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Familial Pure Hair–Nail Ectodermal Dysplasia in Yemen: A Father–Son Case Report with Clinical Correlation

Keywords: Skin; Hair; Nail; Ectodermal Dysplasia

Abstract

Background: Pure hair–nail ectodermal dysplasia (PHNED) is a rare subtype of ectodermal dysplasia characterized by congenital hair and nail involvement, with teeth, sweating, and other ectodermal structures remaining unaffected when the disorder is fully phenotypically assessed. Only a limited number of PHNED cases have been reported, and the present father–son presentation adds to this rare clinical literature. PHNED has been associated with pathogenic variants in KRT74, KRT85, and HOXC13. Reported patients with HOXC13-associated PHNED often show severe hypotrichosis or complete alopecia with nail dystrophy; in the present family, the phenotype included congenital alopecia of the scalp, eyebrows, and eyelashes and dystrophy of all 20 nails.

Case presentation: A 27-year-old Yemeni man and his 7-month-old son presented with congenital total alopecia involving the scalp, eyebrows, and eyelashes, along with dystrophy of all 20 nails. Genetic testing identified an HOXC13 variant in the father; the son was clinically affected but was not genetically tested.

Conclusion: This father–son presentation is clinically consistent with PHNED and, in the genetically tested father, supports the association between HOXC13 variants and PHNED; it adds to the limited literature on HOXC13-associated hair–nail ectodermal dysplasia.

Abbreviations

ED: Ectodermal dysplasia; ***HOXC13***: homeobox C13 gene; **HOXC13**: homeobox C13 protein; **KRTHB5**: Keratin, hair, basic, 5 (hair matrix and cuticle keratin gene); ***KRT74***: keratin 74 gene; **KRT74**: keratin 74 protein; ***KRT85***: keratin 85 gene; **KRT85**: keratin 85 protein; **PHNED**: Pure hair-nail ectodermal dysplasia

Introduction

Pure hair–nail ectodermal dysplasia (PHNED) is an extremely rare subtype of ectodermal dysplasia (ED) limited to the hair and nails, while other ectodermal structures, such as the teeth and sweat glands, remain unaffected. The first case of ED was described by Thurnam in 1848, and the term "ectodermal dysplasia" was later coined by Weech in 1929 [1,2]. PHNED was first described by Hofmann in 1908 and subsequently defined by Pinheiro in 1992; since then, only approximately 70 cases of PHNED have been reported worldwide.

Compared with some reported *KRT74*- or *KRT85*-associated phenotypes, *HOXC13*-associated PHNED has frequently been described with severe hypotrichosis or complete alopecia. Nail dystrophy in PHNED may involve all digits and can present with irregular, fragile, or dystrophic nails; in the present father, all 20 nails were affected and showed distal dystrophy with marked downward curvature.

Open Access Case Report

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Case Presentation

A 27-year-old Yemeni man presented with congenital total alopecia affecting the scalp, eyebrows, and eyelashes, accompanied by dystrophy of all 20 nails (Figure 1). On close examination, sparse short black hairs were visible within some scalp follicles despite clinically apparent total scalp alopecia (Figure 2). All 20 nails were distally dystrophic, with marked downward curvature (Figure 3). The patient had normal dentition and reported normal sweating. Scalp biopsy from the father showed marked follicular hypoplasia, with a substantially reduced number of structurally disorganized hair follicles. The patient was otherwise healthy, with no associated systemic abnormalities. The presence of similarly affected siblings with reportedly unaffected parents raises the possibility of autosomal recessive inheritance in the father's sibship. Although the affected father and son suggest vertical transmission, the unaffected parents and affected siblings of the father also raise the possibility of autosomal recessive inheritance; definitive assessment of inheritance would require segregation analysis, including testing of the son and relevant relatives. (Figure 4).

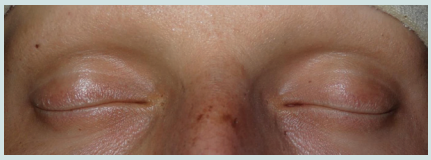

Figure 1: Case 1: Madarosis, with complete absence of the eyebrows and eyelashes.

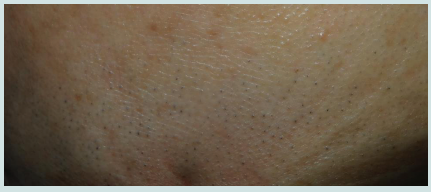

Figure 2: Case 1: Small black hairs were observed within scalp hair follicles.

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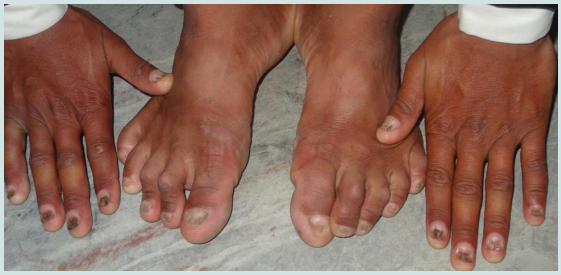

Figure 3: Case 1: Onychodystrophy affecting all 20 nails, with distal downward sloping. Note the crumpled, hyperpigmented, and atrophic distal portions; the fingernails are more severely affected than the toenails.

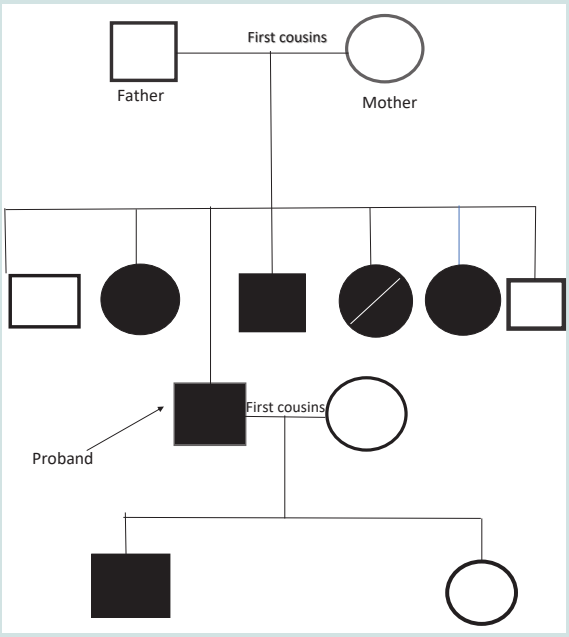

Figure 4: Pedigree of the family.

Case 2

The patient's 7-month-old son showed congenital alopecia of the scalp, eyebrows, and eyelashes and dystrophy of all 20 nails, closely resembling the father's phenotype; genetic testing was not performed (Figure 5).

Discussion

EDs are a rare group of genodermatoses that affect tissues derived from the ectoderm, including the hair, nails, teeth, and sweat glands. The first classification system for EDs was proposed by Freire-Maia and Pinheiro in 1982 and was subsequently updated in 1994 and 2001, when PHNED was included [3,4]. PHNED is a rare subtype of ED with genetic heterogeneity and reported autosomal recessive and autosomal dominant inheritance patterns [5,6]. A summary of the clinical and genetic features of previously reported cases is provided in (Table 1). Congenital absence or marked reduction of scalp, eyebrow, and eyelash hair can overlap clinically with other genodermatoses, including atrichia with papular lesions; however, the combination of congenital alopecia with generalized nail dystrophy favors

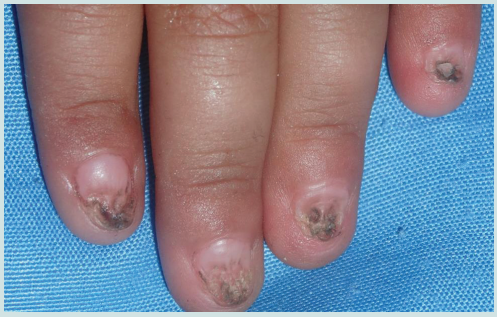

Figure 5: Case 2: Close-up view of the distally crumpled, dystrophic, hyperpigmented fingernails of the left hand.

PHNED in the present family. Hypohidrotic ectodermal dysplasia may present with hypotrichosis, but it is usually distinguished by abnormal sweating and dental anomalies, features not documented in the father in the present report. Alopecia totalis or universalis may rarely occur early in life and can be associated with nail changes, but the congenital onset, familial pattern, and generalized dystrophy of all nails in this family are more consistent with PHNED. In the present father, all fingernails and toenails were distally dystrophic with marked downward curvature.. Congenital hyponychia or micronychia may also be considered, but these conditions primarily involve nail hypoplasia and do not usually account for the combined congenital alopecia and generalized onychodystrophy seen in this family. Our literature review identified a limited number of reported PHNED cases, including two Yemeni siblings previously reported by the first author (Table 1). Pathogenic variants in *KRT85*, *HOXC13*, and *KRT74* have been reported in patients with PHNED or closely related hair–nail phenotypes [7,8]. *KRT85* and *KRT74* encode type II keratins, whereas *HOXC13* encodes a transcription factor involved in regulating keratin and keratin-associated protein genes. Keratins are major intermediate filaments within hair and nail keratinocytes, where they maintain structural integrity and confer mechanical resilience. They are classified into two types: type I keratins, encoded by genes on chromosome 17, and type II keratins, encoded by genes on chromosome 12.

The clinical features observed in the present father and son resemble those in the previously reported Yemeni siblings and in the phenotype described by Naeem et al., who reported a pathogenic variant in the hair keratin gene now referred to as *KRT85* [8,9]. The histopathologic findings of the scalp biopsy were similar to those reported by Lin et al. [7]. Genetic testing of the son was not performed because of financial constraints.

Conclusion

The father and son showed clinical features consistent with previously reported PHNED cases, and the father's scalp histopathology was comparable to findings described in earlier *HOXC13*-associated PHNED reports. To the best of our knowledge, the father represents the first genetically confirmed case of PHNED reported from Yemen, while the son represents a clinically affected familial case without molecular confirmation.

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Table 1

Pub. Year	1st Author	Title	Journal	Country	Age	Male	Female	Total
1908	Hoffmann R	Über Verkümmerung der Augenbrauen und der Nägel bei Thyreoidosen	Arch f Dermatol u Syphilis	Germany	23Y	1	0	1
1908	Hoffmann R	Über Verkümmerung der Augenbrauen und der Nägel bei Thyreoidosen	Arch f Dermatol u Syphilis	Germany	27Y	0	1	1
1913	Eisenstaedt JS	Three cases of family dystrophies of the hair and nails	JAMA	USA	1Y	0	1	1
1913	Eisenstaedt JS	Three cases of family dystrophies of the hair and nails	JAMA	USA	14Y	1	0	1
1913	Eisenstaedt JS	Three cases of family dystrophies of the hair and nails	JAMA	USA	9Y	1	0	1
1919	Barrett AM	Hereditary occurrence of hypothyroidism with dystrophy of nails and hair	Arch NeurPsych	USA	18Y	1	0	1
1928	Jacobsen AW	Hereditary dystrophy of the hair and nails	JAMA	USA	7Y	0	1	1
1928	Jacobsen AW	Hereditary dystrophy of the hair and nails	JAMA	USA	41Y	0	1	1
1936	Joachim H	Hereditary dystrophy of hair and nails in six generations	An. mt. Med.	Canada	24Y	0	1	1
1941	Benedek T	Hereditary dystrophy of the hair and nails	J.Invest Dermatol	USA	17Y	1	0	1
1943	Scully JP	Hereditary dystrophy of the hair and nails	Arch Dermatol Syphilol	USA	21Y	1	0	1
1991	Calzavara	Pili torti and Onychodysplasia: Report of a case	Dermatology	Itly	50Y	0	1	1
1991	Calzavara	Pili torti and Onychodysplasia: Report of a case	Dermatology	Itly	54Y	1	0	1
1991	Calzavara	Pili torti and Onychodysplasia: Report of a case	Dermatology	Itly	38Y	1	0	1
1992	Pinheiro M	Hair-nail dysplasia—A new pure autosomal dominant ectodermal dysplasia	Clin Genet	Brazil	24Y	1	0	1
1997	Barbareschi	Family with “pure” hair-nail ectodermal dysplasia	Am J Med Genet	Italy	50Y	0	1	1
1997	Barbareschi	Family with “pure” hair-nail ectodermal dysplasia	Am J Med Genet	Italy	23Y	1	0	1
2004	Harrison S	Hypotrichosis and nail dysplasia: a novel hidrotic ectodermal dysplasia	Australas J Dermatol	Australia	3Y	0	1	1
2006	Naeem M	A mutation in the hair matrix and cuticle keratin KRTHB5 gene causes ectodermal dysplasia of hair and nail type	J Med Genet	Pakistan	?	0	4	4
2006	Naeem M	A mutation in the hair matrix and cuticle keratin KRTHB5 gene causes ectodermal dysplasia of hair and nail type	J Med Genet	Pakistan	?	4	0	4
2006	Naeem M	Ectodermal dysplasia of hair and nail type: mapping of a novel locus to chromosome	Br J Dermatol	Pakistan	1M	3	0	3
2006	Naeem M	Ectodermal dysplasia of hair and nail type: mapping of a novel locus to chromosome	Br J Dermatol	Pakistan	?	0	4	4
2007	Naeem M	Pure hair-nail ectodermal dysplasia maps to chromosome	Clin Exp Dermatol	Pakistan	?	1	0	1
2010	Rasool M	Autosomal recessive pure hair and nail ectodermal dysplasia linked to chromosome	Eur J Dermatol	Pakistan	?	0	3	3
2010	Rasool M	Autosomal recessive pure hair and nail ectodermal dysplasia linked to chromosome	Eur J Dermatol	Pakistan	?	1	0	1
2010	Shimomura Y	Mutations in the keratin 85 (KRT85/hHb5) gene underlie pure hair and nail ectodermal dysplasia	J. Invest Dermatol	Japan	?	0	4	4
2012	Lin Z	Loss-of-Function Mutations in HOXC13 Cause Pure Hair and Nail Ectodermal Dysplasia	Am J Hum Genet	China	?	2	1	3
2013	Ali RH	Novel mutations in the gene HOXC13 underlying pure hair and nail ectodermal dysplasia in consanguineous families	Br J Dermatol	Pakistan	?	5	0	5
2013	Farooq M	A Homozygous Frameshift Mutation in the HOXC13 Gene Underlies Pure Hair and Nail Ectodermal Dysplasia in a Syrian	Hum Mutat	Japan	6Y	-	1	1
2013	Ali RH	Novel mutations in the gene HOXC13 underlying pure hair and nail ectodermal dysplasia in consanguineous families	Br J Dermatol	Pakistan	?	0	1	1
2014	Raykova D et al.,	Autosomal Recessive Transmission of a Rare KRT74 Variant Causes Hair and Nail Ectodermal Dysplasia: Allelism with Dominant Woolly Hair/ Hypotrichosis	PLoS One	Sweden	?	0	3	3

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2014	Raykova D et al.,	Autosomal Recessive Transmission of a Rare KRT74 Variant Causes Hair and Nail Ectodermal Dysplasia: Allelism with Dominant Woolly Hair/ Hypotrichosis	PLoS One	Sweden	?	1	0	1
2017	Khan AK	A novel mutation in homeobox DNA binding domain of HOXC13 gene underlies pure hair and nail ectodermal dysplasia (ECTD9) in a Pakistani family	BMC Med Genet	Pakistan	37 Y	1	0	1
2017	Mehmood S	Autosomal recessive transmission of a rare HOXC13 variant causes pure hair and nail ectodermal dysplasia.	Clin Exp Dermatol.	Pakistan	?	2	0	2
2017	Li X	Novel Homozygous Missense Mutation in HOXC13 Leads to Autosomal Recessive Pure Hair and Nail Ectodermal Dysplasia.	Pediatr Dermatol.	USA	5M	1	0	1
2017	Khan AK	A novel mutation in homeobox DNA binding domain of HOXC13 gene underlies pure hair and nail ectodermal dysplasia (ECTD9) in a Pakistani family.	BMC Med Genet	Pakistan	31Y	0	1	1
2017	Khan AK	A novel mutation in homeobox DNA binding domain of HOXC13 gene underlies pure hair and nail ectodermal dysplasia (ECTD9) in a Pakistani family.	BMC Med Genet	Pakistan	25Y	0	1	1
2018	Humbatova T	An insertion mutation in HOXC13 underlies pure hair and nail ectodermal dysplasia with lacrimal duct obstruction	Br J Dermatol	Germany	?	0	2	2
2019	Amico S	Compound heterozygosity for novel KRT85 variants associated with pure hair and nail ectodermal dysplasia	J Eur Acad Dermatol Venereol.	France	?	0	2	2
2022	Quinn G	BG08: A new variant in HOXC13 associated with a severe phenotype of pure hair and nail ectodermal dysplasia	Br J Dermatol	Srilanka	2M	0	1	1
2023	Zhu T	Two homozygous KRt85 mutations in Chinese patient with pure hair and nail ectodermal dysplasia	Eur J Dematol	China	?	?	?	1
Total						36	34	70

Patient consent

Permission was obtained from the patients to publish their data in the study.

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