# Plantar keratoderma: a manifestation of tyrosinemia type II (Richner-Hanhart Syndrome)

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Tyrosinemia type II (Richner-Hanhart syndrome) is a distinctive clinical syndrome involving the eye, skin and central nervous system. It is caused by a deficiency of hepatic tyrosine aminotransferase, resulting in elevated plasma tyrosine concentrations and elevated levels of abnormal metabolites of tyrosine in the urine. We describe the case of a middle-aged Saudi male with painful plantar keratoderma since the age of 16 years. He had certain eye signs and moderate mental retardation. To the authors' knowledge the patient described represents only the eighth case of tyrosinemia type II from Saudi Arabia. Furthermore, there have been fewer than 100 such cases reported worldwide.

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## Case

A 38-year-old man was seen in the dermatology clinic at Qatif Central Hospital, Qatif, Saudi Arabia, for evaluation of painful keratinous plantar lesions associated with increased sweating. The cutaneous lesion first manifested at the age of 16 and were never associated with ocular symptoms such as photophobia, redness or tearing. The lesions resolved in the winter and reappeared with increased severity in the summer. There was no exacerbation of the lesions with certain foods. The lesions usually started as bullae and erosions, progressing to crusted painful keratoderma. The degree of pain was so severe that he resorted to walking on tiptoe.

The patient was born to a consanguineous marriage, but there was no other similar history in the family. Treatment with keratolytic ointment and a diet free of fish, chicken and meat—to which he did not strictly adhere—minimally improved his condition. General examination revealed mild mental retardation with an IQ of 68. Skin examination showed symmetrical patchy, hyperkeratotic and foul smelling yellow plaques on the weight-bearing areas (Figure 1). Light pressure over his calluses elicited intense pain. His hands were clear of lesions apart from a single small yellowish hyperkeratotic plaque on the left palm at the metacarpophalangeal joint (Figure 2). This was the most recently developed lesion.

Ophthalmological examination found trachoma scarring with mild post-trachoma degeneration. The cornea showed a mild diffuse haze with superior and inferior accentuation. The left cornea showed an old round superficial stromal opacity. There was no corneal neovascularisation. Incidentally, despite a variety of ocular signs at examination, at no time did the patient complain of eye symptoms.

Laboratory studies found serum tyrosine of 1430 μmol/L (normal 51-91 μmol/L) and excessive excretion of urinary tyrosine and its metabolites, p-hydroxyphenyl-pyruvic acid (PHPPA), p-hydroxyphenyl lactic acid (PHPLA), and p-hydroxyphenyl acetic acid (PHPAA). Results of a complete blood cell count with differential cell count, urinalysis, blood

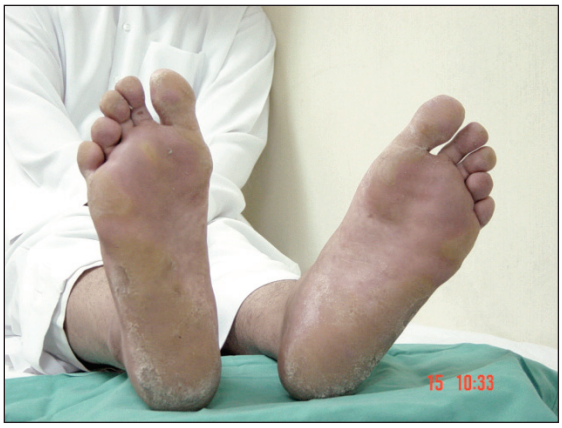


Figure 1. Symmetrical patchy, hyperkeratotic yellow plaques on the weight-bearing areas of both feet. The lesions were exquisitely painful such that the patient resorted to walking on tiptoe.

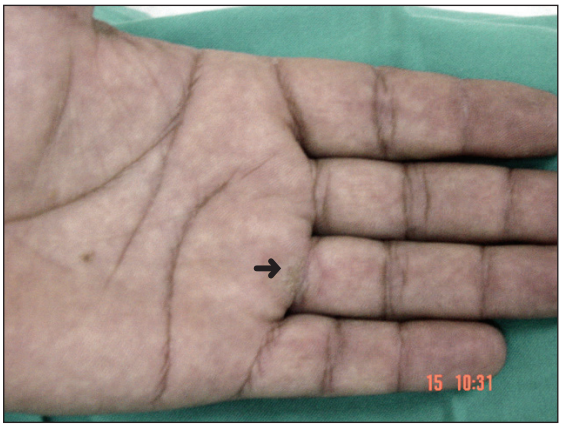


Figure 2. A single small yellowish hyperkeratotic plaque on the left palm at the fourth metacarpophalangeal joint (arrow).

chemistry panel and liver function tests were within normal limits. A skin biopsy specimen of the plaque from the callosity of the foot showed hyperkeratosis, hypergranulosis and acanthosis. There were no other specific features. A diagnosis of tyrosinemia type II was made based on the high serum and urinary tyrosine levels and the clinical features.

## Discussion

Tyrosinemia type II (also known as oculocutaneous tyrosinemia and Richner-Hanhart syndrome) is a rare distinctive disorder with autosomal recessive inheritance, characterized by skin and eye lesions, and occasionally mental retardation.[1] Approximately half of the hitherto reported cases are of Italian descent; fewer than ten cases have been reported from the Arabian peninsula.[2-4] It is distinct from the more severe hepatorenal tyrosinemia (tyrosinemia type I) and from benign transient tyrosinemia of the newborn.

Richner-Hanhart syndrome was first described by Richner, a Swiss ophthalmologist, in 1938,[5] and later by Hanhart, a Swiss geneticist, in 1947.[6] However, it was not until the early 1970s that the association with tyrosine metabolism was made.[1,7,8] The disease is caused by a deficiency of the hepatic enzyme tyrosine aminotransferase (TAT), which leads to increased levels of tyrosine in the blood and urine. The TAT gene is located on the long arm of chromosome 16, the exact locus being 16q22-24.[9,10] The TAT gene has been cloned, and up to twelve different mutations have been identified.[11,12]

The typical oculocutaneous neurologic triad is not always present. Tyrosinemia type II with features confined to the skin has been reported previously.[13,14] The typical dermatologic findings are painful, well-demarcated hyperkeratosis on the palms and soles, although the palms can be unaffected.[15,16] On the palms the distribution usually involves the fingertips, and the thenar and hypothenar eminences, while the lesions on the soles are on the weight-bearing areas. It is uncertain how high the level of tyrosine in the serum must be to induce the clinical manifestations, and why it should be confined to the palmoplanter locations, especially weight-bearing areas. The lesions, which may begin as bullae and erosions that progress to crusted, hyperkeratotic plaques, are often associated with hyperhydrosis.[17] Age at onset of skin lesions can range from the first week of life to the second decade.[13,15,16,18,19] Ocular manifestations can develop as early as the first day of life and alternatively may present for the first time as late as the fourth decade. Early signs are photophobia, pain, tearing and redness, while late signs include corneal clouding and central or paracentral opacities, superficial or deep dendritic ulceration, corneal neovascularization, and corneal scars.[16,18,20,21] Mental retardation of varying degrees is not a constant feature.[16,19,20,22]

The light microscopic features of the cutaneous lesions are not specific. The usual findings are hyperkeratosis, acanthosis, parakeratosis, a faint parakeratotic column in the acrosyringium and multinucleated keratinocytes.[13] Ultrastructural examination of the skin usually shows increases in tonofibrils and keratohyaline, aggregation of the keratin intermediate filaments, multinucleated keratinocytes, and minute tyrosine crystals in keratinocytes and Merkel cells. Deposition of tyrosine crystals in the epidermal

keratinocytes (and corneal epithelium) is the triggering event in the pathogenesis of skin and eye lesions. In the skin, tyrosine in the keratinocyte cytoplasm leads to crystal formation with subsequent cell injury and rupture followed by fusion of two or more keratinocytes. Tyrosine induces excessive noncovalent cross-linking of keratin, causing abnormal tonofilament aggregation.

Management of tyrosinemia type II is largely by dietary restriction to food low in tyrosine and phenylalanine, which reverses ocular and cutaneous abnormalities. Early diagnosis and immediate initiation of diet therapy may prevent the occurrence of other symptoms.[17] Mental retardation can be avoided if treatment is started in the early stage of the disease.[24,25] Systemic retinoid may inhibit disulfide and nondisulfide cross-linking of keratin and decrease tonofilaments. A combined therapy with diet and etretinate would be advisable for those patients who do not follow a strict diet. For those who have no ocular or central nervous system abnormalities, retinoids have been reported to control the skin lesion.[16,18,24]

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