ACRODERMATITIS ENTEROPATHICA AND MARASMIC KWASHIORKOR: REPORT OF A CASE

S. MANIL KATUGAMPOLA, MRCP; SAAD I. EL-MOGARRI, MD;
ABDUL RAHMAN AL-FRAYH, Facharzt; ASUQUO U. ANTIA, MD, FRCP

ACRODERMATITIS ENTEROPATHICA is a severe gastrointestinal and cutaneous disease of early childhood. In 1974, Moynahan demonstrated that the disease was caused primarily by zinc deficiency and inherited as an autosomal recessive disorder.[1] Subsequent reports[2-8] have confirmed the basic causative role of zinc deficiency in this disease, although one case reported by Garretts and Molokhia[9] had no evidence of hypozincemia.

We describe an infant with characteristic clinical features of this rare disease as well as features of severe marasmic kwashiorkor.

Case Report

A 15-month-old Saudi male was referred from a district hospital to King Khalid University Hospital (KKUH) with recurrent diarrhea, vomiting, poor appetite, failure to thrive, skin rashes and ulcerations, and progressive loss of scalp hair, from the age of about 2 months. The child was born at home to a 24-year-old primigravida mother after a normal pregnancy and uncomplicated delivery. The parents were unrelated. He was said to be of average size at birth and was fed infant formula from birth, and no problems were observed until the age of 2 months, when diarrhea started. Bowel movements occurred four or five times a day, and the stools were described as loose, bulky, and varying in color from green to yellow. Appetite became poor, and gradual weight loss occurred. About the same time, skin rashes and later ulcerations were observed around the mouth and nose; subsequently, these lesions involved the anogenital areas as well. He was admitted to the local hospital, where, following 3 months of treatment, the rashes, ulcerations, frequency of stools, and general condition of the child improved somewhat.

About 1 month after discharge from the hospital, symptoms recurred, and the child was readmitted for another 4 months during which time no appreciable improvement occurred. On discharge from the hospital against medical advice, the child was taken to a traditional healer who treated him with "cauterization." There was still no improvement, and the child, now aged 13 months, was taken back to the local hospital for a third admission. He was dehydrated and weighed 4.4 kg; there were rashes and ulcers around the mouth, nose, and anogenital areas, and also infected cautery wounds on the scalp and back. Treatment consisted of intravenous fluids, broad-spectrum antibiotics, and total parenteral nutrition (TPN), containing 5% Aminosol, Vitlipid, and vitamins, but no zinc compound. After 2 months of hospitalization, there was no noticeable improvement, and the child was transferred to KKUH.

Examination revealed a chronically ill, apathetic, severely wasted child (Figure 1) with photophobia. He weighed 4.5 kg; height was 66 cm; head circumference, 41.5 cm; these measurements were below the third percentile. His temperature was 36.5°C; pulse rate, 130 beats per minute; and respiratory rate, 30 breaths per minute. There was total alopecia (Figure 1), loss of hair in the eyebrows, and bilateral blepharitis and conjunctivitis. Infected dermatitis was distributed around the mouth, nose, and anogenital areas and also bilaterally and symmetrically on the knees, hands, and feet. The terminal phalanges were swollen and had features of paronychia, and the nails were dystrophic. There was pitting

From the Department of Pediatrics, College of Medicine, King Saud University and King Khalid University Hospital, Riyadh.
Address reprint requests and correspondence to Dr. Katugampola: Department of Pediatrics (39), King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

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edema in the feet.

Laboratory investigations revealed the following results: hemoglobin, 103 g/L; hematocrit, 0.32; mean corpuscular volume, 80 fL; mean corpuscular hemoglobin, 30 pg; leukocyte count, 4.7 10^9/L with 0.51 segmented neutrophils, 0.11 band cells, and 0.08 eosinophils. Initial serum analysis showed urea, 2 mmol/L; sodium, 132 mmol/L; potassium, 4.9 mmol/L; chloride, 102 mmol/L; carbon dioxide, 23 mmol/L; calcium, 2.69 mmol/L; glucose, 5.1 mmol/L; total protein, 55 g/L; albumin, 34 g/L; and alkaline phosphatase, 24 U/L. Blood cultures performed three times were negative.

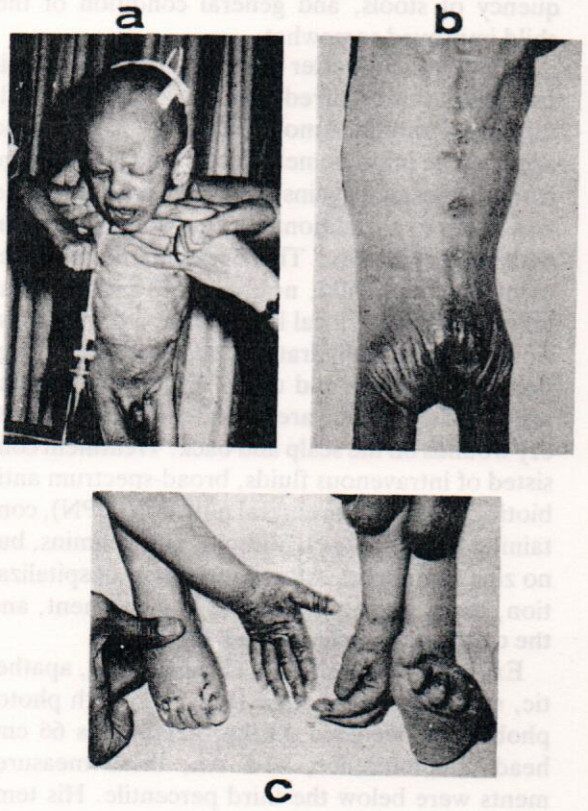

FIGURE 1. Front and back views of the patient (a,b), aged 13 months. Note the marasmic features, total alopecia, eczematous dermatitis around the mouth (dark areas) and cautery marks over the spine (b). Hands and feet (c) were swollen, and there are bilateral and symmetrically distributed eczematous skin lesions.

Cerebrospinal fluid was slightly turbid with total leukocyte count of 7 10^6/L, with 0.40 lymphocytes and 0.60 polymorphs; glucose, 2.1 mmol/L; protein, 0.20 g/L; there were no red blood cells or organisms on Gram stain; culture of the fluid was negative.

Swabs from lesions on the lips, around the mouth and nose, and the perianal area yielded heavy growth of *Staphylococcus aureus*, group B beta-hemolytic streptococcus, and *Candida albicans*. Culture specimens taken from the eyes, yielded moderate growth of *S. aureus*. Results of stool and urine tests were normal. Culture specimens taken from the eyes yielded moderate growth of *S. aureus*. Results of stool and urine tests were normal.

Other serum analyses showed vitamin D level, 62 nmol/L; total bilirubin, 3.4 μmol/L; alanine aminotransferase, 8 U/L; aspartate aminotransferase, 55 U/L; and ammonia, 16.0 μmol/L.

Immunoglobulin levels were IgA, 0.95 g/L; IgG, 8.2 g/L; and IgM, 1.0 g/L; IgE was not done. Chest and skull roentgenograms were normal. Serum zinc level was 2.1 μmol/L (reference range, 11.5 to 18.5 μmol/L).

The provisional clinical diagnosis was severe marasmic kwashiorkor, possible secondary zinc deficiency, septicemia, skin infection, and sterile pyogenic meningitis. Accordingly, treatment was started with TPN, containing trace elements, including zinc sulfate (100 μg/kg/day), antibiotics (ampicillin and chloramphenicol), and daily local application of Kenacomb cream after Savlon baths.

A dramatic clinical improvement, first in the mood of the child, was observed within 24 hours after the start of therapy. Photophobia, however, persisted, but later disappeared. The TPN was continued for 10 days, but after 7 days, oral feeding with soy protein formula with iron was started; appropriate infant diet was introduced gradually during this first 10-day period. From day 11, oral zinc sulfate (110 mg twice daily) was introduced. Healing of the ulcers and dermatitis started from about the second week and was complete by the fourth week of hospitalization. Hair began to grow from about the fourth week. Repeated serum zinc levels were 3.7 μmol/L 6 weeks after zinc therapy, 18.4 μmol/L at 10 weeks, and 11.3 μmol/L at 11 weeks. The remarkable improvement in the general condition of the child is illustrated in Figure 2. The child was discharged home after 12 weeks of hospitalization on oral zinc sulfate, 110 mg twice daily; multivitamins, 2.5 mL

daily; and folic acid, 1 mg daily. An appointment for outpatient follow-up was made, but this was not kept by the parents.

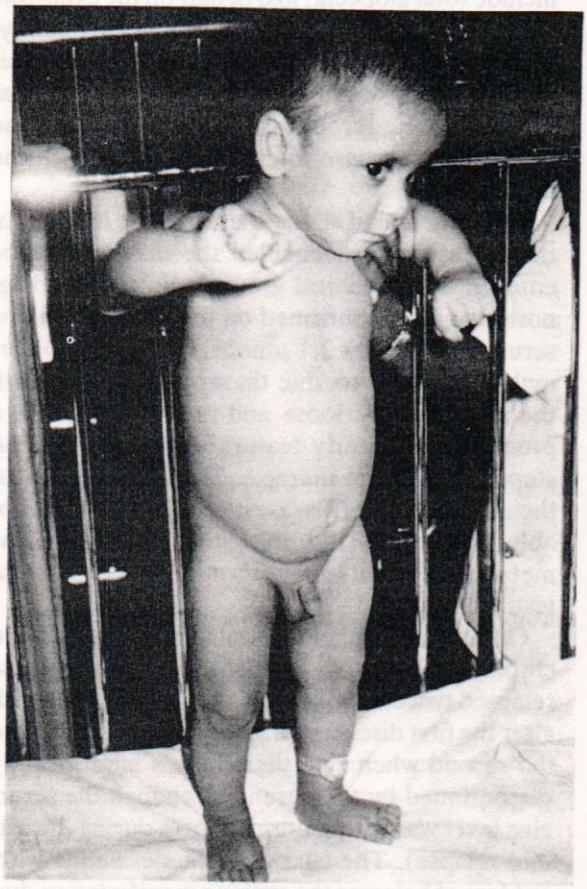

FIGURE 2. Same patient after 12 weeks of hospitalization.

Six months after discharge, the child, now 2 years old, was readmitted with complaints similar to those of the previous admission. Examination revealed a very ill, miserable, and moderately wasted child with edema in the feet (Figure 3) and the characteristically distributed eczematous lesions (Figure 4); there was no accompanying hair loss as had been noted at previous admission. He weighed 6.0 kg, a weight deficit of 2.1 kg from the weight on discharge. Results of investigations were unremarkable, and in particular, the serum zinc level of 13.3 μmol/L was within normal limits. Despite the normal serum zinc level, the child was treated with intravenous zinc (100 mg/kg/day) and partial parenteral nutrition; within a week there was remarkable improvement in the child's behavior, skin lesions, and diarrhea, as observed during the previous admission.

During the second week of admission, there was a sudden onset of features of meningitis, and

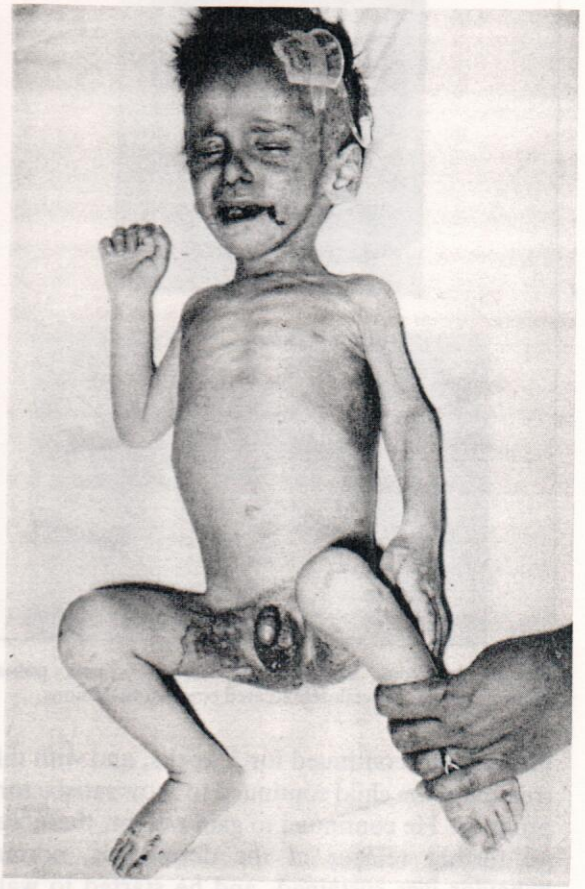

FIGURE 3. Same child at second admission showing a miserable appearance, some degree of wasting, eczematous skin lesions around the mouth, on both knees and feet, and in the perianogenital areas.

lumbar puncture yielded a CSF containing 5 10^6/L leukocytes, with 0.85 polymorphs and 0.15 lymphocytes. Chemical analyses of CSF yielded normal results, and culture was sterile. He was treated with intravenously administered penicillin and chloramphenicol, but a day later signs of intracranial pressure developed. A brain CT scan revealed obstructed hydrocephalus and periventricular edema, and ventriculoperitoneal shunt was performed. The CSF obtained at this procedure showed cellular changes that were considered to be consistent with pyogenic infection; however, early viral meningitis could not be ruled out since antigen detection tests were not undertaken. The fluid was again sterile. The antibiotic

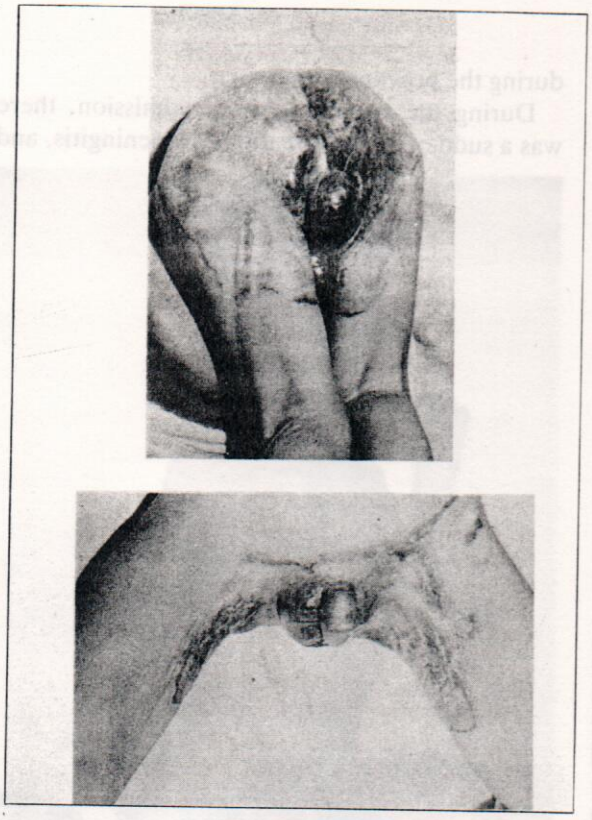

FIGURE 4. Front and perineal views of same patient demonstrating the well-demarcated eczematous lesions.

therapy was continued for 3 weeks, and with this treatment the child continued to show satisfactory progress. He continued to gain weight, there was no further relapse of the dermatosis, normal behavior was sustained, and he started to walk with support. He was discharged home on oral zinc sulfate (110 mg twice daily) and vitamin supplements. Every step, including financial support, was taken to ensure a return for regular follow-up visits and lifelong zinc therapy.

Discussion

Acrodermatitis enteropathica is an inherited disease which usually manifests in infancy and early childhood.[10] The disease is characterized clinically by skin lesions, which may be vesiculobullous, pustular, or eczematous.[7] In the present case, the lesions were eczematous, but with superadded infection during the first hospitalization. The distribution of these eczematous lesions is characteristically around the body orifices; they are symmetric with well-defined edges on the knees and dorsa of the feet, similar to the distribution in our patient. Diarrhea occurs in 90% of cases.[7] Other characteristic features of the disease include total alopecia, loss of hair on the eyebrows and eyelids, mental changes, including irritability, lethargy, and depression.[7,8] Thus, the diagnosis may be made based on these characteristic features alone. Reduced plasma/serum zinc level and a dramatic response to zinc therapy confirm the diagnosis.

Our patient had all the characteristic features of the disease, which enabled the diagnosis to be entertained on clinical grounds alone. The diagnosis was later confirmed on the basis of the low serum zinc level of 2.1 μmol/L which rose to normal in response to zinc therapy. Diarrhea, with the characteristic loose and bulky stools, was a prominent and early feature in this patient and stopped with zinc therapy. The pathogenesis of the diarrhea in this disease is not clear, but is probably related to the inherited defect of zinc metabolism and its malabsorption in the gastrointestinal tract.[7]

Our patient further illustrated the recurrent and chronic nature of the disease. The disease relapsed twice, the first relapse occurring a month after the first discharge from the local hospital and the second when zinc therapy was inadvertently discontinued by the parents (although the serum zinc level was within normal limits during the second relapse). The characteristic dermatitis without loss of hair was the striking manifestation during this normozincemic state. These findings have been reported by others,[9] thus suggesting that in acrodermatitis enteropathica, depletion of zinc from the body tends to occur faster in the skin than in other body tissues. The relapse that followed the withdrawal of the zinc therapy underlines the need for permanent zinc treatment and supports the inherited basis of the disease.

Several authors have demonstrated low plasma levels of zinc in children with various forms of protein-energy malnutrition, including marasmic kwashiorkor.[10-13] Thus, the features of severe marasmic kwashiorkor in our patient raised the possibility of its being an acquired, rather than an inherited form of the disease. However, the skin lesions and their distribution in malnutrition are not similar to those of acrodermatitis. Similarly,

total alopecia and loss of hair in the eyebrows and eyelids, as occurred in this patient, are not recognized features of malnutrition per se. Furthermore, relapse of malnutrition in cases with secondary hypozincemia does not occur with discontinuation of zinc therapy as happened in this patient. It is noteworthy that the nutritional status of children with acrodermatitis enteropathica has received little or no attention from previous investigators. In our patient, the clinical features of marasmic kwashiorkor were clearly evident, although the values of plasma proteins, lipids, and vitamins were within normal limits. This could be due to normalization of these substances by the TPN and plasma infusion therapy that was administered before the referral. Infection is a well-recognized precipitating factor in protein-energy malnutrition. Thus, generalized pyogenic skin infection in an already chronically undernourished child would seem to have precipitated the features of marasmic kwashiorkor in this patient.

Proneness to infection is well-recognized in acrodermatitis enteropathica, and in several previous publications, secondary skin infection with *Staphylococcus* organisms or *C. albicans* has been reported.[7] This marked increase in susceptibility is attributed to depressed cell-mediated immunity which occurs in acrodermatitis enteropathica and protein-energy-malnourished states.[14] In the present case, there was generalized skin infection with mixed organisms comprising *S. aureus*, group B beta-hemolytic streptococcus, and *C. albicans*. Furthermore, repeated CSF examinations showed changes that were compatible with pyogenic meningitis, although several cultures of the fluid were sterile, presumably due to the multiple antibiotic therapy that was instituted at different times.

The mode of inheritance in acrodermatitis enteropathica is autosomal recessive.[1] The gene appears to be worldwide in distribution, although the incidence of the disease in any population is likely to be small, since it is a rare disorder. Here in Saudi Arabia, with a population of over 11 million, only two cases have been reported previously, one of these being an Egyptian child.

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