Adult autoimmune enteropathy presenting initially with acquired Acrodermatitis Enteropathica: a case report

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Abstract

Background: Acrodermatitis enteropathica (AE) is a rare dermatitis secondary to zinc deficiency most commonly seen as an inherited disease in infants. In the last decade, increased number of reports have been published on the acquired form that presents in adulthood. Unlike its inherited counterpart, acquired AE (AAE) is often secondary to underlying pathologic or iatrogenic etiologies that interfere with nutritional absorption, such as inflammatory bowel disease or alcoholism. Various gastrointestinal pathologies have been associated with AAE, but there is currently no report on its association with adult autoimmune enteropathy (AIE), a rare gastrointestinal disorder commonly seen in infants, with limited cases reported in adults. Here we present a case in which AAE was the initial clinical manifestation in an adult patient subsequently diagnosed with AIE.

Case presentation: A 41-year-old African American female presented to our emergency department at the Johns Hopkins Hospital with several months of progressively worsening dermatitis in the legs and acral regions, along with worsening symptoms of diarrhea, alopecia, poor oral intake, lethargy, hematochezia, peripheral edema, and weight loss. Our dermatology team was consulted given a presentation of exquisitely tender, erythematous, and diffusely desquamating skin lesions in the setting of two prior outside hospitalizations in the last 3 months with the same dermatitis that was refractory to topical and oral corticosteroids. Low serum zinc level and positive response to zinc supplementation confirmed the diagnosis of AAE. However, persistent hypovitaminosis and mineral deficiency despite aggressive nutritional supplementation prompted further investigation for an underlying malabsorption etiology. Jejunal biopsy and associated autoantibodies confirmed a diagnosis of adult AIE.

Conclusion: This case highlights the fact that adult AIE can present initially with clinical findings of AE. While proper zinc supplementation can resolve the latter, recognizing this association can trigger earlier diagnosis, minimize unnecessary tests, and establish earlier intervention to improve quality of life and prevent recurrence of AAE. The case also highlights the importance of collaboration between general and subspecialist physicians in identifying a primary etiology to a secondary clinical presentation. This report can be beneficial to general internists and emergency physicians, as much as it can be to dermatologists, rheumatologists, and gastroenterologists.

Keywords: Acrodermatitis enteropathica, Zinc deficiency, Dermatitis, Autoimmune enteropathy, Malnutrition, Case report

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Background
Acrodermatitis enteropathica (AE) is a condition caused by zinc deficiency that classically presents with periorificial and acral papulosquamous eruptions accompanied by diarrhea and alopecia [1]. The inherited form, a rare autosomal recessive trait due to mutations in the gene SCL39A4 on chromosome 8q24.3 [2], is more common and typically seen in infants. However, in the last decade, we have witnessed an increased number of reports on acquired AE affecting adults and the elderlies particularly in association with anorexia nervosa, alcoholism, bariatric surgery, total parenteral nutrition, nephropathy, inflammatory bowel disease (IBD), blind loop syndrome, and celiac disease [3–7]. Here we present a novel case of acquired AE as an initial presentation of autoimmune enteropathy (AIE), itself a rare gastrointestinal disorder characterized by refractory diarrhea and malnutrition that affects less than 1/100,000 infants, with limited case reports in adults [8, 9].

Case presentation
A 41-year-old African American female presented with a 4-month history of progressive, exquisitely tender, nonpruritic leg and acral dermatitis, diarrhea, alopecia, poor oral intake, lethargy, hematochezia, lower extremity edema, and 22lbs of unintentional weight loss. Physical examination revealed erythema and desquamation along the extremities (Fig. 1a), plantar feet (Fig. 1b), and palmar hands (Fig. 1c), paronychia, angular cheilitis with lip fissure, glossitis, ulcerations and satellite erosions in the lumbosacral, perianal, and perineal regions (Fig. 1d), and diffuse alopecia of the scalp.

Her symptoms began initially with dysgeusia, lower extremity edema, along with erythematosus cutaneous eruption and desquamation of the lower extremities and acral region that was refractory to topical triamcinolone 0.1% ointment. By the second month, her symptoms persisted with additional blurring of vision, xerostomia, diarrhea, hematochezia, anorexia, and thrombocytopenia that necessitated a 22-day hospitalization. She was diagnosed with immune thrombocytopenic purpura (ITP) and non-alcoholic steatohepatitis, confirmed by positive anti-platelet antibody and liver biopsy, respectively. She was started on prednisone 60 mg and discharged with a 4-week taper.

By the third month, specifically a day after discontinuing prednisone, she noted recurring edema in her lower extremities that progressed rapidly to painful desquamative and vesiculobullous lesions resulting in a second hospitalization. Skin biopsy revealed mild spongiform dermatitis with alternating hyperparakeratosis and papillary dermal edema without evidence of vasculitis, systemic lupus erythematosus, or autoimmune bullous disease on immunofluorescence. She was diagnosed with an eczematous dermatitis and discharged with another 4-week prednisone taper. During this hospitalization, she also developed sacral pressure ulcer. Two weeks after this last hospitalization, persistent edema, a non-healing sacral ulcer, and worsening desquamative plaques eventually brought her to our institution for the first time with the presentation described above.

Repeat skin biopsy of the right medial malleolus demonstrated an unremarkable epidermis, slightly ectatic superficial dermal vessels with surrounding focal rare
lymphocytes and rare extravasated red blood cells, without evidence of erythema multiforme or Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN). However, her zinc level was found to be 30 μg/dL (normal: 60-130 μg/dL), which improved after 20-days of intravenous supplementation of zinc sulphate 220 mg thrice daily (Table 1). Clinically, her cutaneous findings and gastrointestinal function also showed marked improvements (Fig. 2a-b). Her dermatologic findings and responsiveness to zinc supplement confirmed the diagnosis of acquired AE.

Notably, she had severe hypovitaminosis and mineral deficiencies that improved only minimally despite repletion (Table 1). Given a newly-diagnosed ITP, hematochezia, sicca syndrome, and persistently low pre-albumin level, she underwent an extensive additional work-up to investigate the possibility of an underlying etiology contributing to her nutritional deficiency. Her diagnostic work-up included broad titer analyses (Tables 2 and 3), blood/urine/stool analyses, esophagogastroduodenoscopy with biopsy, and colonoscopy with biopsy. Negative biopsy findings and associated autoantibody, viral, fungal, and bacterial titers ruled out the more common autoimmune and infectious causes of malabsorption, such as IBD and celiac disease (Table 3). Our patient was eventually diagnosed with AIE based on jejunal biopsy findings of mild increase in intraepithelial lymphocytes, crypt apoptosis, reactive epithelial changes, and mild mononuclear and neutrophil expansion of the lamina propria, supported by positive anti-gastric parietal cell and anti-smooth muscle autoantibodies. Other reported associations with AIE, including sicca syndrome, gastritis, nephrotic syndrome, autoimmune hepatitis, and chronic pancreatitis, were also present in this patient, further supporting the diagnosis. She was discharged after 20 days with central parenteral nutrition (CPN), prednisone 15 mg daily, and close outpatient follow-up with markedly improved dermatologic findings. Follow-up visit at our dermatology clinic 15 weeks later was unremarkable with no recurrence of cutaneous findings (Table 4). At the time of manuscript submission, patient has remained stable without further hospitalization nor recurrence of symptoms. She continued to require CPN and oral supplements with weekly nutritionist monitoring and periodic gastroenterology follow-up.

### Table 1

| Nutrient          | Initial Value | Value after 15–20 Days | Reference Range | Repletion |
|-------------------|---------------|------------------------|-----------------|-----------|
| Pre-albuminab     | 7 mg/dL       | 7 mg/dL                | 18–38 mg/dL     | -         |
| Albuminab         | 1.5 g/dL      | 2.3 g/dL               | 3.5–5.3 g/dL    | -         |
| Ionized Calciuma  | 1.07 mmol/L   | 1.20 mmol/L            | 1.13–1.32 mmol/L| -         |
| Copperab          | 51 μg/dL      | 67 μg/dL               | 70–175 μg/dL    | 2 mg PO daily |
| Ironab            | 48 μg/dL      | 44 μg/dL               | 50–170 μg/dL    | 325 mg PO with meals |
| Magnesium         | 2.0 mg/dL     | 1.8 mg/dL              | 1.6–2.4 mg/dL   | -         |
| Phosphorusa       | 2.5 mg/dL     | 3.0 mg/dL              | 2.7–4.5 mg/dL   | -         |
| Seleniumab        | 44 μg/dL      | 48 μg/dL               | 63–160 μg/dL    | 50mcg PO daily |
| Zincab            | 30 μg/dL      | 52 μg/dL               | 60–130 μg/dL    | 220 mg PO TIDd |
| Vit Aab           | 11 μg/dL      | 14 μg/dL               | 38–98 μg/dL     | 200,000 IU PO ×3 |
| Vit B1            | 109 nmol/L    | -                      | 78–185 nmol/L   | 100 mg PO daily |
| Vit B3/Niacin     | <20 ng/mL     | -                      | Variable        | 100 mg PO qhs  |
| Vit B6ab          | <2.0 ng/mL    | -                      | 2.1–21.7 ng/mL  | 100 mg PO daily |
| Vit B9/Folate     | 1743 ng/dL    | 1578 ng/dL             | >498 ng/dL     | -         |
| Vit B12           | 1161 pg/mL    | 1592 pg/mL             | 211–946 pg/mL   | -         |
| Vit D totalab     | 18 ng/mL      | 8 ng/mL                | 30–100 ng/mL    | Vit D2: 50,000 IU PO q7d CaCO3: 1300 mg PO TID |
| Vit E – αabc      | 1.1 mg/L      | 2.5 mg/L               | 5.7–19.9 mg/mL  | 100 mg PO daily |
| Vit E – βc        | 0.4 mg/L      | 1.0 mg/L               | 54.3 mg/L      | 100 mg PO daily |
| Vit K             | 84 pg/mL      | -                      | 80–1160 pg/mL   | -         |

*aInitial value is below normal

bLatest value prior to discharge is below normal

cα = alpha tocopherol; β = beta tocopherol

d200 mg zinc sulphate tablet contains 50 mg of elemental zinc

**Discussion**

Zinc is an essential mineral that plays crucial roles in metabolism, development, tissue repair, and cell proliferation, including proper maturation of basal keratinocytes.
[1]. Zinc deficiency, manifested in AE, can be acquired through decreased intake (e.g. vegetarianism, alcoholism), increased demand (e.g. pregnancy), intestinal malabsorption (e.g. IBD, gastric bypass), increased urinary loss (e.g. diuretics), or state of hypoalbuminemia since zinc binds albumin in the circulation (e.g. liver damage) [1]. Aside from the triad of dermatitis, diarrhea, and alopecia, symptoms of AE can also include angular cheilitis followed by paronychia, glossitis, ophthalmologic disturbances, poor wound healing, anemia, dysgeusia, dysosmia, and profound lethargy [1, 10]. Differential diagnoses include necrolytic migratory erythema, SJS/TEN, blistering diseases, epidermolysis bullosa, and pellagra [6, 10]. Histopathologic findings are typically indistinguishable from other forms of malnutrition dermatitis. Pathognomonic feature of fully-developed necrolysis has been reported, which involves cytoplasmic pallor, vacuolization, ballooning degeneration, and confluent epidermal parakeratosis [1]. More commonly, however, histopathology is either non-specific, such as found in our patient, or displays upper epidermal pallor with psoriasiform hyperplasia and confluent parakeratosis [1, 11]. Diagnosis is made by clinical findings subsequently responsive to zinc supplementation supported by findings of low plasma or serum zinc concentration and/or suggestive histologic findings [1, 11].

AIE is a rare cause of intractable diarrhea and malnutrition associated with gut autoantibodies and predisposition to autoimmunity [9, 12]. Histologically, there is partial or complete small bowel villous blunting, deep crypt lymphocytosis, increased crypt apoptosis, and minimal intraepithelial lymphocytosis. Diagnostic criteria necessitate chronic diarrhea (>6 weeks) with malabsorption refractory

Table 2 Abnormal titre results for autoantibodies, viruses, fungi, and bacterial toxins

| Titre Names                        | Results          | Reference Range          |
|------------------------------------|------------------|--------------------------|
| Anti-Ro (SSA) Ab                   | Moderate Positive| Negative                 |
| Gastric parietal cell Ab           | 55.5 units       | ≤ 20 units = Negative    |
| Smooth muscle Ab                   | Positive         | Negative                 |
| C3, serum                          | 71 mg/dL         | 79–251 mg/dL             |
| CMV viral load                     | 2640 IU/mL       | < 137 IU/mL              |

Ab = antibody  
CMV = Cytomegalovirus  
p-ANCA = perinuclear anti-neutrophilic cytoplasmic antibody  
c-ANCA = cytoplasmic anti-neutrophilic cytoplasmic antibody  
ANA = Antinuclear Antibody  
EBV = Epstein-Barr Virus  
TSH = Thyroid-Stimulating Hormone

Table 3 Titre results within normal range for autoantibodies, viruses, fungi, and bacterial toxins

| Titre Names                      | Results                              |
|----------------------------------|--------------------------------------|
| Alpha-1 anti-trypsin, stool, 24-h | Anti-Jo-1 Ab                         |
| p-ANCA                           | Anti-La (SSB) Ab                     |
| c-ANCA                           | Anti-nuclear Ab (ANA)                |
| Anti-cardiolipin Ab, IgG         | Anti-Scl70 Ab                       |
| Anti-cardiolipin Ab, IgM         | Anti-Smith Ab                       |
| Anti-cardiolipin Ab, IgA         | Anti-URP Ab                         |
| Anti-dsDNA Ab                    | Beta-2 glycoprotein Ab, IgG          |
| Anti-enterocyte Ab, IgG          | Beta-2 glycoprotein Ab, IgM          |
| Anti-enterocyte Ab, IgM          | Beta-2 glycoprotein Ab, IgA          |
| Anti-enterocyte Ab, IgA          | Cyclic citrul peptide Ab             |
| C4, serum                        | EBV viral load                       |
| CH50, serum                      | (1–3)-Beta-D-Glucan Galactomannan, serum |

Ab = antibody  
p-ANCA = perinuclear anti-neutrophilic cytoplasmic antibody  
c-ANCA = cytoplasmic anti-neutrophilic cytoplasmic antibody  
ANA = Antinuclear Antibody  
EBV = Epstein-Barr Virus  
TSH = Thyroid-Stimulating Hormone
Table 4 Case report timeline

| Chronology | Timeline Description |
|------------|----------------------|
| T0-4 months | Clinical presentation: dysgeusia, lower extremity edema, and cutaneous eruption and erythema of the lower extremities and acral region with desquamation. Management: refractory to topical triamcinolone 0.1% ointment. |
| T0-3 months | Clinical presentation: symptoms persisted with additional blurring of vision, xerostomia, diarrhea, hematocrit, anorexia, and thrombocytopenia. Diagnosis: immune thrombocytopenic purpura (ITP) and non-alcoholic steatohepatitis. Management: 2-day hospitalization, prednisone 60 mg and discharged with a 4-week taper. |
| T0-2 months | Clinical presentation: recurring edema in the lower extremities progressing rapidly to painful desquamative and vesiculobullos lesions. Diagnosis: eczematous dermatitis. Diagnostic tests: skin biopsy. Management: second hospitalization, discharged with another 4-week prednisone taper. Comments: developed sacral pressure ulcer. |
| T0 | Clinical presentation: persistent edema, non-healing sacral ulcer, worsening desquamative plaques. Diagnosis: acquired acrodermatitis enteropathica and severe nutrition deficiency. Diagnostic tests: skin biopsy of the right medial malleolus, broad titre analyses, esophagogastroduodenoscopy and colonoscopy with biopsy. Management: broad nutrition repletion. |
| T0 +3 weeks | Clinical presentation: marked improvements of cutaneous findings and gastrointestinal function. Diagnosis: adult autoimmune enteropathy. Management: discharged with central parenteral nutrition (CPN), prednisone 15 mg daily, and close outpatient follow-up. |
| T0 +4 months | Clinical presentation: outpatient follow-up with unremarkable cutaneous findings. Management: continue CPN and oral supplements, close outpatient follow-up with gastroenterology and nutrition. |

Case presentation

Table 4 provides a timeline of the patient’s symptoms and interventions. The patient presented with recurrent edema in the lower extremities progressing rapidly to painful desquamative and vesiculobullos lesions. The diagnosis of adult autoimmune enteropathy was confirmed through skin biopsy, esophagogastroduodenoscopy, and colonoscopy. Management included broad nutrition repletion, CPN, prednisone 15 mg daily, and close outpatient follow-up.

Conclusion

In summary, clinicians should maintain a low threshold of suspicion for acquired AE and check for zinc deficiency in adult patients with associated risk factors for malnutrition who present with a confluence of relevant dermatologic findings that are refractory to standard therapy. Additionally, clinicians should also consider the possibility of a broader nutritional deficiency and an underlying primary malabsorption etiology. In investigating the latter for a patient with acquired AE, recognition of the association with adult AIE can benefit patient care by triggering earlier diagnosis, minimizing unnecessary tests, and establishing earlier interventions that can improve a patient’s quality of life and prevent the recurrence of acquired AE.

Abbreviations

AE: Acrodermatitis enteropathica; AIE: Autoimmune enteropathy; CPN: Central parenteral nutrition; IBD: Inflammatory bowel disease; ITP: Immune thrombocytopenic purpura; SJS: Stevens-Johnson Syndrome; TEN: Toxic epidermal necrolysis

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Availability of data and materials

All laboratory, imaging, and study data relevant to this case report can be found in the “Case presentation” section of this article.
Authors’ contributions
EL performed data collection, photography of clinical images, and was the main contributor in drafting and revising the manuscript. SS was the primary dermatology resident physician during the patient’s hospitalization, served as interdisciplinary liaison with the patient’s other care teams (e.g. internal medicine, rheumatology), and was a key contributor to the revisions of the manuscript. All authors read and approved the final manuscript.

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EL is a fourth year medical student at the Johns Hopkins Hospital currently engaged in a year of research with the Department of Dermatology. SS was a fourth year dermatology resident at the Johns Hopkins Hospital, she has completed her training as of August 2016 and is currently a private practitioner in Seattle, WA. SHY is an Assistant Director of the Cutaneous Translational Research Program and Assistant Professor in the Department of Dermatology at the Johns Hopkins Hospital.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate
Not applicable.

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