CASE REPORT

Oculocutaneous tyrosinaemia or tyrosinaemia type 2: a case report

M Valikhani,† M Akhyani,† AK Jafari,‡ M Barzegari,† S Toosi*†

† Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran
‡ Department of Ophthalmology, Farabi hospital, Tehran University of Medical Sciences, Tehran, Iran

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*Corresponding author, Department of Dermatology, Razi hospital, Vahdat eslami square, Tehran, Iran 119960, tel. +09821569951; E-mail: stoosi@razi.tums.ac.ir

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Abstract

Oculo-cutaneous tyrosinaemia type II is an autosomal recessive disease due to an abnormality of tyrosine metabolism, probably because of a deficiency of cytoplasmic tyrosine aminotransferase. It presents as a varying association of focal palmoplantar keratosis, bilateral keratitis and mental retardation. Herein, we report an 8-year-old boy with palmoplantar hyperkeratosis with peripheral oozing and dendritic keratitis appearing after the skin lesions. There was no mental deterioration despite the long delay in diagnosis of the disorder. The diagnosis was confirmed by the presence of hypertyrosinaemia and the absence of hepatorenal lesion. The child exhibited a remarkable degree of improvement in the hyperkeratotic lesions and keratitis after the dietary modifications were instituted. In conclusion, chronic focal bullous palmoplantar hyperkeratosis along with keratitis should alert the clinician to screen for abnormal serum and/or urine tyrosine level. Awareness of the presenting signs and symptoms may speed up the diagnosis and initiation of a tyrosine and phenylalanine-restricted diet that is most efficient in improving the symptoms and preventing visual and cognitive impairment.

Case report

Our patient was an 8-year-old boy presented with extremely painful, hyperkeratotic lesions on his soles that had started at the age of 2 years. One year after the appearance of the cutaneous lesions he began suffering from photophobia and excessive tearing, which were more severe in the afternoons and particularly in the cold seasons. He had been diagnosed by general ophthalmologists with herpes simplex keratitis and treated with topical trifluridine 1% solution (Viroptic, Monarch Pharmaceuticals, Bristol, UK) and oral acyclovir (Zovirax, GlaxoSmithKline, Middlesex, UK) for 10 days, at least on three separate occasions through the past years, without resolution of the symptoms. When we first visited him, there were areas of extremely tender, thick focal hyperkeratosis with peripheral oozing on both of the soles prompting him to walk on his toes (fig. 1). There were also some bullous eruptions at the margin of the hyperkeratotic lesions. He had periorbital erythema, excessive tearing, photophobia and slight pain around the eyes (fig. 2). There had been a hypopigmented patch on the back of his trunk and hypertrichosis of the upper and lower limbs since his birth. Visual acuity was 8/10 in both eyes. Slit-lamp examination revealed bilateral, stellate, dendritiform epithelial lesions in the central area of both corneas (fig. 3). The lesions stained mildly with fluorescein. Examination of the anterior chamber, lens, and fundus in both eyes was normal. The patient was born at term by normal vaginal delivery without complications. His developmental history was age appropriate. The parents were second cousins. Laboratory investigations including full blood counts, serum biochemistry, hepatic and renal function tests were within normal limits. The patient’s serum tyrosine level was significantly elevated to 6–8 mg/dL (normal, less than 1 mg/dL) and a band was seen on tyrosine RF. Intelligence testing revealed average ability and achievement of approximately 50th percentile. His parents’ plasma tyrosine levels, general physical and ocular examinations were normal.
All topical medications were discontinued, and the patient was started on a low-protein diet and supplementation with a tyrosine and phenylalanine-restricted formula (Mead-Johnson 3200AB). After one month, the visual complaints were almost completely resolved and cutaneous lesions were significantly improved despite an elevated plasma tyrosine. When he returned for follow-up six months after diagnosis, he had discontinued his dietary restrictions. A serum tyrosine level was 8–10 mg/dL. Dietary restrictions were reintroduced. On a follow-up examination one year later, the child was asymptomatic with a visual acuity of 8/10 in both eyes, complete absence of corneal lesions and a considerable improvement in the hyperkeratotic and bullous lesions of the soles (fig. 4). Plasma tyrosine level was 4–5 mg/dL.

**Discussion**

The tyrosinaemias are a group of rare autosomal recessive disorders of tyrosine metabolism. Oculocutaneous tyrosinaemia or Richner–Hanhart oculocutaneous syndrome is a very rare disorder probably due to a deficiency of cytoplasmic tyrosine aminotransferase, mapped to chromosome 16 band q22–q24, the enzyme for tyrosine catabolism. The deficiency leads to tyrosinaemia, tyrosinuria and an increase in the urinary tyrosine metabolites. The eyes, skin and nervous system are the only organs affected. Mild but painful corneal herpetiform erosions and dendritic ulcers develop within the first few months of life. Eye and skin lesions are likely the result of deposition of cellular tyrosine crystals resulting in an inflammatory response at these sites. Despite the wide inconsistency in the onset of ocular and cutaneous symptoms, frequently ocular symptoms begin prior to the cutaneous lesions.
The patient’s case is atypical in that ocular symptoms made a late appearance. Mental retardation occurs in fewer than 50% of patients.\textsuperscript{6,7} Palmoplantar keratosis occurs in 80% and eye lesions in 75% of reported cases, respectively.\textsuperscript{8} The disorder is often associated with consanguinity.\textsuperscript{4} An elevated plasma and/or urine tyrosine level accompanying typical clinical signs and symptoms is generally sufficient for diagnosis.\textsuperscript{4} The skin biopsy, although showing hyperkeratosis and acanthosis, is not diagnostic.\textsuperscript{1} Liver biopsy demonstrating tyrosine aminotransferase deficiency is diagnostic. However, in this case liver biopsy was not performed because of the invasive nature of the procedure and the clinical presentation that was consistent with tyrosinaemia type II. The response of the patient to dietary modification may signify that this diagnostic test is no longer required.

Because the patients may present with cutaneous symptoms, and the ocular manifestations attributed to herpetic keratitis are underestimated, dermatologists must be able to differentiate it from other, more common causes of keratoderma. Mental retardation is variably associated with tyrosinaemia type II and ranges from severe retardation associated with microcephaly to slight decreases in intelligence.\textsuperscript{9} Strict dietary control achieved as early as age 40 months may be inadequate to prevent some language disorders. Reports stress the importance of early diagnosis and dietary intervention in these infants.\textsuperscript{10} Aggressive follow-up and counselling is vital to increase compliance with the strict dietary regimen, avoid recurrence of symptoms, and prevent visual and developmental impairment.

Seasonal variation in ocular and cutaneous symptoms has been previously described for tyrosinaemia type II.\textsuperscript{4} In addition to this characteristic, our patient had exacerbation of his symptoms in the afternoons that has not been mentioned in previous reports. We observed hypertrichosis of the four limbs and a patch of hypopigmentation on the back that may be related to tyrosinaemia.

We observed bullous lesions that are not typically described in conjunction with hyperkeratotic lesions of tyrosinaemia type II. In our patient’s case, despite the long delay in diagnosis and institution of the appropriate diet, there was no mental deterioration. So the psychomotor sequel is not an essential feature of the oculocutaneous tyrosinaemia even after a delay of 8 years. Despite the late institution of diet in this case, the outcome, at 1-year follow-up has been excellent in respect of oculocutaneous sequel, contrasting with the generally unfavourable outcome in most reported cases.\textsuperscript{1}

Presumed recurrent herpetic keratitis, whether responding or not to the conventional antiviral therapy, along with focal palmoplantar hyperkeratotic lesions of the palms and soles should alert the clinician to consider oculocutaneous tyrosinaemia and institute the appropriate diet to prevent the visual and mental complications that threatens the patient. Initiation of a tyrosine-restricted and phenylalanine-restricted diet is the most effective therapy available to aid improvement of the cutaneous and ocular lesions and normalization of cognitive development. Recurrence of cutaneous and ocular lesions can occur with the cessation of dietary therapy, indicating the need for continued dietary restrictions and counselling. As we observed in our patient, despite the long delay of 8 years in diagnosis and institution of the appropriate diet there may be no visual and mental deterioration in tyrosinaemia type II. Although ophthalmic symptoms and keratitis responded completely to the low-protein diet, only a portion of the cutaneous lesions resolved. We think this may be due to a more gradual disappearance of hyperkeratosis with treatment and lack of the patient’s strict adherence to the diet. Hyperkeratosis of tyrosinaemia may be associated with oozing and focal bullous eruptions and may begin earlier than ocular symptoms.

**References**


