A 1-year-old Female with Maple Syrup Urine Disease Presenting with Acrodermatitis-Enteropathica-like Lesions

Rona Maria R. Abad and Johanna Pauline H. Lazo-Dizon

Section of Dermatology, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila

ABSTRACT

A 1-year-old female with maple syrup urine disease presenting with erythematous, partially eroded plaques on the trunk, anogenital area, and extremities experienced metabolic crisis. The skin lesions appeared at 11 months of age and was thought to result from amino acid imbalance secondary to erratic supplementation of specialized milk formula devoid of isoleucine, leucine, and valine. Serial urine monitoring showed persistent ketones and elevated serum leucine and valine. The patient was managed with emollients, intralipid 20%, and addition of isoleucine and valine supplements to counter the neurotoxic effect of leucine. After 8 days of proper feeding and continuous emollient application, the lesions improved and skin biopsy revealed superficial perivascular dermatitis. Although a decrease in erythema and desquamation was noted, the patient had persistent cerebral edema and continued to deteriorate.

Key Words: MSUD, acrodermatitis-enteropathica-like lesions, metabolic disorder

INTRODUCTION

Maple syrup urine disease (MSUD) is an autosomal recessive disease caused by a defect in the branched-chain alpha-ketoacid dehydrogenase (BCKDH) enzyme and has a worldwide incidence of 1 in 185,000 births.[1] In normal people, this enzyme breaks down the branched-chain amino acids (BCAA) leucine, isoleucine, and valine, and branched-chain keto-acids (BCKA). Failure to break down BCAA and BCKA, as seen in patients with MSUD, would lead to their accumulation, resulting in ketoacidosis, neurological disorders, and developmental disturbances. There are five clinical phenotypes of MSUD depending on enzyme activity and symptomatology, the most common being classic MSUD. The classic type, which is the most severe, and has the earliest onset, has <2% residual BCKDH activity,[2] resulting in greater accumulation of leucine, isoleucine, valine, and keto-acids. Newborns with classic MSUD appear normal at birth then develop lethargy, poor feeding, vomiting, ketoacidosis, and neurologic signs between 4-7 days of age and if with poor metabolic control, may progress to seizures and encephalopathy, leading to death.[2] The Institute of Human Genetics developed a national registry for inborn errors of metabolism since 1996, showing a total of 203 registered diagnosed cases of MSUD. As of May 2018, there are 73 patients with MSUD who are alive in the Philippines.[3] The usual neurologic symptoms are constantly being observed in these patients,[4] but reports with cutaneous manifestations are very rare. This case report discusses a

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Corresponding author: Rona Maria R. Abad, MD
Section of Dermatology
Department of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita Manila 1000, Philippines
Telephone: +632 5548400 local 5105
Email: ronabad@gmail.com

female infant with classic MSUD, presenting with eruptive dermatitis, who responded to appropriate dietary therapy and emollient application.

CASE

A 15-month-old female from Pampanga was referred to the dermatology outpatient clinic for erythematous, scaly, partially eroded plaques on the trunk, anogenital area, and both upper and lower extremities. The patient was born full term with an unremarkable birth and maternal history to non-consanguinous parents of different races (Filipino mother, Nigerian father). On her 7th day of life, she presented with lethargy, poor appetite, rotating movement ("bicycling") of arms and legs, grunting, and neck rigidity. Newborn screening test (NST) was done, which was positive for MSUD. On further work-up, she was found to have leucine levels of >1,000, prompting admission for peritoneal dialysis. Specialized infant formula feeding that was devoid of isoleucine, leucine, and valine was also started. Patient was discharged improved on her 29th day of life, and was well until 6 months of age when she presented with frequent episodes of prandial vomiting and aspiration. Only insertion of a nasogastric tube to assist in feeding was done at that time. At 11 months of age, an episode of severe diarrhea and vomiting led to hospital admission. Work-up revealed anemia and transfusion of 2 units packed RBCs was done. She was also given Bacillus clausii, cefuroxime, oral cefixime, racecadotril, and domperidone. After 1 week, the symptoms of diarrhea, vomiting, and pallor resolved, and patient was discharged improved.

At 1 year of age, an erythematous patch was noted on the intergluteal area (Figure 1A). Four days later, the lesion progressed into erythematous papules that involved the upper and lower extremities, back, and lower part of the face. Patient was seen by an allergologist, and was prescribed moisturizing cleansers, lotion, antihistamines, and zinc sulfate. However, the family was non-compliant. They were also advised to get plasma levels of isoleucine, leucine, valine, and zinc, but this was not done due to difficulty in blood extraction. Patient was also referred to the Section of Dermatology, and was prescribed white petrolatum for the lesions. After 8 days, the affected areas of the skin became brown and denuded, revealing fresh pinkish skin underneath (Figure 1B). At this time, the patient was noted to be tachypneic and febrile, and was re-admitted at the same institution for treatment of pneumonia. During admission, patient was referred back to the Section of Dermatology and was advised application of a combination of desonide and white petrolatum twice a day, and application of white petrolatum alone four times a day. The lesions were noted to improve but the desquamation continued. Patient was discharged after 1 week with improved breathing, but still with poor cry and lethargy. In the interim, patient was noted to have decreased sensorium and increased sleeping time, but was still arousable. No consult was done until the patient

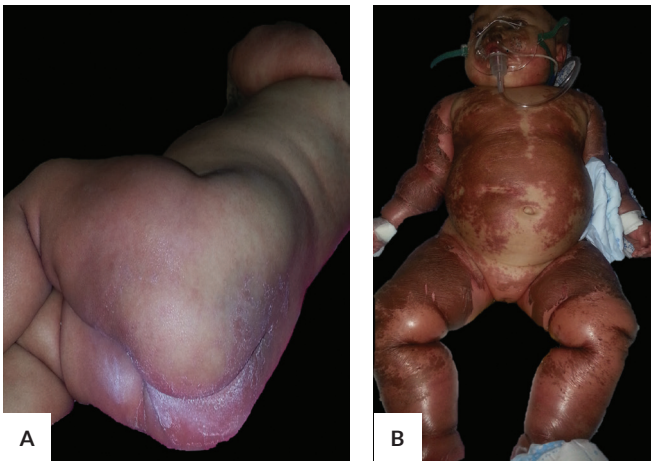

Figure 1. (A) Initial lesions. Erythematous, weeping plaques on the intergluteal area. (B) Two weeks after initial lesions. Development of brown denuded skin with pinkish skin underneath.

developed convulsions and was subsequently admitted at the Philippine General Hospital Emergency Room.

Personal and past medical history revealed that the patient was an only child, with no other comorbidities. There were no similar conditions or known congenital inborn errors of metabolism in either side of the family. Notably, two out of nine of the mother's siblings died at infancy due to unknown cause, both of which were male. The patient's gross motor functioning was notably delayed. She was being formula-fed 8 times a day with specialized milk mixture, in addition to 30 mL of honey-infused water in between feedings. The mixture consisted of 120 mL of BCAA-free formula (*BCAD1®)* and starter infant formula (*NanPro1®),* both of which were supplied by the Institute of Human Genetics of the National Institutes of Health for free. Whenever the patient was ill, however, the parents implemented a zero-protein feeding regimen for long periods of time, without a gradual increase in protein supplementation.

At the ward, the patient was started on intralipid 20% 1cc/hr, isoleucine 50 mg/sachet and valine 50 mg/sachet supplements OD, and *BCAD1®*1 scoop/oz every 3 hours. When the patient was examined, she was tachycardic and tachypneic with no spontaneous eye opening and no spontaneous movement, prompting intubation (Figure 2A). Patient was in the 90th weight-for-length percentile (length 70 cm, weight 9.2 kg). She had equal slowly reactive pupils and no lateralizing signs. Other than rhonchi on the bilateral lung fields, the rest of systemic examination was unremarkable. Dermatologic examination revealed multiple well-demarcated erythematous plaques on the neck (Figure 2B), anogenital area (Figure 2C), shoulder (Figure 3A), flexor aspect of the bilateral upper extremities (Figure 3B), trunk, and bilateral thighs. The areas had scaling and were dry and non-weeping, except for an eroded area on the buttock (Figure 4A). The palms and soles of the bilateral hands and

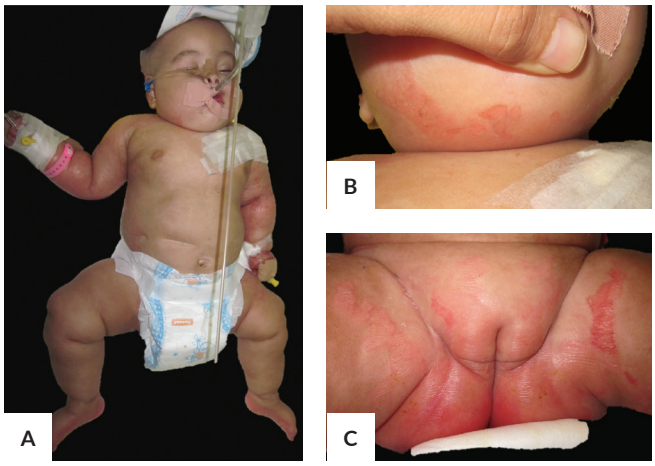

Figure 2. (A) The patient, as first seen in the ward. Erythematous, well-demarcated, irregularly shaped, eroded plaques on the neck (B) and anogenital area (C).

feet were erythematous and desquamating (Figures 3C, 4B, 4C). There was also diffuse scalp thinning (Figure 5). The face, conjunctivae, and oral mucosa were not involved and there were no satellite lesions noted.

She was subsequently admitted at the Pediatric Intensive Care Unit, and the dietary regimen was continued. Daily increments or reduction in amount and frequency of feeding was done, depending on the BCAA levels. White petrolatum was also applied on the areas of desquamation.

Upon review of the laboratory work-up, baseline complete blood count (CBC) showed anemia and thrombocytopenia. On the 2nd hospital day, she developed a predominantly neutrophilic leukocytosis. Serial monitoring of urine ketones showed persistent elevation ranging from +1 to +3, and plasma amino acids were also persistently elevated, with valine levels from 261 to 814, and leucine levels from 440 to 552. Serum electrolytes were normal, with occasional fluctuations in sodium and potassium. Blood culture studies showed gram-positive cocci in pairs, and endotracheal aspirate showed moderate growths of *Enterobacter cloacae* complex, *Staphylococcus aureus*, and *Klebsiella pneumonia* ssp pneumonia. Cerebrospinal fluid studies were unremarkable, while chest radiography revealed patchy infiltrates on bilateral lung fields. Cranial ultrasound was normal for age, and cranial computed tomography (CT) scan showed diffuse white matter edema, with no detection of masses. Serum zinc level was requested but was not carried out due to difficulty in obtaining adequate sample.

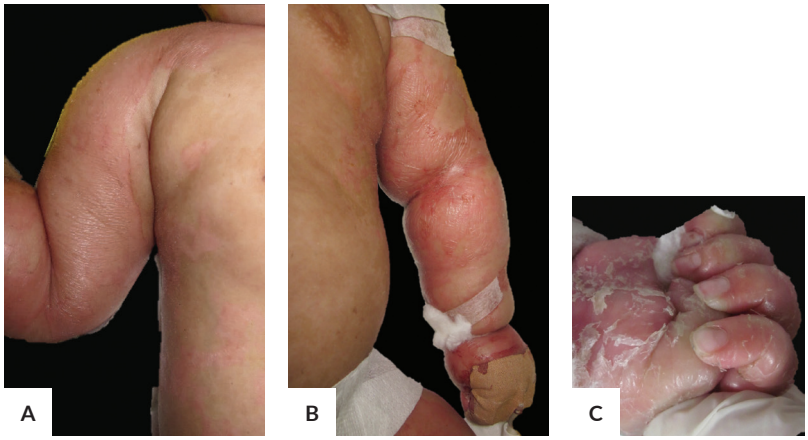

Figure 3. Erythematous, well-demarcated, irregularly shaped, eroded plaques on the bilateral shoulder and upper extremities (A and B). Erythema, scaling and desquamation of the palms and fingers (C).

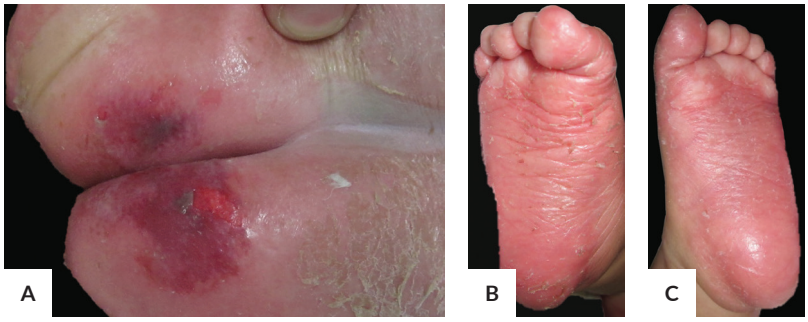

Figure 4. Area of weeping erosion of the buttock (A). Erythema, scaling and desquamation of the soles (B and C).

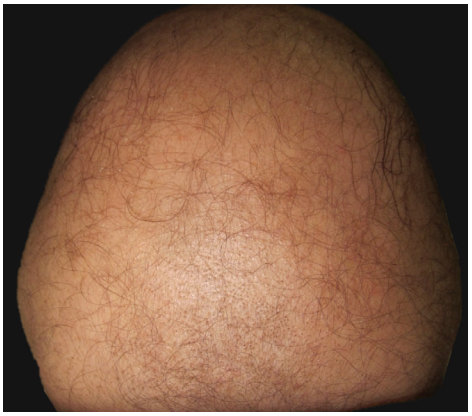

Figure 5. Diffuse scalp hair thinning.

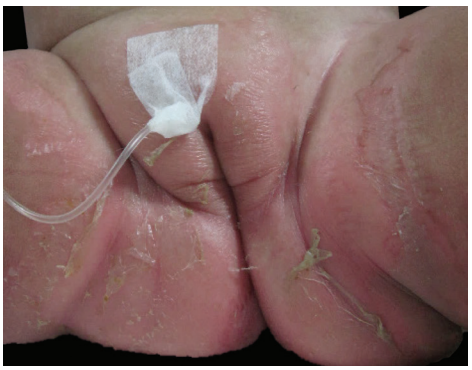

Figure 6. Improvement in the anogenital lesions 8 days upon starting appropriate dietary management.

A 3 millimeter punch biopsy was obtained on the left thigh 8 days upon starting the patient on intralipid 20%, isoleucine and valine supplementation, and *BCAD1®*. On gross examination, there was notable decrease in erythema and desquamation from baseline (Figures 6 and 7). Histopathologically, it showed basket weave orthokeratosis, a normal granular cell layer, and mild superficial perivascular lymphocytic infiltrate (Figure 8). Notably, there was absence of parakeratosis, psoriasiform hyperplasia, spongiosis, interface change, epidermal splitting, necrotic keratinocytes, and eosinophils.

Although the skin lesions improved, the patient continued to deteriorate with persistent cerebral edema. Poor metabolic control and persistence of infection eventually led to her demise.

Consent to publish the patient's course and images were obtained from the child's mother.

DISCUSSION

The eczematous lesions on the perianal and acral sites of the patient mimic a condition called acrodematitis enteropathica (AE), which is caused by zinc deficiency. MSUD is a different clinical entity, with its pathogenesis involving a defect in the branched-chain alpha-ketoacid dehydrogenase(BCKDH) enzyme resulting in accumulation of leucine, isoleucine, valine, and ketoacids. This subsequently results in neurologic and developmental disturbances. Cutaneous eruptions are uncommon.

Elevated blood levels of ketoacids and leucine are responsible for the typical symptoms of MSUD.[5] When leucine levels rise above a certain threshold (~400 umol/L), the patients show neurologic problems.[2] The neurotoxicity of leucine stems from its ability to interfere with transport of other large neutral amino acids across the blood-brain barrier, reducing the brain's supply of tryptophan, methionine, tyrosine, phenylalanine, histidine, valine, and threonine. This cerebral amino acid deficiency has adverse consequences for brain growth and synthesis of neurotransmitters such as dopamine, serotonin, norephinephrine, and histamine.[2]

The cutaneous lesions of the patient may be attributed to isoleucine, as it was found to be an essential amino acid responsible for normal growth and differentiation of keratinocytes.[6] Moreover, several reports support the role of isoleucine deficiency in skin lesions in MSUD patients receiving BCAA-free formula.[7-12] It has been observed that 1-2 weeks upon starting a BCAA-free diet therapy, infants developed periorificial and acral dermatitis, and weeping, sharply demarcated, erythematous erosions over the face, neck, anogenital area, and bilateral antecubital fossae and extremities, correlating with a low plasma isoleucine level and normal serum zinc. Isoleucine supplementation resulted in resolution of lesions in 1-2 weeks.

In another study, patients with various congenital metabolic disorders like phenylketonuria, MSUD, organic acidemias, and urea cycle defects, presented with the same weeping, sharply demarcated, erythematous erosions over the face, neck, acral sites, anogenital area, and bilateral antecubital fossae and extremities.[13] These lesions mimicked the pathognomonic acrodermatitis enteropathica of zinc deficiency, as they were documented to have normal plasma zinc levels. Hence, the term Acrodermatitis dysmetabolica or acrodermatitis enteropathica-like eruption was adapted to describe these lesions in the background of normal plasma zinc. Instead of zinc, these patients were deficient in fatty acids and essential amino acids. Particularly, low plasma isoleucine was observed in all maple syrup urine disease cases, suggesting that these uncommon lesions may arise from amino acid deficiency.[13, 14]

In this patient, a decrease in erythema and desquamation was noted after 8 days of appropriate dietary management. *BCAD1* was given to avoid the neurotoxic effects of excess

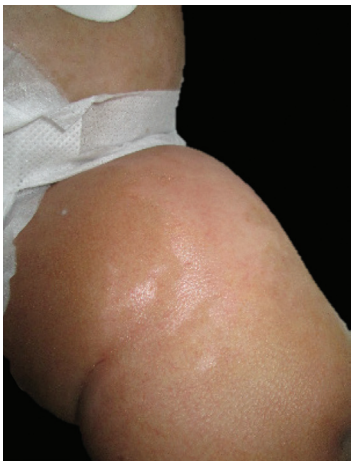

Figure 7. Biopsy site on left thigh 8 days upon starting diet of intralipid 20%, isoleucine and leucine supplementation, and BCAD1®.

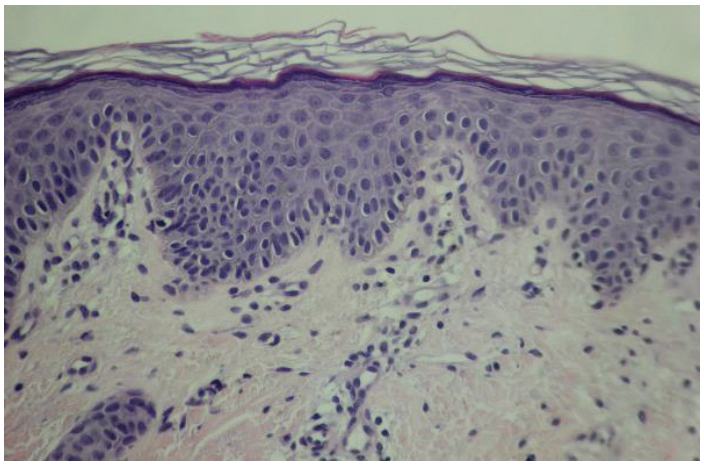

Figure 8. A 3-mm punch biopsy of the thigh showing basketweave orthokeratosis, normal granular cell layer, and mild superficial perivascular lymphocytic infiltrate.

leucine, and isoleucine and valine supplements were given simultaneously to compete with leucine and lessen its neurotoxic effects. Application of a bland emollient such as white petrolatum was also a helpful substitute for the denuded skin barrier as it is still in the process of regeneration.

Difficulty in obtaining adequate blood for zinc measurement in this patient was a limitation, but the clinical history and other diagnostics sufficed to ascertain the diagnosis. The positive newborn screening test, classic symptoms, persistent ketonuria and elevated leucine and valine, with the non-specific skin biopsy findings, support that this is an acrodermatitis enteropathica-like eruption and not of other dermatoses of nutritional deficiency. Histologic features of acrodermatitis enteropathica and pellagra of confluent parakeratosis, granular layer dimunition and focal dyskeratosis, epidermal pallor from intracellular edema, psoriasiform hyperplasia, and architectural disarray and dismaturation[15] were absent in the patient's biopsy.

As the pathophysiology in MSUD involves excess leucine that leads to neurotoxicity, protein restriction is critical in the acute management in states of crisis. One major problem in this case was the improper institution of the "sick regimen". The said regimen involves limiting protein intake to zero to remove the toxins, with a then gradual increase. The patient's recurrent infections led to an overzealous implementation of the regimen by her parents, and a net effect of a cumulative protein deficiency that further put the patient at risk for infection. Because of prolonged protein deficit, isoleucine deficiency could have also ensued, which further led to recurrent infections caused by the diminished capacity of skin regeneration brought about by low levels of this amino acid. This vicious cycle was a major contributor to the patient's demise. Perhaps unaware or misinformed, the parents' rigid restriction was detrimental. MSUD patients are at high risk of metabolic decompensation during illness because the body goes into a catabolic state as it strives to maintain equilibrium. Improper dietary management led to isoleucine deficiency, predisposing to recurrent infections due to disrupted skin barrier, and resulting in a metabolic crisis. Thus, although the skin lesions improved, the patient continued to deteriorate and eventually expired.

The study recognized that despite astute diagnosis and management of MSUD in the Philippines, the clinical outcome remains poor, mainly due to late referral and inadequate long-term management. The overall metabolic control of these patients remains poor in general due to the unavailability of resources for continuous MSUD-appropriate milk supply and regular monitoring of the BCAA levels due to high financial cost.

CONCLUSION

Dietary management is the cornerstone treatment of MSUD, with a low-protein diet, amino acid supplementation, and adequate calorie intake. Monitoring of growth and development is also a standard of care for pediatric patients. Careful monitoring of BCAA levels is likewise essential to assess the effectiveness of dietary intervention and to detect deficiencies or excesses[16] and make the necessary adjustments.

It is fundamental to understand when to withhold and to give protein. Rigid protein restriction for too long a period of time without supplementation leads to isoleucine deficiency resulting in AE-like lesions. Moreover, protein deficiency contributes to poor healing of the disrupted skin barrier, leading to recurrent infections. Dietary management should be closely followed up with a multidisciplinary team of dermatologists, geneticists, and metabolic disease specialists to ensure adequate supplementation and calorie intake, BCAA monitoring, and caregiver education for optimal outcome.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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