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Case Report

Early Systemic Acitretin Response in Genetically Confirmed Neonatal ERCC2-related Trichothiodystrophy

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ABSTRACT

A term male neonate presented with generalized erythroderma, scaling, alopecia, and brittle hair. Genetic testing revealed a homozygous pathogenic ERCC2 variant. Oral acitretin resulted in marked clinical improvement within one week, without adverse effects.

Keywords: Acitretin, ichthyosis, trichothiodystrophy

Introduction

Trichothiodystrophy (TTD) is a rare autosomal recessive inherited disorder characterized by multisystem involvement affecting the skin, hair, nervous system, and, in some cases, photosensitivity (1). The features of TTD are brittle hair, ichthyosiform skin changes, mental disability, growth retardation, and recurrent infections. Unlike other DNA repair disorders, such as xeroderma pigmentosum (XP), TTD is not associated with an increased risk of malignancy (1,2). At the molecular level, photosensitive forms of TTD result from defects in genes encoding the transcription factor IIH (TFIIH) complex, including ERCC2 (XPD), ERCC3 (XPB), and GTF2H5 (TTDA) (3).

Neonatal presentation of TTD may be challenging, as generalized erythroderma, scaling, and hair abnormalities overlap with other forms of congenital ichthyosis. Early recognition is critical as affected neonates are at risk of hypothermia, dehydration, electrolyte imbalance, and infections. Here, we present a neonate with ERCC2-related TTD who showed rapid clinical improvement following the early initiation of systemic acitretin therapy. Based on prior reports indicating the favorable efficacy and safety of acitretin in congenital ichthyosis, systemic acitretin was initiated in the neonate with TTD, resulting in rapid clinical improvement (4-7).

Case Report

A male neonate was born to a 37-year-old mother in her fourth pregnancy. He was delivered vaginally at 37 weeks of gestation with a birth weight of 2,500 grams. The pregnancy was uneventful. The parents were second-degree relatives. After birth, he was admitted to the neonatal intensive care unit due to respiratory distress, hypothermia, generalized skin fissures, and thick scaling.

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Family history revealed that the patient's 7-year-old sister had presented with similar skin findings at birth. According to parental report, she experienced recurrent hospitalizations due to severe skin dryness and frequent infections, required long-term emollient therapy, and had mild intellectual disability for which she was receiving special education.

On admission, the patient's body temperature was 34° C, with associated bradycardia and mild respiratory distress. Anthropometric measurements were appropriate for gestational age. Dermatological examination revealed generalized erythroderma with scaling and focal desquamation. The scalp showed frontoparietal alopecia, with sparse, brittle, curled, and clumped hair (Figure 1). The patient's eyebrows and eyelashes were markedly reduced. Other systemic examinations were unremarkable. Laboratory investigations, including complete blood count, biochemistry, infection markers, and thyroid function tests, were within the normal limits. Cranial and abdominal ultrasonography and echocardiography were normal.

Genetic analysis identified a homozygous ERCC2 c.2164C>T pathogenic variant. In addition, a heterozygous SPINK5 c.2468del variant was detected. Based on the molecular findings and clinical presentation, a diagnosis of ERCC2-related TTD was established.

Initial supportive skin care with emollients did not result in any clinical improvement. On the fifth day of life, oral acitretin therapy was initiated at a dose of 1 mg/kg/day. Within one week of treatment, a marked reduction in erythema and scaling was observed, accompanied by improved skin integrity and clinical stability. The neonate tolerated therapy without early biochemical or clinical adverse effects and was discharged with close outpatient follow-up. Sustained clinical improvement was observed, with no treatment-limiting adverse effects during three months of follow-up (Figure 2).



Figure 1. On postnatal day 3, during the period when only liquid vaseline was applied



Figure 2. Outpatient clinic follow-up during the third month of acitretin treatment

Written informed consent was obtained from the patient's parents for the publication of this case report. Ethics committee approval was not required for this case report in accordance with our institutional guidelines.

Discussion

TTD is a clinically and genetically heterogeneous disorder arising from defects in DNA repair and transcription due to TFIIH dysfunction. ERCC2 (XPD) encodes a DNA helicase essential for nucleotide excision repair and transcription initiation (1). Pathogenic variants in ERCC2 can lead to a spectrum of disorders, including TTD, XP group D phenotypes (2,3).

In neonates, TTD may present with severe erythroderma and scaling, closely resembling other congenital ichthyoses. Therefore, molecular genetic testing plays a pivotal role in establishing the correct diagnosis and also in guiding its management. In this patient, the homozygous ERCC2 c.2164C>T variant was considered the primary disease-causing mutation, consistent with previously reported pathogenic variants associated with TTD. A heterozygous SPINK5 variant was also identified and was interpreted as a carrier state. At present, there is insufficient evidence to conclude that this heterozygous SPINK5 variant modified the patient's clinical phenotype, and its clinical significance in this context remains uncertain. An additional heterozygous SPINK5 variant was identified and interpreted as a carrier state. Further studies are required in order to clarify whether heterozygous SPINK5 variants have any modifier effects in ERCC2-related TTD.

Management of TTD is largely supportive and multidisciplinary. Skin care with emollients, infection prevention, nutritional support, and temperature regulation are essential, particularly in the neonatal period. Based on prior reports indicating the favorable efficacy and safety of acitretin in congenital ichthyosis, systemic acitretin

was initiated in the neonate with TTD, resulting in rapid clinical improvement. To the best of our knowledge, this represents one of the few genetically confirmed neonatal ERCC2-related TTD cases treated with systemic acitretin in the neonatal period.

Systemic retinoids have been used in various forms of congenital ichthyosis to reduce hyperkeratosis and improve skin barrier function (4-6). However, reports describing the neonatal initiation of systemic acitretin in genetically confirmed ERCC2-related TTD remain extremely limited (7). Acitretin, a second-generation retinoid, is considered to have a relatively favorable safety profile and a shorter half-life compared with other systemic retinoids. Although data regarding its use in neonates with TTD are scarce, our patient showed rapid and sustained clinical improvement without treatment-limiting adverse effects (5,6). Nevertheless, careful clinical and biochemical monitoring for potential adverse effects, including hepatotoxicity, hyperlipidemia, and skeletal toxicity, is essential, particularly during prolonged treatment.

In conclusion, TTD should be considered in the differential diagnosis of neonates presenting with severe erythroderma, scaling, and hair abnormalities. Early molecular diagnosis is essential for accurate classification and timely therapeutic decision-making. Early initiation of systemic acitretin may represent a safe and effective therapeutic strategy for controlling severe neonatal ichthyosiform manifestations in ERCC2-related TTD when applied with careful monitoring.

Ethics

Informed Consent: Informed consent was obtained from the parents before including the patient details in this manuscript.

Footnotes

Authorship Contributions

Concept: S.G., E.K.Ç., İ.K., Design: H.C., E.K.Ç., Data Collection or Processing: S.G., H.C., Analysis or Interpretation: S.G., İ.K., Literature Search: S.G., İ.K., Writing: S.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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