

Congenital Palmoplantar Keratoderma and Woolly Hair in a Child: A Quiz

Lucie HARPAIN¹ , Christiane PEES², Julian HENO² and Sonja RADAKOVIC^{1*}

¹Department of Dermatology, Medical University of Vienna, Vienna, Austria, and ²Department of Pediatrics, Medical University of Vienna, Vienna, Austria. *Email: sonja.radakovic@meduniwien.ac.at

A 3-year-old girl of Syrian origin was referred for evaluation of congenital palmoplantar hyperkeratosis. The skin changes had been present since birth and were characterized by recurrent blistering, erythema and progressive hyperkeratosis of the feet. Symptoms worsened during febrile episodes, heat exposure and mechanical friction. Walking was painful and the patient poorly tolerated socks and closed footwear. The family history revealed a second-degree of consanguinity between the parents and similar skin manifestations in a patient's paternal uncle. Two older sisters were unaffected. Physical examination showed diffuse palmoplantar keratoderma predominantly involving the soles, toes and lateral plantar surfaces, accompanied by fissures and occasional blister formation. Mild hyperkeratosis of the fingers

was noted. Hair examination demonstrated sparse tightly, lusterless and curled "woolly hair" on the scalp and eyebrows (Fig. 1) Her eyelashes were long and curled outward. Teeth, oral mucosa and nails were largely unremarkable. Electrocardiography, Holter monitoring and echocardiography were normal.

What is your diagnosis?

- 1: Ectodermal dysplasia–skin fragility syndrome (PKP1-associated).
 - 2: Naxos syndrome (JUP-associated).
 - 3: Pachyonychia congenita (KRT6A/KRT6B/KRT16/KRT17-associated).
 - 4: Carvajal syndrome (DSP-associated).
- See next page for answer.



Fig. 1. Clinical features of the patient. (A) Woolly hair involving the scalp and eyebrows; although not visible in this image, the eyelashes were also affected. (B) Plantar keratoderma with marked hyperkeratosis, bullae on the right plantar arch, and fissures. (C) Palmar hyperlinearity with distal hyperkeratosis and fissures, predominantly affecting areas of pronounced hyperkeratosis and mechanical stress. (D) Plantar interdigital region showing conspicuous macerated hyperkeratosis.

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Diagnosis: Carvajal Syndrome Caused by a Homozygous desmoplakin (DSP) Mutation

Carvajal syndrome (CS) is a rare autosomal recessive cardiocutaneous disorder belonging to the spectrum of desmosomal diseases. The syndrome is characterized by the triad of woolly hair, palmoplantar keratoderma (PPK) and cardiomyopathy and is most commonly caused by pathogenic variants in the desmoplakin gene (DSP). Dermatological manifestations usually precede the frequent and often very severe episodes of arrhythmia, some of which are already fatal at the time of initial onset. Morphological cardiac involvement with irregular structure or scarring of the myocardium, ventricular dilatation or impaired function is often detected only later in life (by echocardiography and even by the more sensitive MRI), therefore dermatological manifestations provide an important opportunity for early diagnosis and surveillance (1). The present patient demonstrated the classical cutaneous phenotype of congenital woolly hair and progressive palmoplantar keratoderma with recurrent blistering and skin fragility. The diagnosis was confirmed by identification of a homozygous DSP variant (c.7097G>A, p.Arg2366His). At the time of diagnosis, comprehensive cardiological evaluation including electrocardiography, Holter monitoring and echocardiography were normal, representing a genotype-positive/phenotype-negative cardiac stage at initial cardiological evaluation. Desmoplakin is an essential intracellular plaque protein of the desmosome, linking intermediate filaments to desmosomal cadherins and thereby ensuring tissue integrity in mechanically stressed organs such as the epidermis and myocardium. Loss of normal desmoplakin function leads to impaired cell adhesion, epidermal fragility, hyperkeratosis and progressive myocardial disease. The clinical spectrum associated with DSP variants has expanded considerably during the last decade and ranges from isolated arrhythmogenic cardiomyopathy to syndromic cardiocutaneous disorders (2). Carvajal syndrome was originally described in Ecuadorian families and classically associated with dilated left ventricular cardiomyopathy (3, 4). In contrast to Naxos syndrome, which is caused by pathogenic variants in plakoglobin (JUP) and predominantly affects the right ventricle, DSP-associated disease more commonly involves the left ventricle or even both ventricles (5). However, contemporary studies suggest that strict distinctions between “Carvajal syndrome” and “Naxos syndrome” may oversimplify a broad spectrum of desmosomal cardiomyopathies (2). The diagnosis may be challenging in early childhood because dermatological findings often

precede cardiac abnormalities by several years (6). In our patient, the combination of woolly hair, palmoplantar keratoderma, recurrent blistering, positive family history and parental consanguinity strongly suggested an inherited desmosomal disorder before molecular confirmation became available. Naxos syndrome as the most important differential diagnosis share woolly hair and PPK with CS. The cardiac symptoms in Naxos syndrome classically progress to arrhythmogenic right ventricular cardiomyopathy. It is important to note that both JUP and DSP mutations are of varying penetrance and clinical expression can occur later in adolescence or adulthood. Therefore, cardiac manifestation cannot be excluded and regular cardiological routine examinations (echocardiography, cardiac MRI, ECG and Holter ECG) are necessary (6). Genetic testing is therefore essential for accurate classification and prognostic assessment (2, 6, 7).

The additional differential diagnosis includes ectodermal dysplasia–skin fragility syndrome (McGrath syndrome), caused by biallelic PKP1 mutations. These patients typically exhibit generalized skin fragility, erosions, sparse hair and ectodermal abnormalities, but cardiomyopathy is not part of the disease spectrum (8). Pachyonychia congenita may present with painful palmoplantar keratoderma in childhood but is usually associated with prominent nail dystrophy, oral leukokeratosis and keratin gene mutations. The identified DSP variant, p.Arg2366His, affects the C-terminal region of desmoplakin, which is critical for intermediate filament binding. Variants involving this region have repeatedly been associated with cardiocutaneous phenotypes characterized by keratoderma, woolly hair and later-onset cardiomyopathy. Although genotype–phenotype correlations remain incomplete, patients carrying biallelic DSP variants appear to have a substantial lifetime risk of developing ventricular dysfunction and arrhythmias (2, 9). The major clinical implication of establishing the diagnosis is the requirement for lifelong cardiological surveillance. Even when baseline investigations are normal, disease progression may occur during childhood, adolescence or adulthood. Current recommendations include regular electrocardiography, ambulatory rhythm monitoring and echocardiography, with cardiac magnetic resonance imaging considered when age and clinical circumstances permit. Family screening and genetic counselling are equally important, particularly in consanguineous families. Dermatological management remains largely symptomatic. Keratolytic treatment with urea-containing preparations, topical retinoids, emollients and friction reduction may substantially improve quality of life. Specialized footwear and pressure-relieving measures are often necessary. In severe cases, systemic retinoids have been reported to reduce keratoderma, although their use must be balanced against potential adverse effects (10). This case emphasizes that congenital palmoplantar keratoderma associated with woolly hair should immediately raise suspicion for a desmosomal disorder. Recognition of these cutaneous hallmarks can lead to early genetic diagnosis and institution of

cardiac surveillance before the development of potentially life-threatening cardiomyopathy.

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