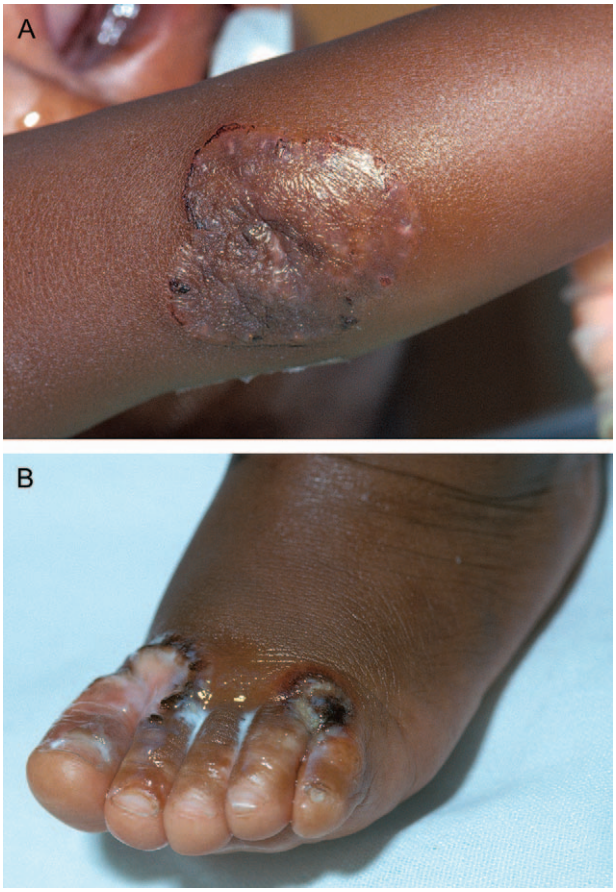

Fig. 4. A) Crusted plaque on elbow of patient 2. B) Hypopigmented, crusted, acral plaques of patient 2.

Given her clinical examination, a bullous disorder such as epidermolysis bullosa was suspected. Biopsies were performed from a scaly patch on the hand and later a fresh blister on the foot. These biopsies were initially interpreted as an intra-epidermal vesicular dermatitis.

A histopathological consult was obtained from a dermatopathologist. The consulting physician identified mild spongiosis, scattered dyskeratotic keratocytes and prominent epidermal necrosis surrounding intra-epidermal vesiculation. There was stranding of necrotic keratocytes lining the vesicles, in addition to an inflammatory infiltrate consisting of lymphocytes and neutrophils. Within the dermis, there was a superficial and perivascular mononuclear infiltrate (Fig. 5A,B). Direct immunofluorescence was negative. Based on the histopathological findings, a diagnosis of AE was suspected and confirmed by a serum zinc level of 1.4 μmol/l (range 10.3–18.1 μmol/l).

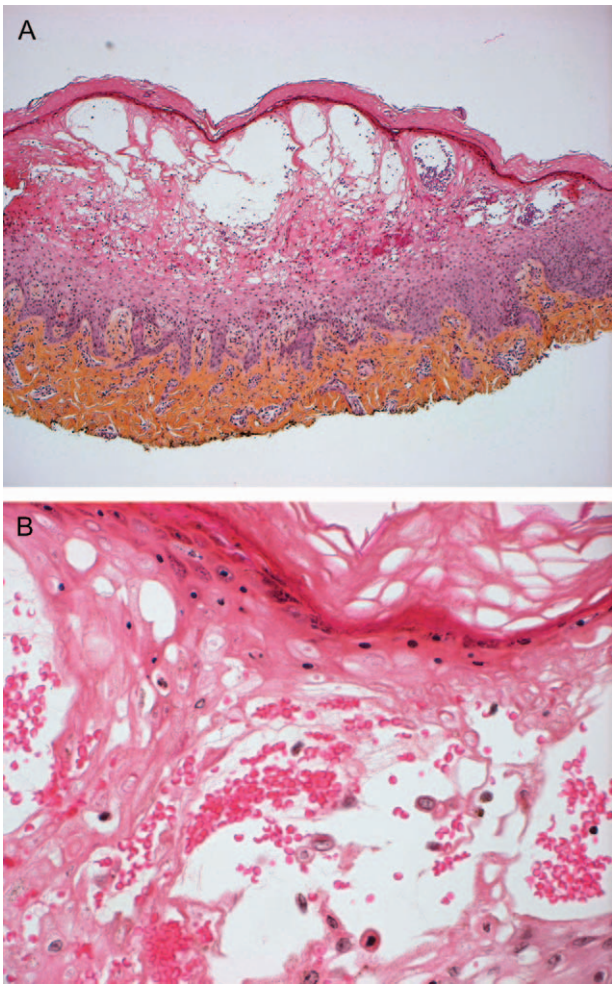

Fig. 5. Hematoxylin and eosin-stained (H&E) scanning magnification of initial biopsy of patient 2 showing intra-epidermal bullae and mononuclear infiltrate. B) H&E higher power of initial biopsy of patient 2 showing eosinophilic, necrotic epidermis with intra-epidermal bullae with scattered dyskeratotic keratocytes within the surrounding epidermis.

Zinc supplementation resulted in rapid and significant improvement of the oral and cutaneous lesions. Her weight increased and psychomotor development subsequently improved.

She was discharged in her mother's care with oral zinc supplementation of 40 mg twice a day and Neocate 24 cal/oz. She remains healthy on a diet with zinc supplementation.

Discussion

Pathophysiology

Zinc is the one of the most important trace elements vital to humans, which is present in nuts, whole grains, leafy vegetables and shellfish. Deficiency of zinc occurs in a genetic and acquired form. The genetic form is known as AE and is a rare autosomal recessive condition. The acquired form is simply referred to as *dermatitis associated with zinc deficiency.* Affected individuals suffer from zinc deficiency because of decreased uptake of zinc in the duodenum[1] and jejunum.[2]

The genetic condition arises usually few days to weeks after birth in infants fed solely bovine milk or it occurs soon after weaning older babies from breast to bovine milk. While human and bovine milk contain the same concentrations of zinc, the zinc within breast milk is more bioavailable to infants than is bovine milk. Zinc within human milk is bound to a low-molecular-weight ligand secreted by the pancreas, while bovine milk is bound to a high-molecular-weight ligand. The ligand binds to zinc in the intestinal lumen and aids in transport through the mucosa. Malfunction in the production, structure or function of this low-molecular-weight ligand may be the basic defect in AE.[3]

A gene thought to be involved in AE, SLC39A4, located on chromosome 8q24.3, was identified recently in eight families affected with the disorder. The gene encodes a protein with features characteristic of a zinc/iron-regulated transporter-like protein zinc transporter.[4] The exact mechanism of this gene and its significance in AE have not been explained fully; however, it is thought to be involved centrally in the pathogenesis of AE.

The acquired form of zinc deficiency results from either interference with absorption of zinc or unsuspected deficient sources of zinc fed exogenously to the infant. Malabsorption can occur secondary to high-fiber diet or to malabsorption syndromes, such as cystic fibrosis.[5] Acquired zinc deficiency has also been associated with chronic renal failure, malignancy, drugs, ethanol, pregnancy,[6,7] malnutrition[8] and total parenteral nutrition.[9,10] Occasionally, zinc deficiency can be seen in infants fed maternal milk;

these patients suffer from low zinc levels in the maternal milk and they improve clinically when weaned off breast milk. This mimics hereditary zinc deficiency clinically and is simply an acute, dietary zinc deficiency.[6]

Clinical presentation

The classic presentation of hereditary zinc deficiency is a periorificial and acral cutaneous eruption. The findings are varied, as described in Table 1, and range from 'eczematous' patches and psoriasiform plaques to vesicles, bullae and erosions. While the lesions are characteristically periorificial and acral, they may be more diffuse in severe cases. Nail changes include onychodystrophy, onycholysis and paronychia. Mucosal lesions consist of stomatitis and angular cheilitis. Ocular findings include conjunctivitis and photophobia. Failure to thrive because of anorexia, apathy and irritability may occur. Patients with zinc deficiency suffer from impaired immune function; the erosive and periorificial nature of the lesions led to secondary infection.

Establishing the diagnosis

The definitive diagnosis is established by a reduced serum zinc level. Biopsy of clinical lesions is useful to further support the diagnosis and to rule out other diagnoses in the differential.

Treatment

Therapy requires supplementation with oral zinc. Lesions respond within 2–7 days of administration. Within 2–4 weeks, lesions are usually healed.[3,6]

Clinical and histopathological findings as reported in literature

A summary of the literature on AE is given in Table 1, including type of lesions, age at onset or presentation, presence of infection, whether the AE was considered innate or acquired, whether vesicles or bullae were described and, when reported, any histopathological findings.[5–8,10–13,15–38]

The reported clinical features of AE have been described mainly through isolated case reports and range clinically from erythematous, scaly patches to psoriasiform plaques and erosive to vesiculobullous lesions.[3,14] Corresponding to the broad spectrum of clinical lesions of AE, histopathological descriptions in the literature are equally varied and include hyperkeratosis,[10,11,14] parakeratosis, [8,10,11,39] acantholysis,[10,11,12] epidermal pallor[7,40] and dilated and tortuous capillaries.[8,14,41]

These histopathological features of AE are either omitted from these case reports or, more often, considered non-specific and, therefore, not used in establishing the diagnosis.[3,5,6,41]

Because of the varied findings and lack of specific criteria to diagnose AE, Gonzalez, Botet and Sanchez[42], in 1982, devised a prospective study to better define the clinical and histopathological features of the lesions as they evolved over time. Their article described 12 patients with AE. They identified four corresponding clinical and histopathological patterns.

In 1992, Borroni et al.[43] further examined the histopathological features of bullous lesions of AE. Two patients of their study had lesions 'characterized by intra-epidermal vacuolar changes with massive ballooning, leading to intra-epidermal vesiculation and blistering, with prominent epidermal necrosis but no acantholysis'. They averred that the histological features of true bullae are rarely described in this condition.

Comparison of the histopathological findings of bullous AE with its mimickers

The histopathological findings of our two patients are similar to those described by Borroni et al. The lesions of patients in our study showed prominent intra-epidermal vesiculation, surrounded by clusters and strands of highly eosinophilic, necrotic keratocytes with mild, if any, spongiosis. The infiltrate within the vesicles comprised lymphocytes and neutrophils. The dermis contained a moderate superficial, perivascular mononuclear infiltrate.

Considering these histopathological findings, the leading diagnosis in the differential is a spongiotic dermatitis. The histopathology of AE differs from that of spongiotic dermatitis, showing prominent vesiculation in the midst of absent to scant spongiosis, adjacent eosinophilic to necrotic keratocytes and a predominately lymphoneutrophilic infiltrate. The lack of immunofluorescence positivity excludes an immunobullous disorder such as linear IgA dermatosis. While infection may be considered and is sometimes secondarily present, the persistence of lesions, despite appropriate therapy, should motivate further evaluation for a more definitive diagnosis.

The findings of bullous AE vary subtly, but significantly, from other diagnoses within the differential of vesicular lesions in the pediatric population. Given the appropriate clinical context, histopathological features of individual and clustered necrotic keratocytes, intra-epidermal vesiculation and a predominant lymphoneutrophilic infiltrate should alert the pathologist to the diagnosis of AE, particularly when not considered in the clinical impression.

Table 1. Summary of prior reports of AE

References	Original diagnosis	Gender	Age at onset of disease or age at presentation	Skin lesions	Presence of bullae	Secondary infection	Innate or acquired	Family history	Other features of disease or concomitant medical conditions	Pathology
Brandt[15] (four patients described – patients 2, 3 and 4 being siblings)	Patient 1: ND; patient 2: ND; patient 3: ND; patient 4: ND	Patient 1: M; patient 2: F; patient 3: M; patient 4: F	Patient 1: 17 months; patient 2: 7–8 months of age; patient 3: 9–12 months of age; patient 8 months of age	Patients 1–4: perioral and acral red isolated papules, confluent in patches with areas of brownish crusting, varied presence of vesicles and pustules over hands and feet, scalp alopecia	Patient 1: vesicles; patient 2: ND; patient 3: occasional vesicles; patient 4: ND	Patient 1: *Staphylococcus aureus*; patient 2: ND; patient 3: ND; patient 4: ND	Patient 1: innate; patient 2: innate; patient 3: innate; patient 4: innate	Patient 1: brother died at 2.5 years of age because of skin disease; patients 2, 3 and 4 are siblings	Patient 1: poor appetite, thin; patient 2: poor appetite, thin, occasional diarrhea; patient 3: poor appetite, thin, signs of rickets, fever with diarrhea; patient 4: Occasional cough	Patient 1: hyperkeratosis, degenerative changes of epidermis, sparse inflammatory cell infiltrate; patient 2: ND; patient 3: ND; patient 4: ND
Danbolt and Closs[16] (original paper in German, identified AE as a definite disease, later summary in English in 1979)				Pustular dermatitis of the natural openings of the body and protruding parts of the head, trunk and extremities; alopecia; paronychia and mucous membrane affections					Diarrhea	ND
Guy[17] (three patients described)	Patient 1: ND; patient 2: ND; patient 3: ND	Patient 1: M; patient 2: M; patient 3: M	Patient 1: 17 years, developed blisters at 1 year of age; patient 2: 9 years; patient 3: 7 years	Patients 1–3: bullae, skin fragility, coated tongue, erythematous desquamation at knees, elbows, periorally and hands and feet, dystrophic nails	Patient 1: Bullae; patient 2: bullae; patient 3: bullae	Patient 1: ND; patient 2: ND; patient 3: ND	Patient 1: ND; patient 2: ND; patient 3: ND	Patient 1: ND; patient 2: ND; patient 3: ND	Patient 1: ND; patient 2: ND; patient 3: ND	Patients 1–3: parakeratosis, mild separation of cornified layer, moderate acanthosis with parenchymatous and interstitial edema present in the rete, moderate perivascular inflammatory infiltrate, dilated vessels and dermal edema; subepidermal separation with epidermal acanthosis, parenchymatous and interstitial edema in the rete, polymorphonuclear infiltrate, vessel dilatation and endothelial swelling and dermal edema
Danbolt[18]	Impetigo	F	9 months	Alopecia; exanthema symmetrically on eyelids, nasal openings and mouth, as well as a marked erythema on the elbows, wrist, fingers, knees and toes; and paronychia	ND	ND	ND	ND	ND	ND
Ugland[19]	ND	F	1.5 years	Erythema on posterior thighs, conjunctival injection, rhagades in lateral angle of left eye, gingivitis, reddish tongue, thinned hair, worsened to develop eroded plaques and aphthous sores	ND	ND	ND	Unknown, two siblings died at 2 and 9 months of age	Cystic fibrosis	ND
Dillaha CJ, Lorincz AL, Aavick OR	ND	F	2.5 years	Recurrent, vesicular, erythematous, crusted dermatitis of the ankles, heels, knees, elbows, fingers, wrists, and perioral and anal areas	Vesicles	*Candida albicans*	ND	No	Total alopecia, tongue coating and severe halitosis	Impetigenized superficial dermatitis with marked papillary edema

Table 1. *Continued*

References	Original diagnosis	Gender	Age at onset of disease or age at presentation	Skin lesions	Presence of bullae	Secondary infection	Innate or acquired	Family history	Other features of disease or concomitant medical conditions	Pathology
Bloom and Sobel[20]	Eczematoid epidermitis and aphthous stomatitis with perleche, epidermomycosis and onychomycosis, cutaneous moniliasis, epidermolysis bullosa	M	3 months	Intermittent perianal and intergluteal erythema, erythemato-vesiculo-pustular scaly plaques at acral sites and in groin and buttocks	Vesicles	Pathogenic bacteria and *C. albicans*	Innate	ND	Scalp alopecia, white spots on buccal mucosa	Erythemato-bullous lesion: acanthotic epidermis with large intra-epidermal vesicles filled with serum and few leukocytes, dilated dermal blood vessels and papillary dermal and perivascular lymphocytic infiltrate; scaly, erythematous plaque: hyperkeratosis, hypergranulosis and epidermal hyperplasia, dilated blood vessels and a superficial, perivascular lymphocytic infiltrate
Danbolt[21] (two patients described)	Patient 1: ND; patient 2: ND	Patient 1: F; patient 2: F	Patient 1: presented at 2.5 years, signs of eczema at 1 month of age, which worsened after weaning from breast milk at 1 year of age; patient 2: 8 months old	Patients 1–2: large, red, weeping, crusted areas of skin and peripheral vesicles and vesicopustules, nail dystrophy	Patients 1 and 2: vesicles and vesiculopustules at periphery of lesions in both patients	Patients 1 and 2: past cultures of yellow hemolytic staphylococci	Patient 1: ND; patient 2: ND	Patient 1: no; patient 2: sibling died at 1 year of age with similar disease as patient	Patient 1: ectropion	Patient 1: ND; patient 2: ND
Vedder[22]	5 of 12 siblings affected with condition and described; ND	Patient 1: F; patient 2: M; patient 3: F; patient 4: M; patient 5: F	Patient 1: 8 months; patient 2: 5 months; patient 3: 4 months; patient 4: 4 weeks; patient 5: 5 months	Patients 1–5: lesions around body orifices; nail loss; extensive vesicular crusting; erythematous lesions in the face, scalp, diaper area and digits and severe paronychia	Patients 1, 3 and 5: ND; patients 2 and 4: vesicular	Patient 1: *C. albicans*, staphylococci; patient 2: *C. albicans*; patient 3: ND; patient 4: ND; patient 5: ND	Patients 1–5: innate	Patients 1–5: yes	Patient 1: recurred during pregnancy; patient 3: total alopecia and photophobia	Patients 1–5: ND
Piper[11]	ND	F	46 years, developed initially at 7 years of age (intermittently affected thereafter)	Scaling dermatitis with pustules involving distal extremities, perineal area and face; angular stomatitis and blepharitis as well as shallow acral bullae with crusts	Bullous	Candidal paronychial infection	Innate	ND	Thinning of hair, anorexia and frequent stools	Intra-epidermal vesiculation, marked hyperkeratosis and parakeratosis, with benign dyskeratotic cells present; subepidermal separation with neutrophils and eosinophils
Wells and Winkelmann[23]	Patient 1: AE; patient 2: congenital ectodermal defect; pachyonychia congenital; patient 3: epidermolysis bullosa, celiac disease, total alopecia; patient 4: mediastinal sarcoma, chronic granulomatous disease, cystic lung disease; patient 5: celiac syndrome, moniliasis; patient 6: neurodermatitis	Patient 1: F; patient 2: M; patient 3: F; patient 4: M; patient 5: F; patient 6: M	Patient 1: 1 week; patient 2: 14 months; patient 3: 6 weeks; patient 4: 15 months; patient 5: 1 week; patient 6: 1 month	Patients 1–4: varied clinical appearance including, erythematous, impetiginous dermatitis over face, ears, hands, fingers, feet, perineum, buttocks and postauricular regions; vesicular and bullous lesions of diaper region, face, extensor surfaces of elbows, knees and buttocks	Patient 1: No; patient 2: no; patient 3: vesicular and bullous lesions; patient 4: Vesicular lesions; patient 5: ND; patient 6: bullous and pustular lesions	Patient 1: *C. albicans*; patient 2: *C. albicans* and bacterial infections on occasion; patient 3: *C. albicans*; patient 4: *S. aureus*; patient 5: *C. albicans*; patient 6: pacterial infection and candidiasis	Patient 1: ND; patient 2: ND; patient 3: ND; patient 4: ND; patient 5: ND; patient 6: ND	Patient 1: No; patient 2: No; patient 3: deceased brother with similar history; patient 4: no; patient 5: ND; patient 6: Yes	Patient 1: conjunctivitis, mucous membrane involvement, otitis; patient 2: conjunctivitis, mucous membrane involvement, perleche; patient 3: photophobia, mucous membrane involvement; patient 4: conjunctivitis, mucous membrane lesions, anemia; patient 5: mucous membrane lesions, anemia; patient 6: conjunctivitis, stomatitis	Patient 1: non-specific changes; patient 2: consistent with erythroderma ichthyosiform congenitum; patient 3: No; patient 4: No; patient 5: No; patient 6: diagnosed as neurodermatitis

Table 1. *Continued*

References	Original diagnosis	Gender	Age at onset of disease or age at presentation	Skin lesions	Presence of bullae	Secondary infection	Innate or acquired	Family history	Other features of disease or concomitant medical conditions	Pathology
Lindstrom[24]	Acrodermatitis continua Hallopeau	M	1.5 years	Facial papules, vesicles and pustules; acral and genital maceration and erosion	Vesicles	ND	ND	Yes, two siblings died of similar disease at 12 and 14 years of age	Scalp alopecia, dizziness/vertigo, numbness and stiffness of extremities	ND
Hansson[25]	Patient 1: eczema impetiginosum; patient 2: ND	patient 1: M; patient 2: M	Patient 1: 5 months; patient 2: 6 months	Patients 1 and 2 described clinically as skin lesions characteristic of AE	ND	Patient 2: *S. aureus*, beta-hemolytic streptococci and *C. albicans* cultured from the skin	ND	ND	ND	Patient 1: ND; patient 2: skin biopsy showed non-specific dermatitis consistent with AE
Rodin and Goldman[26] (1969)	Factitial dermatitis	M	6 years	Eczematoid lesions of the elbows, knees and gluteal folds; and small, firm, erythematous, non-tender lesions of the left forearm; bullae of the left thigh, leg and dorsal foot	Bullous lesions	ND	ND	ND	Diarrhea, depression and anorexia, *Pseudomonas aeruginosa* sepsis causing death	Necropsy tissue showed diffuse and focal lymphocytic infiltrate with edema and congestion as well as large areas of necrosis to deep dermis with mixed infiltrate of neutrophils, lymphocytes, histiocytes and eosinophils; bullous lesions showed separation at the dermal–epidermal junction with red blood cells within
Tompkins and Livingood[27]	ND	F	3 months	Blisters and sores described as a child; crusted eczematous lesions or psoriasiform plaques as an adult	Vesicles in childhood	*S. aureus*	ND	Yes, older sibling with similar illness, died at 1 year of age	Alopecia, depression, blepharitis, perleches, glossitis, conjunctivitis, stomatitis, an photophobia and dystrophic nails	ND
Juljulian and Kurban[12]	ND	F	7 months	Reddish, pruritic and eroded patches over nape, face, extremities, perigenital region	ND	ND	ND	ND	ND	Serrated and clefted epidermis containing acantholytic cells, dermal edema and basophilic degeneration of collagen
Julius R, Schulkind M, Sprinkle T, Rennert O[28]	ND	M	1 week	Scaling erythematous facial dermatitis, generalized to his neck, shoulders and chest	ND	ND	ND	ND	ND	Necropsy tissue of skin showed focal hyperkeratosis with a non-specific infiltrate of macrophages, neutrophils and eosinophils
Moynahan and Barnes[29]	ND	F	2 months	Crusted and scaled eruption in perivulvar and perianal skin	ND	ND	Innate	Sister with similar eruption, treated successfully with zinc	Loose stools and psychic changes (irritability and withdrawal)	ND
Verberg DJ, Burg LI, Hoxtell EO, Merrill LK[30]	ND	F	21 years at presentation, first developed dermatitis periorificially at 10 weeks of age	Dermatitis on face and anogenitally at delivery of baby	ND	ND	Innate	Sibling died at 1 year of age due with severe diarrhea and dermatitis	Flare of disease occurred during pregnancy	ND

Table 1. *Continued*

References	Original diagnosis	Gender	Age at onset of disease or age at presentation	Skin lesions	Presence of bullae	Secondary infection	Innate or acquired	Family history	Other features of disease or concomitant medical conditions	Pathology
Nelder and Hambidge[31]	ND	F	22 years at time of publication, first signs of disease at 1.5 years of age	Erythematous dermatitis of acral areas, blister formation on knees and aphthous-like oral ulcerations, along with paronychia	Blister formation	ND	Innate	ND	ND	ND
Olholm-Larsen[32]	Two affected siblings described. Patient 1: impetigo, keratosis cutis hereditaria and acne vulgaris; patient 2: keratosis disseminate congenital, folliculitis universalis, pustulosis pedum, psoriasis	Patient 1: M; patient 2: F	Patient 1: 33 years at time of publication, developed dermatitis at few months of age; patient 2: 40 years at time of publication, original eruption at 1.5 years	Patients 1–2: perioral papules, pustules and deep scars; truncal papules and pustules with scarring; bullae and erythema at feet and paronychial inflammation with normal nails	Patient 1: bullae; Patient 2: ND	ND	Innate	Yes, two of four siblings affected	Patient 1: ND; patient 2: flare during pregnancies, neurological symptoms and depression	ND
Brazin and Johnson[10]	ND	M	17 years	Erythematous, tender, 'eruptive' lesions on palm as well as perinasal scaling and erythema; angular cheilitis, papulonodules overlying joints of hands and over palms and paronychia	ND	ND	Acquired secondary to multiple small bowel resections for midgut volvulus and suture line necrosis	ND	Granulation tissue overlying prior arteriovenous anastomoses on bilateral wrists	Hyperkeratosis, parakeratosis, extensive necrosis of the granular layer and eosinophilic staining with loss of nuclei of the stratum malpighii, also exhibiting microvesiculation with acantholysis, elongated rete ridges, spongiosis, exocytosis of neutrophils and mononuclear cells
Sjolin[8]	Dermatitis and dehydration	F	76 years	Dry, scaly, almost ichthyotic skin with erosive areas in perioral and perianal regions	ND	ND	ND	ND	Poor general condition	Parakeratosis, irregular acanthosis with club-shaped rete ridges, edema of epidermis and papillary dermis, elongated and edematous dermal papillae with tortuous dilated capillaries with surrounding lymphocytes and neutrophils with mild exocytosis
Bonfazi[33]	ND	M	55 days	Burn-like lesions in diaper region, buttocks, thighs, knees and elbows, and at mouth and eyes and, later, on fingers and toes	ND	No	ND	ND	ND	

Table 1. *Continued*

References	Original diagnosis	Gender	Age at onset of disease or age at presentation	Skin lesions	Presence of bullae	Secondary infection	Innate or acquired	Family history	Other features of disease or concomitant medical conditions	Pathology
Owens[34]	Stasis eczema	F	82 years	Itchy, confluent, erythematous and excoriated rash with lichenification on bilateral legs and, to a lesser extent, on both forearms, dorsal hands, upper legs, knees and inner thighs	ND	ND	Acquired, low-protein diet (associated with low zinc levels)	ND	Brain stem ischemic episode, Myocardial infection history and anterior resection of sigmoid colon for carcinoma, depression	Parakeratosis and changes compatible with stasis eczema
Gonzalez JR, Botet MV Sanchez JL (12 patients described and divided into four clinical and pathological stages)[42]	ND for any patients	5 males; 7 females	Ages ranged from 19 days to 5 months	(Clinical findings of all stages occurred in an acral and periorificial distribution) Stage 1: early reddish plaques	ND	ND	ND	ND	ND	Characterized by loss of the granular layer; slight paleness of the upper one third of the epidermis
				Stage 2: brightly reddish scaly plaques	ND	ND	ND	ND	ND	Main features included paleness of the upper two thirds of the epidermis accompanied by slight to fully developed psoriasiform hyperplasia
				Stage 3: scaly psoriasiform plaques	ND	ND	ND	ND	ND	Psoriasiform hyperplasia and focal pallor within the upper epidermis
				Stage 4: late reddish or brownish patches with desquamation	ND	ND	ND	ND	ND	Confluent parakeratosis, slight epidermal hyperplasia, no pallor seen
Bronson DM, Barsky R, Barsky S[7]	Herpes gestationis, impetigo herpetiformis	F	23 years	Widespread pustular, vesiculobullous and psoriasiform eruption with elbows, knees, distal extremities most severely affected, as well as an erosive pustular dermatitis of the perioral and perineal regions, thinned hair and glossitis	Vesiculobullous eruption	*S aureus*, *Proteus mirabilis*, *C. albicans*	Probable innate with exacerbation during pregnancy	Sister died in early childhood of a generalized blistering disease	Eruption occurred with two of patient's pregnancies, also had a similar eruption as a child at 2 years of age with partial and then complete remission later in childhood	Initial biopsy at first pregnancy showed subcorneal pustulosis; subsequent eruption with second pregnancy showed 'spongiotic dermatitis' with intra-epidermal vesicles and numerous neutrophils and negative indirect and direct immunofluorescence
Lee MG, Hong KT, Kim JJ[6]	ND	F	5 month	Erythematous, desquamating skin eruption periorally, scalp, face, perineal, buttocks and distal extremities, also had crusted vesicles and blisters on fingers and toes, as well as alopecia	Vesicles and blisters	No fungus identified	Uncertain if innate or acquired, thought to be secondary to unexplained low zinc levels in maternal breast milk	ND	Exclusively breast-fed, otherwise healthy	Non-specific dermatitis from buttock lesion

Table 1. *Continued*

References	Original diagnosis	Gender	Age at onset of disease or age at presentation	Skin lesions	Presence of bullae	Secondary infection	Innate or acquired	Family history	Other features of disease or concomitant medical conditions	Pathology
Mori H, Matsumoto Y, Matsumoto Y, Tamada Y, Ohashi M[35]	ND for any patients	Patient 1: F; patient 2: F; patient 3: M; patient 4: M; patient 5: M; patient 6: M; patient 7: M	Patient 1: 73 years; patient 2: 73 years; patient 3: 45 years; patient 4: 78 years; patient 5: 79 years; patient 6: 65 years; patient 7: 40 years	Patient 1: erythema, vesicle and pustule; patient 2: erosion, pigmentation; patient 3: pustule; patient 4: pustule, red papule; patient 5: prust, pustule; patient 6: prust pustule; patient 7: hyperkeratosis, pigmentation, erythema and pustule	Patient 1: vesicle; patient 2: ND; patient 3: ND; patient 4: ND; patient 5: ND; patient 6: ND; patient 7: ND	ND for any patients	ND for any patients	ND for any patients	Patient 1: gastric cancer; patient 2: subarachnoid hemorrhage; patient 3: ileus; patient 4: cerebral thrombosis; patient 5: cerebral thrombosis; patient 6: extramural hemorrhage; patient 7: Crohn's disease	Pathological findings of all seven patients described in article were summarized as showing intra-epidermal vesiculation with lymphocytes and irregular acanthosis. Some lesions showed vesiculation with the presence of apoptosis; however, those with simply hyperkeratosis did not show apoptosis
Kumar S, Sehgal VN, Sharma RC[36]	Four patients described; no previous diagnosis described	ND	Range from 6 to 9 months of age	Vesiculobullous eczematous lesions involving anogenital region, periorificial areas and acral extremities	Vesiculobullous lesions	ND	ND	ND	Photophobia in two cases, diarrhea in another two	ND
Khanna and D'Souza[37]	ND	F	8 months	Psoriasiform plaques on occiput, neck, buttocks and extensor extremities, as well as perioral and perigenital macerated lesions and paronychia involving several fingers and toes	ND	ND	ND	ND	Weight loss	ND
Ozkan S, Ozkan H, Fetil E, Corapcioglu F, Yilmaz S, Ozer E[38]	ND	M	9 months	Erythematous, scaly, vesiculobullous lesions and crusted ulcerations on face (particularly periorally), and within the diaper area; commissural maceration present as well	Vesiculobullous lesions	*P. aeruginosa* within blister as well as oral candidiasis	ND	ND	ND	Bullous lesion on right gluteal region showed an intra-epidermal blister, perivascular lymphocytic infiltrate and superficial dermal edema
Ozturkcan S, Icagasioglu D, Akyol M, Cerit O[41]	ND	F	17 months	Vesiculobullous and psoriasiform lesions located periorally, acrally and within the perineal region	Vesiculobullous lesions	ND	ND	ND	ND	Biopsy from an area of plantar desquamation showed non-specific keratosis
Perafan-Riveros C, Sayago Franca LF, Alves ANF, Sanches JA Jr.[3]	ND	M	21 month	Periorificial and acral erythematous, scaly plaques with crusts and ulcerations, maceration and fissures within the inguinal regions, alopecia and paronychia	ND	*S. aureus*	ND	Brother with similar skin lesions died at 14 months of age	Chronic, intermittent diarrhea, Klebsiella sepsis	Biopsy of ulcerated plantar lesion showed a non-specific superficial and psoriasiform perivascular dermatitis

AE, acrodermatitis enteropathica; F, female; M, male. ND, not discussed.

Conclusions

Patients with the bullous form of AE may be misdiagnosed for months after initial presentation, as in the case of our two patients. Our first patient was originally diagnosed with allergic contact dermatitis. Only after further investigation, 2 months following her initial presentation, she was correctly diagnosed with AE. In our second patient, abuse was considered in the diagnosis and resulted in the child being placed in foster care. Her diagnosis was eventually made after a delay of 6 months. As evidenced by our patients' cases, the bullous presentation of AE may elude a correct diagnosis. Because of the rarity of the disease, clinicians and pathologists are often unaware of its clinical and histological spectrum and, therefore, do not suspect the diagnosis initially.

The findings of our two patients, along with those reported by Borroni et al., further establish the diagnostic features of bullous AE and should alert the pathologist to the possibility of the diagnosis of AE. In the appropriate clinical setting, the findings of individual and coalesced intra-epidermal necrotic keratocytes, intra-epidermal vesiculation among scant spongiosis and a predominant lymphoneutrophilic infiltrate should alert the pathologist to the diagnosis of AE, particularly when not suspected clinically. Bullous AE should be included in the differential of intra-epidermal vesiculation, in addition to the more commonly encountered pediatric dermatitides.

Early recognition and treatment are necessary, particularly because of concerns of immunodeficiency and infection in these patients. Skin biopsy plays a very important role in the diagnostic work up of AE. As illustrated by the reported cases, the histological features are varied but may be specific enough to exclude clinical and histological mimickers of AE and to support the correct diagnosis.

We hope to raise physicians' clinical and histopathological suspicion of AE when presented with a bullous dermatitis. The delay in achieving the correct diagnosis in our cases emphasizes the need for a high index of suspicion of zinc deficiency. Heightened awareness of the bullous form of this condition may provide earlier diagnosis and therapeutic intervention for these patients.

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