Bullous Presentation of Acrodermatitis Enteropathica in Three Female Siblings: A Case Series

Katherine Joy B. Sayo-Aguiling, MD, DPDS[1], Abelaine Venida-Tablizo, MD, FPDS[2], Melanie Joy D. Ruiz, MD, FPDS[1]

ABSTRACT

Acrodermatitis enteropathica is a rare autosomal recessive disease that results from a defect in zinc metabolism. It is clinically characterized by a phenotypic triad of periorificial and acral dermatitis, diarrhea, and alopecia. Oral zinc therapy gives a rapid excellent clinical response and reduces mortality. We report three female pediatric siblings who presented with periorificial and acral dermatitis, diffuse alopecia, nail dystrophy, irritable mood, and stunted growth. A diagnosis of acrodermatitis enteropathicawas confirmed with markedly decreased levels of serum zinc. The patients were successfully treated with oral zinc sulfate at a dose of 5mg/kg/day for the first two weeks then maintained on a dose at 2mg/kg/day.

Keywords: acrodermatitis enteropathica (AE), zinc, bullae, congenital zinc deficiency

OBJECTIVE

To present a case series of three female pediatric siblings with acrodermatitis enteropathica, a rare condition

INTRODUCTION

Zinc is an essential trace element and it plays an important role in growth and development.[1] Deficiency in zinc results to an autosomal recessive disorder called acrodermatitis enteropathica (AE).It is caused by a mutation of the *SLC39A4* gene which encodes the ZIP4 zinc transporter and is located on chromosome 8q24.3.[2] Clinically, it is characterized by the triad of acral and periorificial dermatitis, alopecia, and diarrhea which can be resolved by oral zinc supplementation.[1,2,3] This is a case series of three female siblings - a pair of twins and a younger sister who came at our clinic for consultation due to a periorificial and acral eczematous and erosive dermatitis accompanied with thinning of hair and nail dystrophy. History of consanguinity was present in the parents. Serum zinc levels were significantly decreased and patients improved upon oral zinc supplementation.

Disclosures: *The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

***Department of Dermatology, Jose R. Reyes Memorial Medical Center, Manila, Philippines**
[1]Consultant Dermatologist at Jose R. Reyes Memorial Medical Center, Manila, Philippines
[2]Former Consultant Dermatologist at Jose R. Reyes Memorial Medical Center, Manila, Philippines

CASE SERIES

CASE 1

A five-year-old female born normally at full term to healthy, related (second cousins) parents presented with a three-year-history of having bullous lesions over the periorificial and acral areas. Spontaneous rupture of bullae was observed leaving well demarcated erythematous to hyperpigmented plaques with fissures and crusts. Birth history was unremarkable. Milestones were normal. The child was exclusively breastfed since birth up to two months of age and mixed feeding followed. Immunizations were unrecalled but were incomplete. Similar lesions were also evident on her twin sister. The patient had been treated unsuccessfully for presumed atopic dermatitis and bacterial infections with topical steroids and oral and topical antibiotics in the province.

On the day of examination, we saw an afebrile, irritable child weighing 11.7kg, severely of paronychia. Scalp hair was light brown, thin, and sparse. A delay in consultation led to the appearance of painful eroded and fissured plaques over the feet (see figures 1-3).

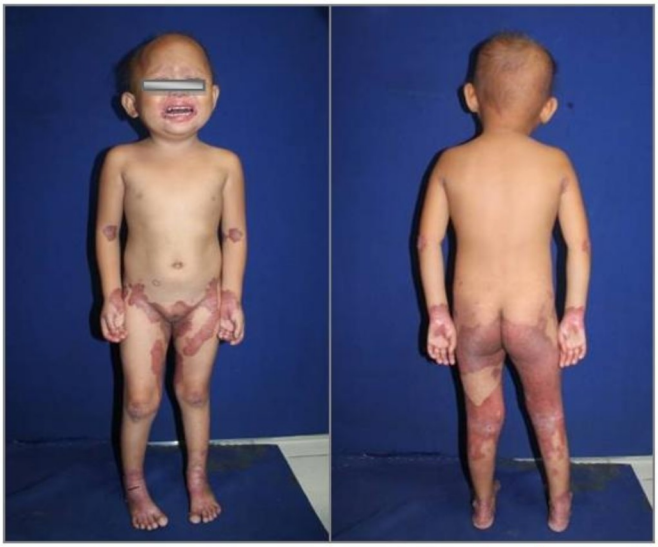

Figure 1*. Before treatment. Profile of the patient (front and back) showing well demarcated erythematous scaly plaques over the periorificial, acral, and flexural areas as well as diffuse alopecia.*

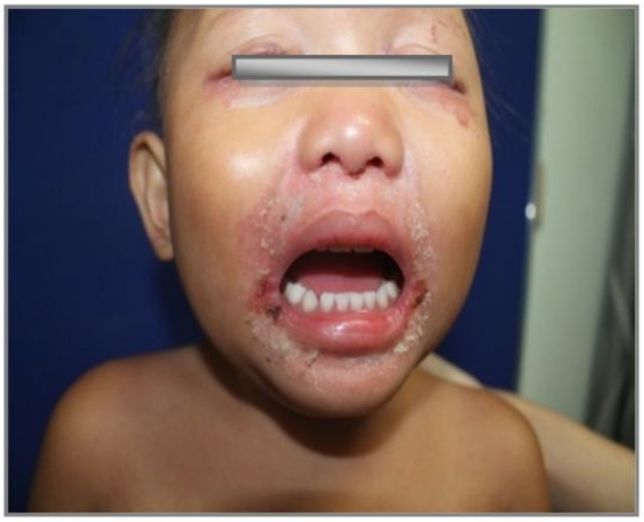

Figure 2. *Patient 1 with angular cheilitis and scaling around the eyes.*

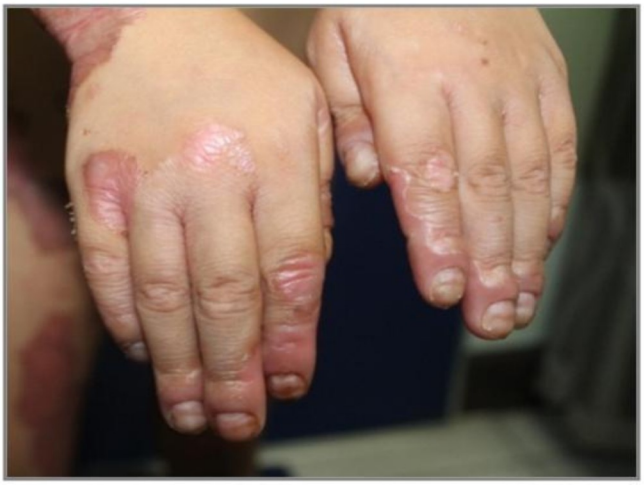

Figure 3. *Nail dystrophy: Beau's lines and paronychia.*

The patient was initially assessed as a case of epidermolysis bullosa and co-management with pediatric service was ordered. She was given oral antibiotics for pneumonia and topical antibiotics for the crusted lesions. Laboratory work up was done revealing non-contributory results. Wound care and trauma precaution were emphasized to the caregivers. Mechanical induction of vesicle was unsuccessful. A 6mm skin punch biopsy of a fresh pustule on the left thigh was done.

Histopathologic examination revealed a subcorneal separation with neutrophils, hyperkeratosis, and irregular acanthosis in the

epidermis. There were dense infiltrates of lymphocytes with neutrophils in the dermis (refer to figures 4-5). These changes are not specific for an autoimmune blistering disease hence re-assessment was done.

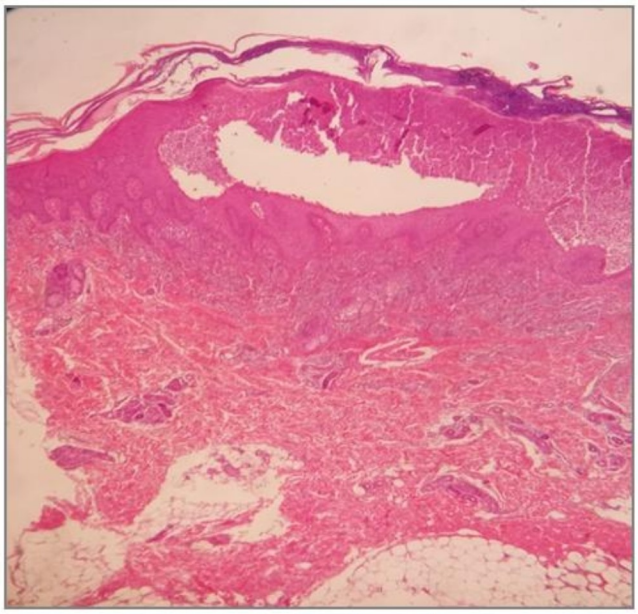

Figure 4. *On scanning view, the epidermis showing subcorneal separation and hyperkeratosis.*

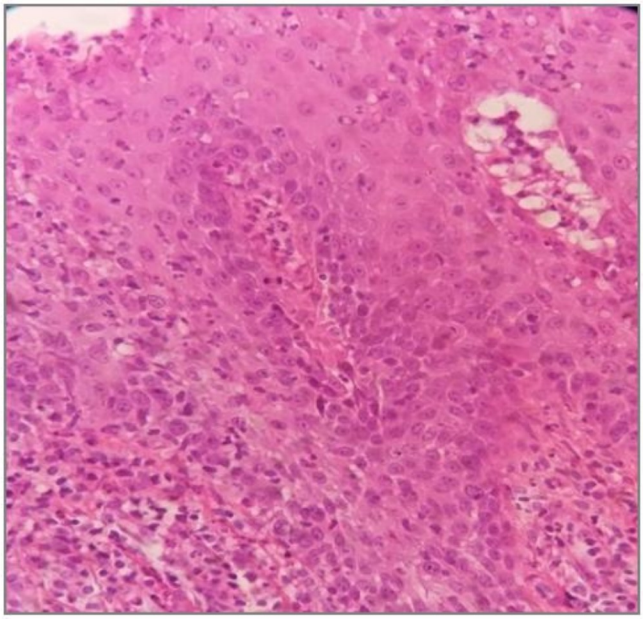

Figure 5. *On closer magnification, the dermis is infiltrated with lymphocytes and neutrophils.*

Serum zinc determination was ordered and revealed a decreased amount of 52 µg/dL (normal: 70-250 µg/dL). Alkaline phosphatase level: 55 U/L (normal: 70 – 160 U/L) was also noted. On the basis of clinical and biochemical findings, we arrived at a diagnosis of acrodermatitis enteropathica. An overall rapid response to treatment of zinc sulfate 5mg/kg/day was seen in one week (see figures 6-8). The incessant crying and whining first disappeared followed by the improvement of the plaques and the hair and nails. The patient is still on zinc maintenance therapy at 2mg/kg/day.

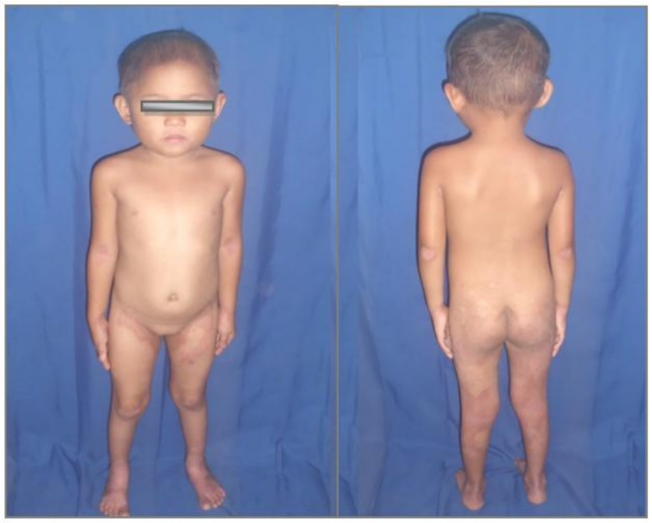

Figure 6. *After treatment. Improvement of plaques and growth of hair.*

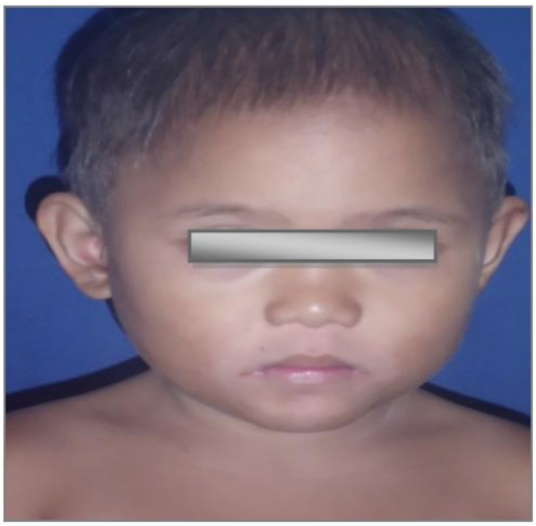

Figure 7. *After treatment. Improved periorificial dermatitis*

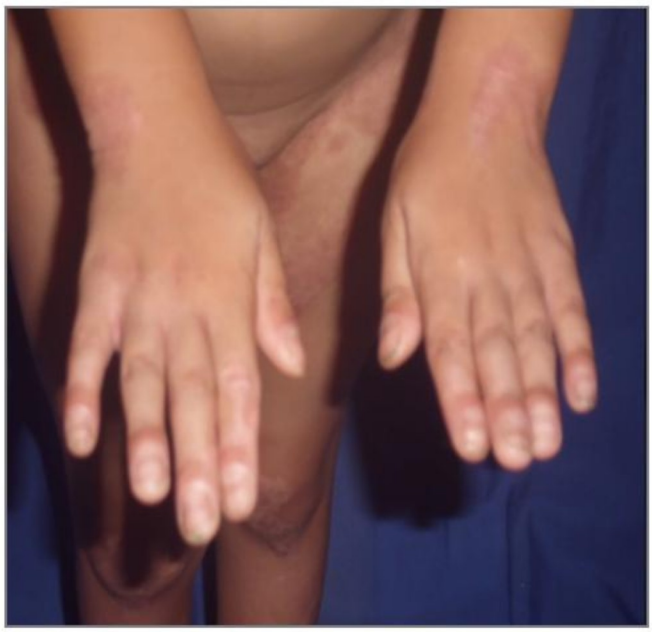

Figure 8. *After treatment. Improved nail dystrophy.*

CASE 2

A five-year-old female, twin sister of patient 1, was born term via normal spontaneous vaginal delivery to a then 30-year-old gravida 1 mother. Their parents are second cousins. Birth history was unremarkable. Milestones were at par with age. The child was exclusively breastfed since birth up to two months and mixed feeding followed. Immunizations were unrecalled but were incomplete. At the age of two years old, bullae were noted over the inguinal areas. Spontaneous rupture of bullae left well-defined erythematous scaly plaques. Interval history showed progression of lesions particularly seen on the periorificial and acral areas. Similar lesions were also evident on her twin sister. The patient had been treated unsuccessfully for presumed atopic dermatitis and bacterial infections with topical steroids and oral and topical antibiotics in the province.

Examination revealed an afebrile, irritable child weighing 12kg, underweight and severely stunted. Dermatologic findings showedwell-defined erythematous to hyperpigmented plaques with peripheral scaling over the upper extremities particularly the hands, wrists, antecubital fossae and elbows, and over the lower extremities on the inguinal and anogenital areas, anterior and posterior aspects of the legs, and ankles. The back of the trunk was relatively spared. Crusted scaly plaques were seen around the canthi, alar creases, and oral commissures. There were erythema and fissuring at the angles of the mouth. All fingernails were dystrophic showing beau's lines and some degrees of paronychia. Scalp hair was light brown, thin, and sparse. A delay in consultation led to appearance of painful eroded and fissured plaques over the feet (see figures 9-11).

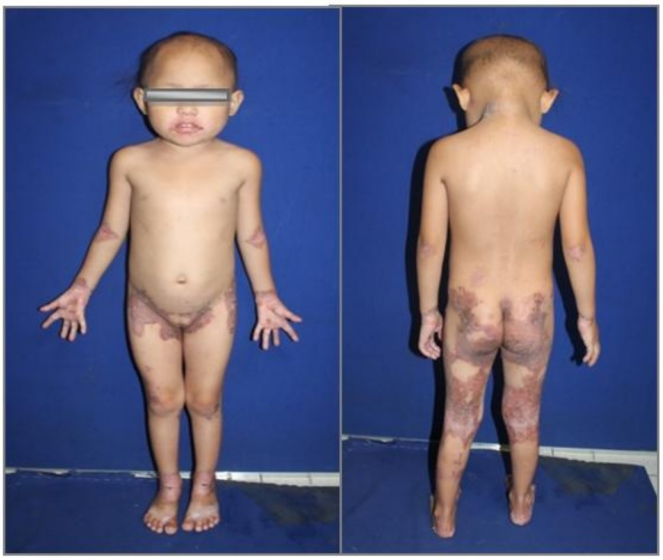

Figure 9*. Before treatment. Profile of the patient (front and back) showing well demarcated erythematous scaly plaques over the periorificial, acral, and flexural areas as well as diffuse alopecia.*

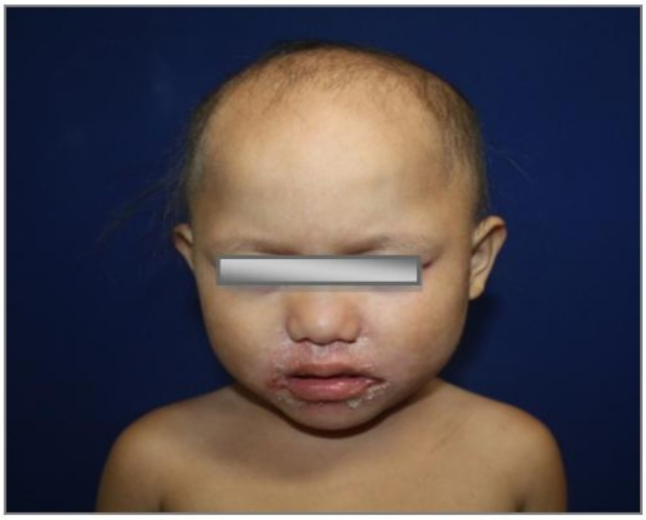

Figure 10. *Patient 2 with angular cheilitis and scaling around the eyes.*

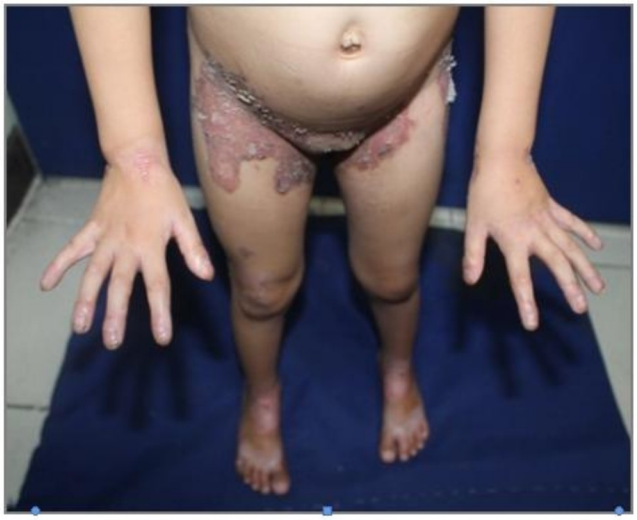

Figure 11. *Nail dystrophy: Beau's lines and paronychia.*

The patient was initially assessed as a case of epidermolysis bullosa and co-management with pediatric service was ordered. She was given oral antibiotics for pneumonia and topical antibiotics for the crusted lesions. Laboratory work up was done revealing non-contributory results. Wound care and trauma precaution were emphasized to the caregivers. The lesions were observed not to be trauma induced hence re-assessment.

Serum zinc determination was ordered and revealed a markedly decreased value of 18µg/dL (normal: 70-250 µg/dL). Alkaline phosphatase level: 43 U/L (normal: 70 – 160 U/L) was also noted. On the basis of clinical and biochemical findings, we arrived at a diagnosis of acrodermatitis enteropathica.

A 4mm skin punch biopsy was done over the right leg. Histopathology showed hyperkeratosis, irregular acanthosis, and hypogranulosis in the epidermis. There were dilated blood vessels in the upper dermis and moderate superficial perivascular infiltrates of lymphocytes (see figures 12-13). These findings are non-diagnostic but may be consistent with acrodermatitis enteropathica

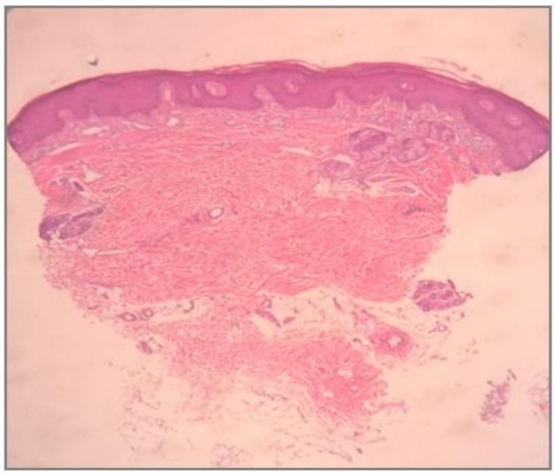

Figure 12. *On scanning view, the epidermis shows hyperkeratosis and irregular acanthosis.*

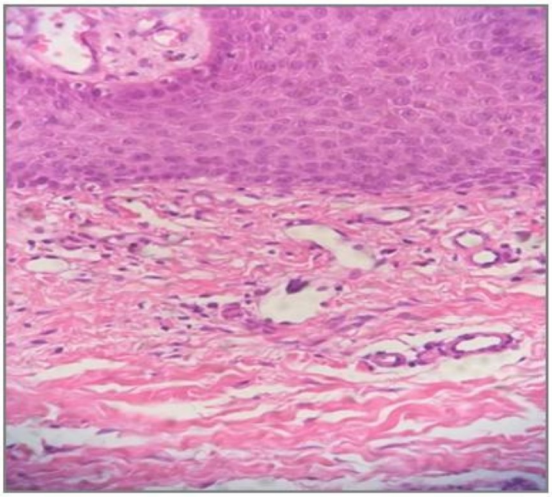

Figure 13. *On closer magnification, the dermis is infiltrated with lymphocytes.*

An overall rapid dramatic response to treatment of zinc sulfate 5mg/kg/day was seen in one week (see figures 14-16). The incessant crying and whining first disappeared followed by improvement of the plaques and the hair and nails. The patient is still on zinc maintenance therapy at 2mg/kg/day.

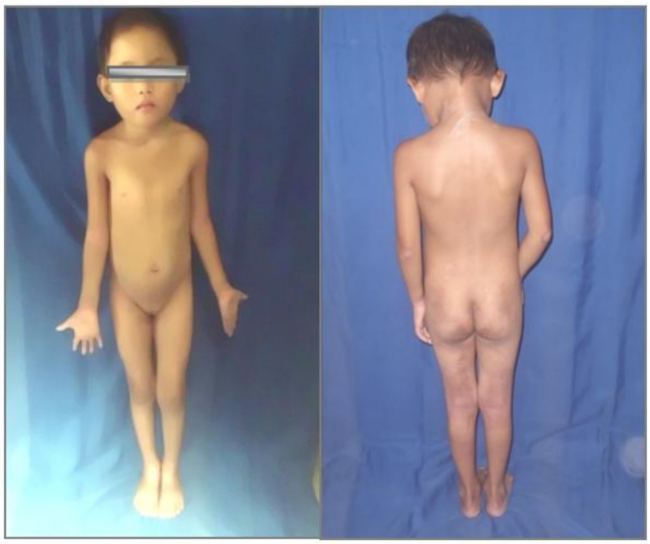

Figure 14. *After treatment. Improvement of plaques and growth of hair.*

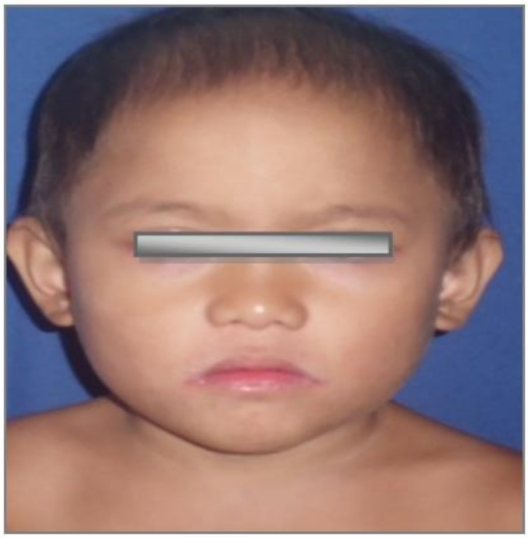

Figure 15. *After treatment. Improved periorificial dermatitis.*

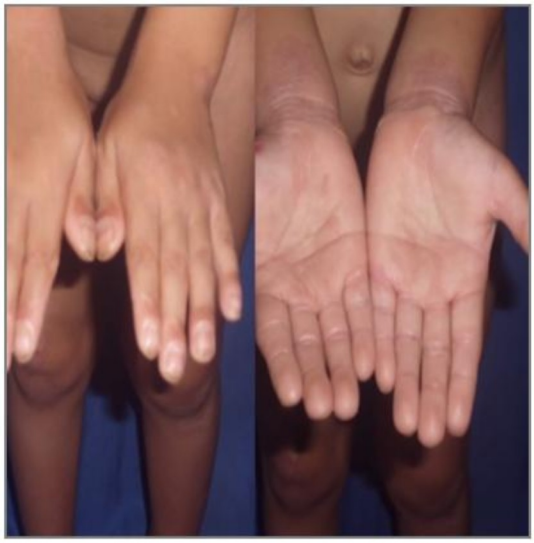

Figure 16. *After treatment. Improved nail dystrophy.*

CASE 3

This is a case of a two-year-old female who was born term via normal spontaneous vaginal delivery. There is a history of consanguineous marriage of parents. Birth history was unremarkable. Milestones were at par with age. The child was exclusively breastfed since birth up to six months of age and mixed feeding followed. Immunizations were unrecalled but allegedly complete. Six months prior to consult, bullae were noted over both inguinal areas. Spontaneous rupture of bullae left well-defined erythematous scaly plaques. Interval history showed progression of lesions particularly seen on the flexural areas. Similar lesions were also observed in her two older sisters. The patient had been treated unsuccessfully for presumed atopic dermatitis and bacterial infections with topical steroids and oral and topical antibiotics.

Examination revealed an afebrile, irritable child weighing 10.2kg, underweight and stunted. Dermatologic findings showed well-defined erythematous to hyperpigmented plaques with minimal peripheral scaling over the nape, axillary areas, upper extremities particularly the hands, wrists, antecubital fossae and elbows, and over the

lower extremities on the inguinal and anogenital areas, posterior aspect of the legs, ankles and dorsum of feet. There was a solitary hyperpigmented ill-defined patch over the back. Angular cheilitis was mild. There was no nail dystrophy. Scalp hair was thin and sparse (see figures 17-19).

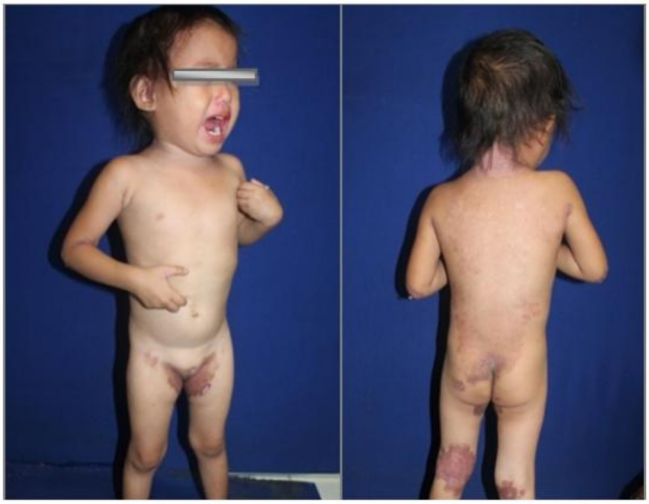

***Figure 17**. Before treatment. Profile of the patient (front and back) showing well demarcated erythematous scaly plaques over inguinal and flexural areas.*

***Figure 18.** Angular cheilitis, mild.*

The patient was initially assessed as a case of epidermolysis bullosa and co-management with pediatric service was ordered. She was given oral antibiotics for pneumonia and topical antibiotics for the crusted lesions. Laboratory work up was done revealing non-contributory results. Wound care and trauma precaution were emphasized to the caregivers. The lesions were observed not to be trauma induced hence re-assessment.

Serum zinc determination was ordered and revealed a markedly decreased value of 0.15µg/dL (normal: 70-250 µg/dL). Alkaline phosphatase level: 51 U/L (normal: 70 – 160 U/L) was also noted. On the basis of clinical and biochemical findings, we arrived at a diagnosis of acrodermatitis enteropathica.

A 4mm skin punch biopsy was done on the left arm. Histopathology showed hyperkeratosis with scale crust, irregular acanthosis, and hypogranulosis in the epidermis. There were dilated blood vessels in the upper dermis and moderate superficial perivascular infiltrates of lymphocytes. These findings are non-diagnostic but may be consistent with acrodermatitis enteropathica (see figures below).

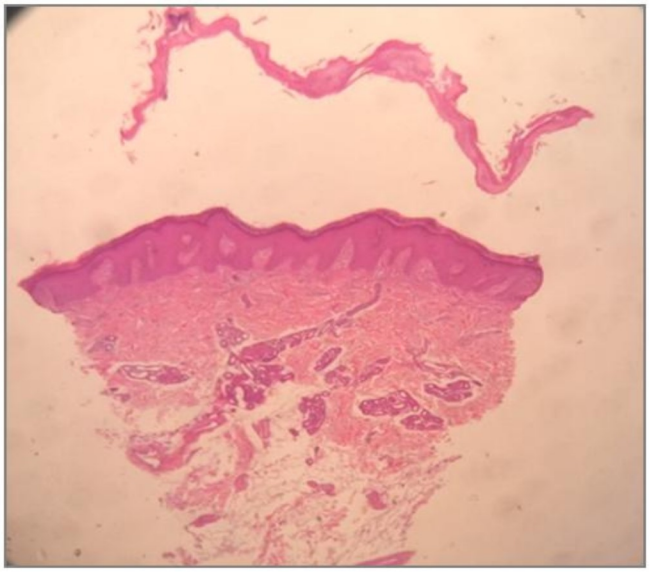

***Figure 19.** On scanning view, the epidermis shows hyperkeratosis with scale crust, irregular acanthosis.*

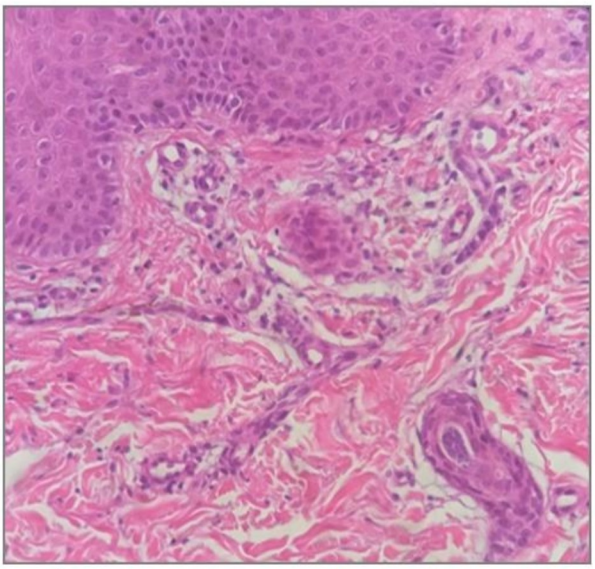

Figure 20. *On closer magnification, the dermis is infiltrated with lymphocytes and there are dilated blood vessels.*

An overall rapid dramatic response to treatment of zinc sulfate 5mg/kg/day was seen in just one week. The incessant crying and whining first disappeared followed by improvement of the plaques and the hair. The patient is still on zinc maintenance therapy at 2mg/kg/day.

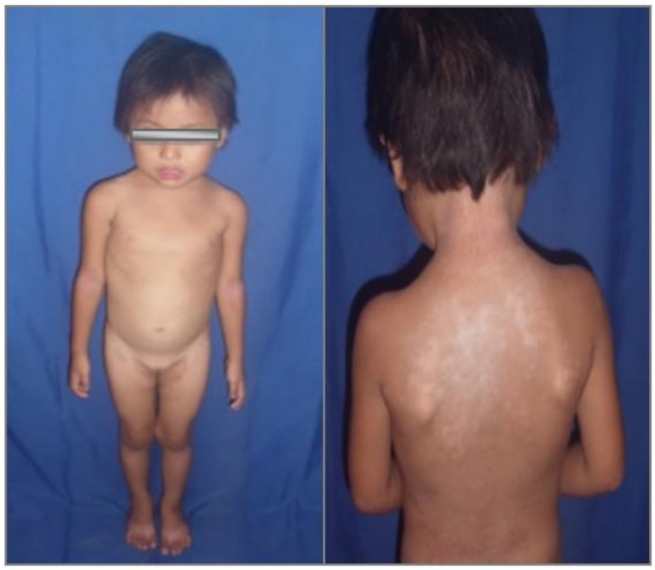

Figure 21. *After treatment. Improvement of plaques now seen as patches of hypopigmentation.*

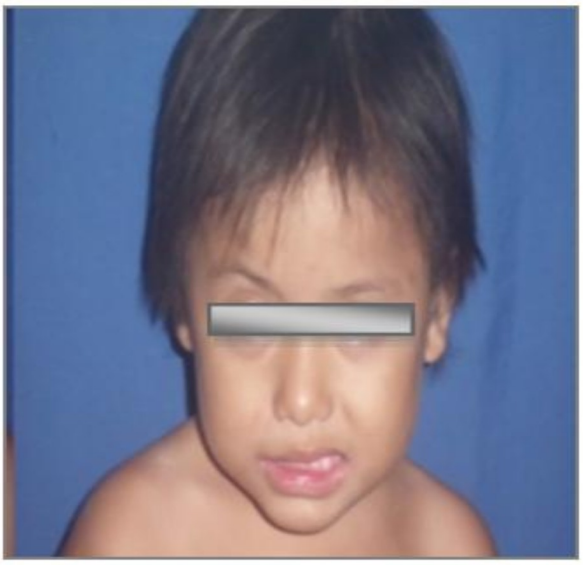

Figure 22. *After treatment. Improved angular cheilitis.*

DISCUSSION

Zinc is an essential trace element required by living organisms for its diverse biochemical and physiologic roles. It has functions in enzyme catalysis, cell signaling and division, and DNA synthesis.[4,5] It is also vital for growth and development and brain and immune function. Nutritionally, zinc may be found in leafy vegetables, whole grains, nuts, whole wheat bread, beans, cheese, cereals, and animal protein in lean meat and pork.

Deficiency in zinc may be inherited or acquired. It is primarily caused by defective zinc absorption in the duodenum and jejunum resulting in plasma zinc levels below the normal (normal: 70-250 µg/dL). Acquired cases may be due to dietary inadequacy, premature and low birth weight infants, deficient zinc in maternal milk, parenteral nutrition and various malabsorption syndromes such as inflammatory bowel disease, celiac disease, and cystic fibrosis as well as alcoholism, low calcium diet, and kwashiorkor.[1,6]

The genetic type referred to as acrodermatitis enteropathica (AE) was first

recognized by Swedish dermatologist Thore Brandt in 1936.[3,7] It is a rare autosomal recessive condition due to a mutation in the *SLC39A4* gene located on chromosome 8q24.3 that encodes the zinc transporter ZIP4. Studies and reports of AE cases with history of consanguineous marriages lead to higher carrier state of the mutation in the said gene.[2] In fact, the study on the homozygosity mapping of AE gene was tested in consanguineous Jordanian and Egyptian families.[8]Incidence rate of AE is approximately at 1 per 500,000 children worldwide without predilection for race or gender.[2,6,7]Population at particular risk are the premature infants due to inadequate zinc stores, suboptimal absorption and high zinc requirement.[9]Locally, for the past fiveyears, there have been 12 cases diagnosed with pediatric AE according to the health information system task force of the Philippine Dermatologic Society, three of which werefrom our institution.

AE classically manifests during infancy upon weaning from breast milk to formula or cereal which has lower zinc bioavailability than breast milk. AE usually presents after weaning in affected patients on the fourth to tenth week of life in infants who are not breastfed.[10]

The classical triad of AE is clinically characterized by acral and periorificial (perioral, periocular, anogenital) eczematous and erosive dermatitis, alopecia, and diarrhea. However, this triad only occurs altogether 20% of the time.[1]Cutaneous lesions present with well demarcated erythematous scaly plaques but pustules, blisters, and bullae may also develop.[7]Other clinical features include angular cheilitis and stomatitis, nail dystrophy, anorexia, neurologic disturbances, growth retardation, failure to thrive, and recurrent infection with *Candida albicans* or *Staphylococcus aureus*.

The diagnosis is mainly based on clinical manifestations and can be confirmed by low serum zinc levels and a dramatic response upon oral zinc replacement. However, a normal serum zinc level may be observed in approximately 30% of all cases.[11] Serum alkaline phosphatase – a zinc-dependent-enzyme may be measured since it may also serve as an indicator of hypozincemia. Histopathologic findings are non-specific and have a little contribution in the diagnosis. Typical features showvariable psoriasiform hyperplasia with confluent parakeratosis, spongiosis and pallor of the upper epidermis, focal dyskeratosis, and variable epidermal atrophy.[10]

Treatment of AE is simple and is done by giving oral zinc supplementation. Most authors suggest an initial dose of 3-10mg/kg/day followed by a maintenance dose of 1-2mg/kg/day. Rapid clinical response is usually seen in a matter of days. Irritability and whining would disappear first followed by improvement of skin lesions. Zinc and copper should be monitored as excess zinc may interfere with copper metabolism. With adherence to life-long zinc substitution, the prognosis is good. Only when infants are left untreated can the disease be fatal.

CONCLUSION

Herein, we present three female siblings aged five, five, and two, seen with periorificial and acral scaly eroded plaques, diffuse alopecia, nail dystrophy, failure to thrive,stunted growth, and irritable mood. An initial presentation of bullae caused diagnostic delay. Markedly reduced serum zinc levels were obtained and patients were diagnosed with acrodermatitis enteropathica, a rare genetic autosomal recessive disorder. Replacement with oral zinc sulfate given at the dose of 5mg/kg/day led to a rapid clinical improvement. To confirm the diagnosis of congenital zinc deficiency, we recommend molecular genetic studies on these patients by direct sequencing analyses.

REFERENCES

1. Kaur S, Sangwan A, Sahu P, Dayal S, Jain VK. Clinical variants of acrodermatitis enteropathica and its co-relation with genetics. Indian J Paediatric Dermatol. 2016; 17: 35 – 7.
2. CH Park, MJ Lee, HJ Kim, G Lee, JW Park, YW Cinn. Congential Zinc Deficiency from Mutations of the SLC39A4 gene as the Genetic Background of Acrodermatitis Enteropathica. J Korean Med Sci. 2010; 25: 1818-1820.
3. Rashmi M, Sudha R, Murugan S, Adikrishnan, Shobana S, Anandan S. Acrodermatitis enteropathica – a case report. *Sri Ramachandra Journal of Medicine.* 2007; 1 (2): 57 – 9.
4. Ackland ML, Michalezyk A. Zinc Deficiency and its Inherited Disorders – A Review. Genes & Nutrition. 2006; 1 (1): 41-50.
5. Gozdasoglu S, et al. Acrodermatitis Enteropathics: Case Report Analyses of Zinc Metabolism Electron Microscopic Examination and Immune Function. The Journal of Trace Elements in Experimental Medicine. 2000; 13: 317-325.
6. Nistor N, Ciontu L, Frasinariu OE, Lupu VV, Ignat A, Streanga V. Acrodermatitis enteropathica – a case report. Medicine journal. 2016; 95 (20): 1-3.
7. Iyengar S, Chambers C, Sharon V. Bullous acrodermatitis enteropathica: a case report of a unique clinical presentation and review of the literature. Dermatology online journal . 2015; 21 (4). Available from: eScholarship. Accessed June 20, 2016.
8. Wang K, et. al. Homozygosity Mapping Places the Acrodermatitis Enteropathica Gene on Chromosomal Reion 8q24.3. Am J. Hum Genet. 2001; 68 (4): 1055 – 1060.
9. James W, Berger T, Elston D. Andrews' Diseases of the Skin Clinical Dermatology 11th edition. Saunders Elsevier Inc. 2011.
10. Goldsmith LA, Katz SI, Gilchrest BA, et.al. Fitzpatrick's Dermatology in General Medicine 8th edition. New York: The McGraw-Hill Companies, Inc., 2012.
11. SY Lee, YJ Jung, TH Oh, EH Choi. A Case of Acrodermatitis Enteropathica Localized on the hands and feet with a normal serum zinc level. Ann Dermatol. 2011; 23 (1): S88-90.
12. Centilli M, Legacy M, Legacy M, Seiger E. Acrodermatitis enteropathica with atypical features and delayed presentation. Consultant 360. 2014; 54 (7).