Palmoplantar Keratoderma and Woolly Hair Revealing Asymptomatic Arrhythmogenic Cardiomyopathy

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The association of woolly hair and palmoplantar keratoderma (PPK) has been found in 2 autosomal recessive syndromic disorders: Naxos diseases (OMIM 601214) and Carvajal syndrome (OMIM 605676), both also presenting progressive arrhythmogenic cardiomyopathy. Naxos disease is characterized by the triad of diffuse PPK, woolly hair and right ventricular (RV) arrhythmogenic cardiomyopathy (AC) and is caused by homozygous mutations in the plakoglobin gene (*JUP*) (1). Carvajal syndrome manifests with striated and fokal PPK, woolly hair and left-dominant dilated cardiomyopathy and is due to recessive mutations in the desmoplakin gene (DSP) (2). Few patients with these syndromes have been described (3–6). AC due to autosomal dominant *DSP* mutations, with (OMIM: 615821) or without (OMIM 607450) hypo/oligodontia, may be also associated with PPK and woolly hair (5–7).

CASE REPORT

A 5-year-old female child first presented for hypotrichosis to the Rare Skin Disease outpatient clinic of IDI-IRCCS. She was born at term from healthy non-consanguineous parents. Physical examination revealed light-coloured woolly, sparse and fragile hair, which had never required cutting (**Fig. 1**a), focal plantar hyperkeratosis localized at pressure areas (Fig. 1b) and minimal striated hyperkeratosis of the palmar aspect of the first 3 digits of the hand (Fig. 1c). The patient also had dry skin and mild keratosis pilaris of the arms and thighs. Her parents reported that hair abnormalities had been present since birth, while plantar keratoderma manifested approximately at 1 year of age, followed by palmar lesions. Her nails and teeth were normal. The patient was otherwise in good general health. Histological examination of a plantar hyperkeratosis biopsy revealed massive hyperkeratosis, parakeratosis and acanthosis of the epidermis with acantholytic clefts between neighbouring keratinocytes and widened intercellular spaces in the suprabasal cell layers (Fig. 1d). Although histopathological findings were highly suggestive for involvement of a desmosomal protein component, molecular testing for the corresponding genes was not available at that time in Italy. The patient was therefore discharged with a diagnosis of epidermolytic PPK with woolly hair, and the recommendation to have a cardiological evaluation and follow-up in Sicily where the family lived. An electrocardiogram (ECG) and echocardiogram did not reveal any abnormality. Five years later (age 10 years), the family was contacted again as in the meantime molecular diagnosis became available at Bambino Gesù Children's Hospital. Following written informed consent, genomic DNA was extracted from EDTA-blood and submitted to next-generation sequencing of a gene panel associated with cardiomyopathies (*DES, DSC2, DGS2, DSP, JUP, LAMP2, PKP2*). The analysis revealed 2 heterozygous truncating mutations in *DSP* (NM_004415): c.4788delA (p.Glu1597Serfs*5) and c.6091_6092delTT (p.Leu2031Glyfs*29) affecting exon 23 and 24, respectively. The former mutation was inherited from the father and the latter from the mother, as confirmed by Sanger sequencing (Fig. S1[1]). The patient was then referred to the Cardiology and Arrhythmology Unit. Cardiological examination findings are presented in Table SI[1] and Fig. S2[1]. After a complete cardiac work-up, Carvajal syndrome was diagnosed on the basis of combined phenotype of woolly hair, striate PPK, left-dominant arrhythmogenic cardiomyopathy and molecular analysis findings. Therefore, the patient received an implantable subcutaneous cardioverter-defibrillator (ICD) and started anti-congestive heart failure treatment with angiotensin-converting enzyme inhibitors, beta-blockers and diuretics. At follow-up visits, the patient was in a fair general condition.

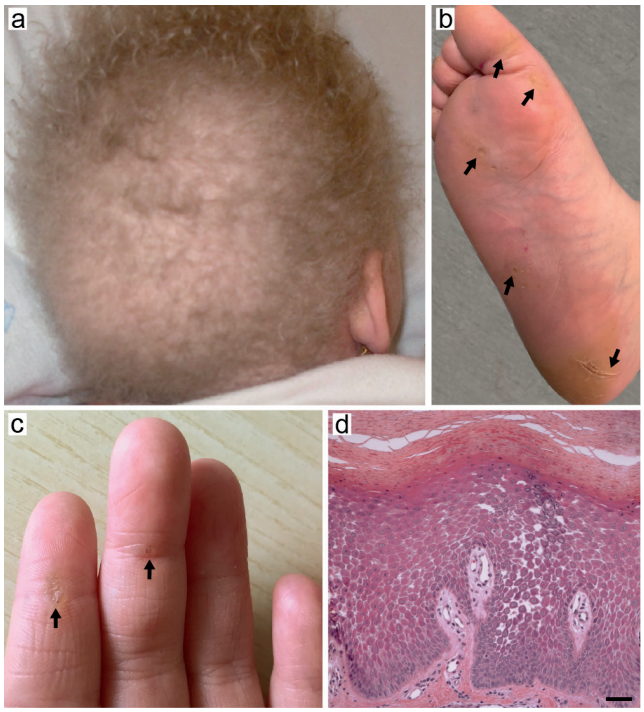

Fig. 1. Clinical and histopathological findings. (a) Woolly and sparse hair. (b, *arrows*) Focal plantar hyperkeratosis localized at pressure areas. (c, *arrows*) Minimal striated hyperkeratosis of the palmar aspect of the first 3 digits of the hand. (d) Hyperkeratosis with focal parakeratosis and suprabasal epidermal acantholysis in the haematoxylin-eosin staining. Bar: 50 μm.

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DISCUSSION

We describe here a patient presenting the triad of woolly hair, PPK and biventricular arrhythmogenic cardiomyopathy due to compound heterozygous *DSP* mutations. The c.6091_6092delTT deletion (p.Leu2031Glyfs*29) is a previously reported *DSP* mutation described in compound heterozygosity with c.6079C>T (p.Arg1934*) mutation in a lethal acantholytic epidermolysis bullosa case (8). It results in truncation of the C-terminal tail of all 3 desmoplakin isoforms, I, Ia and II (9). The novel c.4788delA falls within the rod domain of desmoplakin and predicts truncation of only isoform I, while it spares the isoforms Ia and II that lack amino acid regions 1351-1793 and 1195-1793, respectively. Its functional consequences at protein level are expected to be similar to c.4778_4790del (p.Lys1593Serfs*5) mutation identified in compound heterozygosity with c.6310delA deletion in a patient presenting with skin fragility, PPK, alopecia and cardiomyopathy (10). Genotype-phenotype correlations in disorders with mutant *DSP* cannot be easily predicted. Truncating mutations in most patients developing cardiac disease are located in exons 23 and 24 (5, 6). In our patient both mutations are predicted to truncate the 3 C-terminal plakin-repeat subdomains from the longest desmoplakin (DSPI) isoform, resulting in protein loss-of-function. Indeed, plakin repeats are essential for coalignment and binding of intermediate filaments (11). Ablation of only DSPI, the major isoform expressed in the heart, due to the homozygous exon 23 mutation p.Arg1267* was shown to result in a Naxos-like syndrome associated with a severe heart phenotype in a child (12). Thus, it seems that DSPII can only in part compensate the function of the full isoform in both cardiac tissue, where it is almost absent, and in skin (6, 9, 12, 13).

AC is characterized clinically by life-threatening ventricular arrhythmias and pathologically by acquired and progressive changes with fibro-fatty replacement of the myocardial tissue (14). AC currently comprises several variant patterns: RV, left ventricular (LV) and biventricular involvement (15). AC diagnosis is exceptionally made under the age of 10 years (5, 10, 16). Indeed, in the current case, cardiac abnormalities were not detected at 5 years of age, and the patient remained free of clinical signs of cardiac disease until the age of 10 years. Nevertheless, molecular diagnosis and the consequent in-depth cardiac examinations in a tertiary care centre allowed timely detection of the AC, ICD implantation and appropriate medical treatment initiation. Therefore, the combination of congenital woolly hair and PPK in a young child should always prompt serial cardiac diagnostic work-up, which can be life-saving.

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The authors have no conflicts of interest to declare.

REFERENCES

1. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 2000; 355: 2119–2124.
2. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 2000; 9: 2761–2766.
3. Baykan A, Olgar Ş, Argun M, Özyurt A, Pamukçu Ö, Üzüm K, et al. Different clinical presentations of Naxos disease and Carvajal syndrome: case series from a single tertiary center and review of the literature. Anatol J Cardiol 2015; 15: 404–408.
4. Antonov NK, Kingsbery MY, Rohena LO, Lee TM, Christiano A, Garzon MC, et al. Early-onset heart failure, alopecia, and cutaneous abnormalities associated with a novel compound heterozygous mutation in desmoplakin. Pediatr Dermatol 2015; 32: 102–108.
5. Pigors M, Schwieger-Briel A, Cosgarea R, Diaconeasa A, Bruckner-Tuderman L, Fleck T, et al. Desmoplakin mutations with palmoplantar keratoderma, woolly hair and cardiomyopathy. Acta Derm Venereol 2015; 95: 337–340.
6. Polivka L, Bodemer C, Hadj-Rabia S. Combination of palmoplantar keratoderma and hair shaft anomalies, the warning signal of severe arrhythmogenic cardiomyopathy: a systematic review on genetic desmosomal diseases. J Med Genet 2016; 53: 289–295.
7. Maruthappu T, Posafalvi A, Castelletti S, Delaney PJ, Syrris P, O'Toole EA, et al. Loss-of-function desmoplakin I and II mutations underlie dominant arrhythmogenic cardiomyopathy with a hair and skin phenotype. Br J Dermatol 2019; 180: 1114–1122.
8. Jonkman MF, Pasmooij AM, Pasmans SG, van den Berg MP, Ter Horst HJ, Timmer A, et al. Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. Am J Hum Genet 2005; 77: 653–660.
9. Cabral RM, Wan H, Cole CL, Abrams DJ, Kelsell DP, South AP. Identification and characterization of DSPIa, a novel isoform of human desmoplakin. Cell Tissue Res 2010; 341: 121–129.
10. Vahlquist A, Virtanen M, Hellström-Pigg M, Dragomir A, Ryberg K, Wilson NJ, et al. A Scandinavian case of skin fragility, alopecia and cardiomyopathy caused by DSP mutations. Clin Exp Dermatol 2014; 39: 30–34.
11. Choi HJ, Park-Snyder S, Pascoe LT, Green KJ, Weis WI. Structures of two intermediate filament-binding fragments of desmoplakin reveal a unique repeat motif structure. Nat Struct Biol 2002; 9: 612–620.
12. Uzumcu A, Norgett EE, Dindar A, Uyguner O, Nisli K, Kayserili H, et al. Loss of desmoplakin isoform I causes early onset cardiomyopathy and heart failure in a Naxos-like syndrome. J Med Genet 2006; 43: e5.
13. Cabral RM, Tattersall D, Patel V, McPhail GD, Hatzimasoura E, Abrams DJ, et al. The DSPII splice variant is crucial for desmosome-mediated adhesion in HaCaT keratinocytes. J Cell Sci 2012; 125: 2853–2861.
14. Pilichou K, Thiene G, Bauce B, Rigato I, Lazzarini E, Migliore F, et al. Arrhythmogenic cardiomyopathy. Orphanet J Rare Dis 2016; 11:33.
15. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. Circ Res 2017; 121: 784–802.
16. Daliento L, Turrini P, Nava A, Rizzoli G, Angelini A, Buja G, et al. Arrhythmogenic right ventricular cardiomyopathy in young versus adult patients: similarities and differences. J Am Coll Cardiol 1995; 25: 655–664.