

What Is Your Diagnosis?



A 54-year-old woman was referred to our clinic with diffuse keratoderma of the palms and soles (right top and bottom) that presented at 1 year of age. Hyperkeratosis, resulting in a yellow waxy appearance without extension to dorsal surfaces, and fissures also were present. Woolly, curly, rough hair covered the head area (left), and the fingers were inflexible, short, and conical. Her medical history included depression as well as heart failure due to second degree atrioventricular block and arrhythmias for which she underwent an automatic cardioverter/defibrillator implant 10 years prior. Her cousin's son had the same clinical findings and died of heart failure, while another relative was diagnosed with the same disease. Fissure cultures grew *Staphylococcus aureus*, indicating secondary infection. A biopsy specimen from the plantar area revealed nonepidermolytic hyperkeratosis with hypergranulosis and papillomatosis. A mild lymphocytic infiltrate was present in the papillary dermis.

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The Diagnosis: Diffuse Nonepidermolytic Palmoplantar Keratoderma With Woolly Hair and Cardiomyopathy (Naxos-Carvajal Syndrome)

Naxos disease or Naxos-Carvajal syndrome is a diffuse nonepidermolytic palmoplantar keratoderma (NEPPK) with woolly hair and cardiomyopathy. Although the disorder is rare, diffuse NEPPK has been reported worldwide. Early diagnosis by dermatologists is imperative because it may spare patients the possibility of sudden death with a timely defibrillator implant.

We report a woman with Naxos-Carvajal syndrome whose keratoderma partially responded to topical tazarotene. A diagnosis of diffuse NEPPK with woolly hair and cardiomyopathy was made based on clinical and pathologic findings (Figures 1 and 2). We initially administered salicylic acid 8% in white paraffin under occlusion for 1 week without satisfying results. Then we increased the potency of salicylic acid to 15%, but it was too irritating for the contiguous healthy tissues. Subsequently, the patient was instructed to apply tazarotene cream 0.1%, which resulted in moderate improvement after 4 weeks.

This syndrome, prevalent on the Greek island Naxos, was first described by Protonotarios et al¹ in 1986 and has an autosomal recessive inheritance pattern. It is characterized by arrhythmogenic

right ventricular cardiomyopathy, NEPPK, and woolly hair, and pathogenesis is mapped to band 17q21.²

Keratoderma usually appears during the first year of life. It is thick and diffuse in nature with a yellow waxy appearance as well as an erythematous border without extension to dorsal surfaces. The hair phenotype is unique, characterized by congenital woolly, curly, rough hair and sparse eyebrows.

Cardiac disease manifests during late puberty and often is severe and progressive. Patients present with ventricular arrhythmias (91%), heart failure (30%), and sudden death (28%).³ Histologic examination of the affected myocardium reveals the typical myocardial loss with myofibrofatty and fibrous replacement at the subepicardial and mediomural layers. Treatment modalities include antiarrhythmic drugs, implantable cardioverter/defibrillator, antiarrhythmic surgery, or heart transplant.⁴

The differential diagnosis in our patient included other hereditary palmoplantar keratodermas that could have been considered if the patient had not yet exhibited cardiac involvement. The Unna-Thost type of palmoplantar keratoderma shows epidermolytic keratoderma on histology, mal de Meleda



Figure 1. Woolly hair (A) and palmo-plantar yellow waxy hyperkeratosis (B and C).

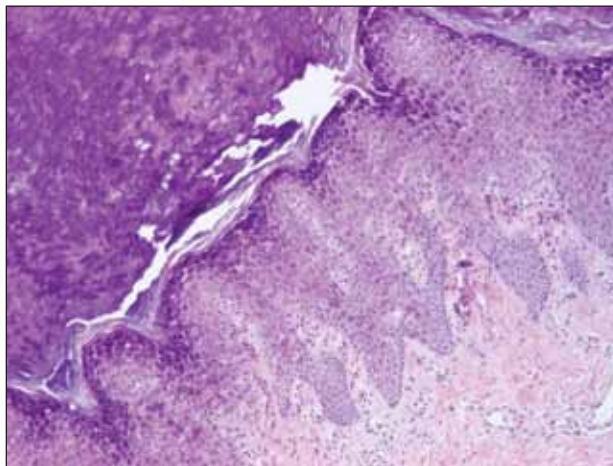


Figure 2. Hyperkeratosis, hypergranulosis, and papillomatosis were present, as well as a mild lymphocytic infiltrate (H&E, original magnification $\times 250$).

exhibits a keratoderma that gradually progresses onto the dorsal aspects of the fingers and toes, Papillon-Lefèvre syndrome often is accompanied by early loss of the primary teeth, and Vohwinkel syndrome involves sensorineural deafness in most patients. Woolly hair on the scalp and woolly eyelashes are rarely described in other patients with keratoderma.^{5,6}

McKoy et al⁷ discovered a homozygous mutation of the plakoglobin gene in 19 individuals with Naxos disease. Plakoglobin is an important component of cell-cell and cell-matrix adhesion complexes of many tissues, including the dermoepidermal junction of the skin and the cytoplasmic plaque of cardiac junctions. A similar autosomal recessive syndrome consisting of striate epidermolytic palmoplantar keratoderma, dilated left ventricular cardiomyopathy, and woolly hair in 3 families from Ecuador was shown to be due to a gene mutation that encodes desmoplakin.⁸ It is still not clear why plakoglobin and desmoplakin mutations would primarily affect the skin, heart, and hair.

Tazarotene is an acetylenic retinoid with documented therapeutic results in psoriasis. Its active metabolite, tazarotenic acid, selectively binds to retinoic acid receptor- β and retinoic acid receptor- γ , normalizing epidermal differentiation and exhibiting a potent antiproliferative effect.⁹ The moderate effect of topical tazarotene on our patient's

keratoderma might be attributed to these pharmacologic properties.

Naxos-Carvajal syndrome is not restricted to Greece and Ecuador, as global incidence has been documented with cases in several Mediterranean countries as well as other parts of the world, including Greece, Italy, India, Ecuador, Israel, and Turkey.³ Early diagnosis of the syndrome is imperative. Consequently, clinicians should always evaluate any patient with keratoderma and woolly hair for cardiac disease, an evaluation that might prove life sparing.

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