Skin lesions in tyrosinosis: response to dietary treatment

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SUMMARY

A chronic form of tyrosinosis was diagnosed in a mentally retarded girl, aged 13. Concomitant findings were skin lesions of localized epidermolytic hyperkeratosis existing without remission from infancy. A diet low in phenylalanine and tyrosine was started to reduce the patient's blood tyrosine to a normal level. After 6 months of successful dietary control of blood tyrosine, an unexpected result was a complete remission of the skin lesions. The diet was abandoned after a total period of 14 months and the abnormality of tyrosine metabolism became immediately prominent again. Some 4 months later, the skin lesions have recurred.

A possible relationship between the congenital skin disorder and the abnormal tyrosine metabolism in this case is considered.

It is well known that some inborn errors of amino acid metabolism may be associated with skin lesions.

The most common of the amino-acidaemias, phenylketonuria (PKU) is characteristically associated with decreased pigmentation. Infantile eczema, dry skin and non-specific rashes are also frequent occurrences and sensitivity to sunlight may be a problem. In some adult phenylketonuric subjects, eczema may persist in spite of topical treatment and, in our experience, such cases occasionally respond to a modified PKU diet and the lesions may heal in 4–5 weeks.

In Hartnup disease, a pellagra-like skin rash aggravated by sunlight is typically associated with periods of ataxia, mental retardation and characteristic amino-aciduria. Skin signs in homocystinuria are mild, consisting of livedo reticularis, a malar flush and light-coloured hair and skin.

In some cases of tyrosinosis, mild hyperpigmentation has been noted.

We wish to report an unusual skin lesion occurring concomitantly with elevated blood tyrosine and excretion of tyrosine and its derivatives in urine (tyrosyluria) in a mentally retarded girl diagnosed as a chronic form of tyrosinosis (Zaleski & Hill, 1973).

PATIENT AND METHODS

The patient was a girl aged 13 who was discovered on routine screening for inborn errors of metabolism of the residents at the provincial institution for the mentally retarded. Quantitative measure-
ments of successive blood specimens, using an amino acid analyser, showed plasma tyrosine to be 25-30 mg/100 ml (normal <2.5 mg/100 ml).

Examination of the patient showed normal physical development and the only positive findings were nystagmus, strabismus and a chronic skin disorder. Extensive laboratory investigations, other than those mentioned above, were within normal limits. The patient was mentally grossly subnormal and had a severe behaviour disorder.

The patient's history indicated an uneventful pregnancy, birth and neonatal period. Corneal ulcers of obscure etiology appeared in infancy and persisted until the child was 4 years old. When the infant was 8 months old, the family noted 'blisters' on the flexor aspects of her fingers and on her soles. The family history revealed consanguinity and a case of psoriasis in one of the grandparents but otherwise was negative for cutaneous disorders. In spite of continuous topical treatment, the skin lesions became gradually worse, with the appearance of deep fissures and suppuration. With only minor variations, these changes persisted until the time of our investigation. At times the lesions were more than half an inch thick and caused such discomfort that the patient was unable to walk, but crawled on her knees. Eventually, the management of this child at home became impossible and at the age of 9 years she was admitted to an institution.

At that time, her skin lesions were described as clusters of linear, firm, hyperkeratotic, verrucous papules localized to the palms, the flexor aspects of the fingers, the soles and the flexor aspects of the toes, and surrounded by erythema and desquamating hyperkeratosis. Fissures were prominent over the joints.

**Skin biopsy**

A skin biopsy of a well-developed plantar lesion revealed changes of epidermolytic hyperkeratosis with epidermal acanthosis and a thick hyperkeratotic papillomatous surface. There was a bulla in the upper epidermis with a reticulated pattern in the underlying stratum spinosum associated with intercellular and intracellular oedema. The bulla was covered by thick hyperkeratosis and parakeratosis (Fig. 1). The cells of the thickened granular layer were large, contained coarse granules and exhibited perinuclear halos. Cells in the base of the bulla were eosinophilic and had perinuclear vacuolization (Fig. 2). There were occasional areas of individual cell keratinization and multinucleated cells in the epidermis. The bulla contained red blood cells, bacteria and leucocytes from secondary infection. The PAS stain indicated an intact basement membrane. The dermal papillae were oedematous with a perivascular infiltrate. An earlier palmar lesion presented similar histological changes with no evidence of infection.

**Results of treatment**

A diet, with restricted tyrosine-phenylalanine intake and supplementary amino acids, was started with the object of reducing the blood tyrosine to a normal level (Hill, Nordin & Zaleski, 1970).

We were successful in stabilizing the blood tyrosine at approximately 5 mg/100 ml, and after 6 months of treatment the lesions on both hands and feet had completely disappeared and the skin looked quite healthy except for some glossiness and a very mild hyperaemia. This improvement in the skin was maintained for a further 8 months during which the patient continued the phenylalanine-tyrosine-restricted diet. The patient was very active and quite comfortable throughout this period; no new local skin treatment was given.

As the diet was considered only experimental, it was abandoned after a total period of 14 months.

After approximately 4 months on a regular diet, the skin condition on the palms and soles began to deteriorate. After 6 months, marked hyperkeratotic areas reappeared and are spreading and thickening gradually. The patient is receiving topical applications and vitamin supplements, without much effect.
**Figure 1.** Biopsy of plantar lesion showing hyperkeratotic papillomatous surface, bulla, prominent granular layer and vacuolar changes in the epidermis (H & E, ×13).

**Figure 2.** Higher magnification of bulla base, perinuclear spaces in the stratum spinosum and stratum granulosum with increased basophilic keratohyalin-like bodies (H & E, ×128).
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FIGURE 3. Recurrence of skin lesions on feet 6 months after discontinuation of phenylalanine-tyrosine restricted diet. Similar changes were present on both soles.

FIGURE 4. Recurrence of skin lesions on hands 6 months after discontinuation of phenylalanine-tyrosine restricted diet.
During the most recent dermatological examination, the skin was lichenified on the knuckles. Linear clusters of slightly raised hyperkeratotic lesions were found on the medial aspects of the heels and on pressure areas of the soles (Fig. 3). Linear hyperkeratotic papules were present on the hypothenar eminences, with extension to the little fingers (Fig. 4). There were no buccal or nail changes.

**DISCUSSION**

The clinical and histological features of this patient’s lesions classify her condition as localized naevoid epidermolytic hyperkeratosis.

Ebling & Rook (1968) refer to circumscribed palmo-plantar keratoderma with these histological changes and state that this rare form may be a feature of more than one genetically distinct syndrome but that detailed case reports are too few to allow any firm conclusion. It is mentioned that these lesions may be associated with mental retardation and corneal dystrophies, as in our patient.

Reed, Galvanek & Lubritz (1964) described four cases of bullous congenital ichthyosiform hyperkeratosis. They surveyed similar cases in the literature and refer to the localized forms of this disorder. Mental retardation was noted in one of the children reported by the authors as well as in several previously reported cases. However, there is no indication that investigations for abnormal amino acid metabolism were done in any of the cases.

Frost & Van Scott (1966) discuss both the generalized and localized forms of ichthyosiform dermatoses, showing similar histological pictures, but again there is no indication of measurement of amino acid levels in blood or urine.

In an electron microscopic study of epidermolytic hyperkeratosis, Wilgram & Caulfield (1965) suggest that there are morphological signs of increased metabolic activity in the epidermal cells.

In his discussion of the inherited ichthyoses, Schnyder (1970) suggests that in epidermolytic hyperkeratosis, the most essential changes revealed by electron microscopy consist of faulty and increased formation of tonofibrils in the prickle cells. This author stresses that ‘biochemical analyses should be the next step in the research of ichthyoses’. One might consider whether, in certain circumstances, the over-abundance of an important substrate such as tyrosine might selectively stimulate cellular metabolism in the epidermis.

In its most frequent form, tyrosinosis presents clinically as an acute progressive illness with signs of liver and kidney failure appearing in infancy. The biochemical manifestations include high plasma tyrosine and increased quantities of tyrosine and its metabolites in urine (Hill & Zaleski, 1971). The clinically mild variant with high plasma tyrosine is rare and only three other cases in the literature closely resemble our patient (Wadman et al., 1968; Holston et al., 1971; Buist, Campbell & Koler, 1969).

Kogut, Shaw & Donnell (1967) describe a case of tyrosinosis with liver and kidney failure where, during the course of dietary treatment, the patient developed a severe, desquamating rash. This was considered to be due to vitamin deficiency and responded to biotin therapy. The rash was similar to those seen in cases of phenylketonuria and galactosaemia on a synthetic diet.

Three possible explanations for the improvement in the chronic dermatological anomaly associated with tyrosinosis in our patient should be considered. The first possibility is that any apparent relationship of the skin condition to the abnormal tyrosine metabolism was fortuitous. The second explanation, which we favour, assumes a relationship of the skin lesions to the abnormal tyrosine metabolism. Although such an association has not been observed in other cases of tyrosinosis, the variant reported here may involve unknown factors which are responsible for the different phenotypical manifestations. It is possible that a subclinical naevoid skin condition may be aggravated by the raised blood tyrosine. The third possibility which might be considered is that there is no relationship of the patient’s skin
lesion to the abnormal tyrosine metabolism and that the improvement after several months of dietary treatment occurred, because of some supplement which the patient received in the protein hydrolyzate used to provide her amino acid requirements. The product used contains all the essential amino acids, minerals and vitamins, but only minimal quantities of phenylalanine and tyrosine (experimental product '3200 AB' provided through the courtesy of Mead Johnson (Canada) Ltd, Toronto).

Finally, it would be interesting to investigate whether undetected abnormalities in tyrosine metabolism might be present in association with other poorly understood congenital dermatoses which frequently defy diagnosis and treatment.

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REFERENCES

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