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Howel-Evans Syndrome: A Variant of Ectodermal Dysplasia

Novie Sroa, MD; Patricia Witman, MD

Howel-Evans syndrome is a rare form of palmoplantar keratoderma associated with esophageal cancer and is inherited in an autosomal dominant fashion. First described in 2 kindreds in the United Kingdom, Howel-Evans syndrome has subsequently been reported in only one American family. We present a previously unreported case of Howel-Evans syndrome from this American kindred demonstrating a distinct clinical phenotype. The patient manifests both cutaneous and ectodermal abnormalities, supporting the reclassification of Howel-Evans syndrome as a variant of ectodermal dysplasia.

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Howel-Evans syndrome also is known as tylosis with esophageal cancer (Online Mendelian Inheritance in Man 148500). It is an autosomal dominant condition characterized by thickening of the skin on the palms and soles in association with a high risk for esophageal cancer. The gene locus for this rare disorder has been mapped to band 17q24, demonstrating loss of heterozygosity of the tylosis with esophageal cancer gene, *TOC* (a tumor suppressor gene).[1,2] First described in 2 kindreds in the United Kingdom,[3] Howel-Evans syndrome has subsequently been reported in only one American family.[2] We describe a previously unreported case of an affected member of this American family who not only manifests cutaneous abnormalities but also demonstrates changes signifying a wider ectodermal defect.

Dr. Sroa is from The Ohio State University Division of Dermatology, Columbus. Dr. Witman is from Nationwide Children's Hospital, Columbus.

The authors report no conflict of interest.

Correspondence: Novie Sroa, MD, 2012 Kenny Rd, Columbus, OH 43221 (novie.sroa@osumc.edu).

Case Report

A 7-year-old boy presented with painful focal plantar keratoderma on the weight-bearing areas of his feet that began with onset of walking (Figure 1). His palms were spared. Diffuse hyperkeratotic follicular papules were present on his trunk, upper extremities, and face (Figures 2 and 3). He had tight, curly, coarse hair and partial loss of his eyebrows. He had premature loss of his primary incisors and required multiple crowns on his molars due to poor dental enamel (Figure 4). He had developed symptoms of episodic abdominal pain and anorexia at 5 years of age. Further evaluation with endoscopy indicated gastroesophageal reflux disease.

His family history was remarkable for similar cutaneous and gastroenterological findings (Figure 5). The patient's father reported mild hyperkeratosis of his palms and soles. Two paternal uncles had a history of esophageal ulcers and thickened skin on the palms and soles. The paternal aunt had follicular hyperkeratosis of the arms and legs with thickening of skin on her palms and soles. All 3 of the father's siblings had oral leukoplakia. The paternal grandfather was not affected; however, the paternal grandmother had thickened skin of her palms and soles as well as esophageal strictures requiring dilatation multiple times. None of the patient's maternal family members were affected.

The patient's plantar keratoderma was treated with urea cream 40% daily to alleviate tenderness and hyperkeratosis. He also was treated with a proton pump inhibitor for the gastroesophageal reflux disease with plans for close continued surveillance by the gastroenterology department.

Comment

Howel-Evans syndrome was first described in 1958 by Howel-Evans et al[3] in 2 kindreds in Liverpool, United Kingdom. Affected patients developed palmoplantar keratoderma with complete penetrance by puberty and had an increased risk for esophageal

Figure 1. Focal plantar keratoderma on the weight-bearing areas of both feet.

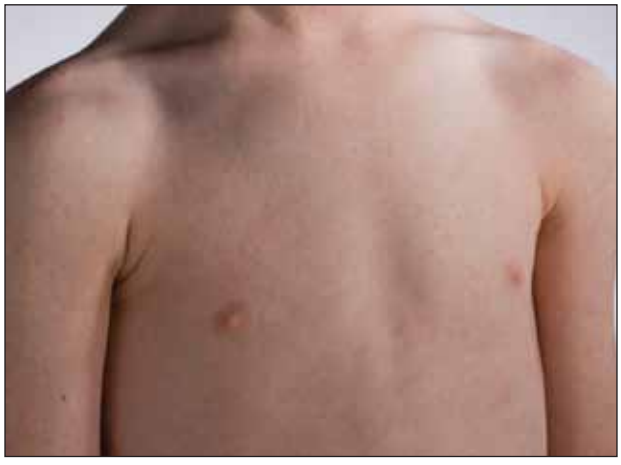

Figure 2. Diffuse hyperkeratotic follicular papules on the trunk and upper extremities.

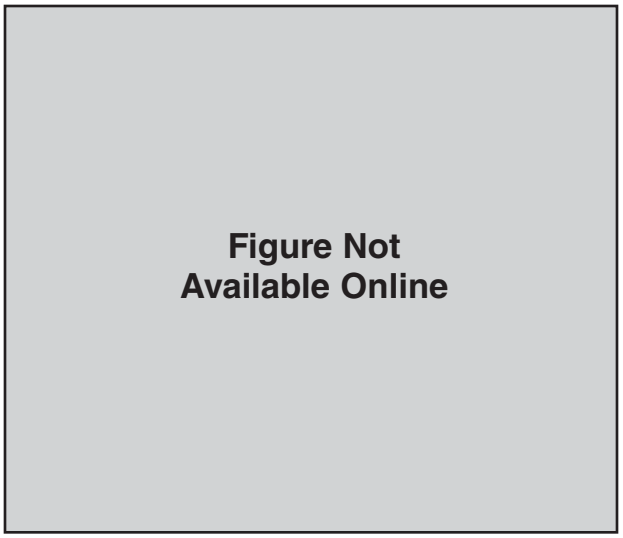

Figure 3. Hyperkeratotic follicular papules on the face, as well as tight, curly, coarse scalp hair with partial loss of the eyebrows.

Figure 4. Premature loss of the primary incisors due to poor dental enamel.

carcinoma developing at a mean age of 45 years.[3] In contrast, the only known American family affected with Howel-Evans syndrome had a later age of onset (in the sixth and seventh decades of life).[4] Stevens et al[4] performed linkage analysis on the affected American pedigree first described by Marger and Marger[5] and found that of the 125 affected members spanning 7 generations, 8 members were diagnosed with squamous cell carcinoma of the esophagus.

We present a previously unreported 7-year-old boy from this American kindred with Howel-Evans syndrome. Although keratoderma in his affected family members typically presented between 6 and 12 years of age, this boy's focal plantar keratoderma began in infancy on the weight-bearing areas of his feet with onset of walking. He is the youngest to present with esophageal symptoms. None of the affected family members including his father developed esophageal symptoms before 50 to 60 years of age. It has been recommended that esophageal cancer screening commence at 20 years of age for this patient, with serial biopsies of the proximal, mid, and distal esophagus. In comparison to the other affected family members with oral leukoplakia, this patient currently does not have oral mucosal involvement.

The clinical phenotype in this patient is representative of his family and includes focal hyperkeratotic skin related to physical activity with regression on bed rest; presence of oral and follicular hyperkeratosis; and focal palmoplantar keratoderma. However, our patient also demonstrated additional abnormalities in hair and teeth, signifying that the palmar lesions

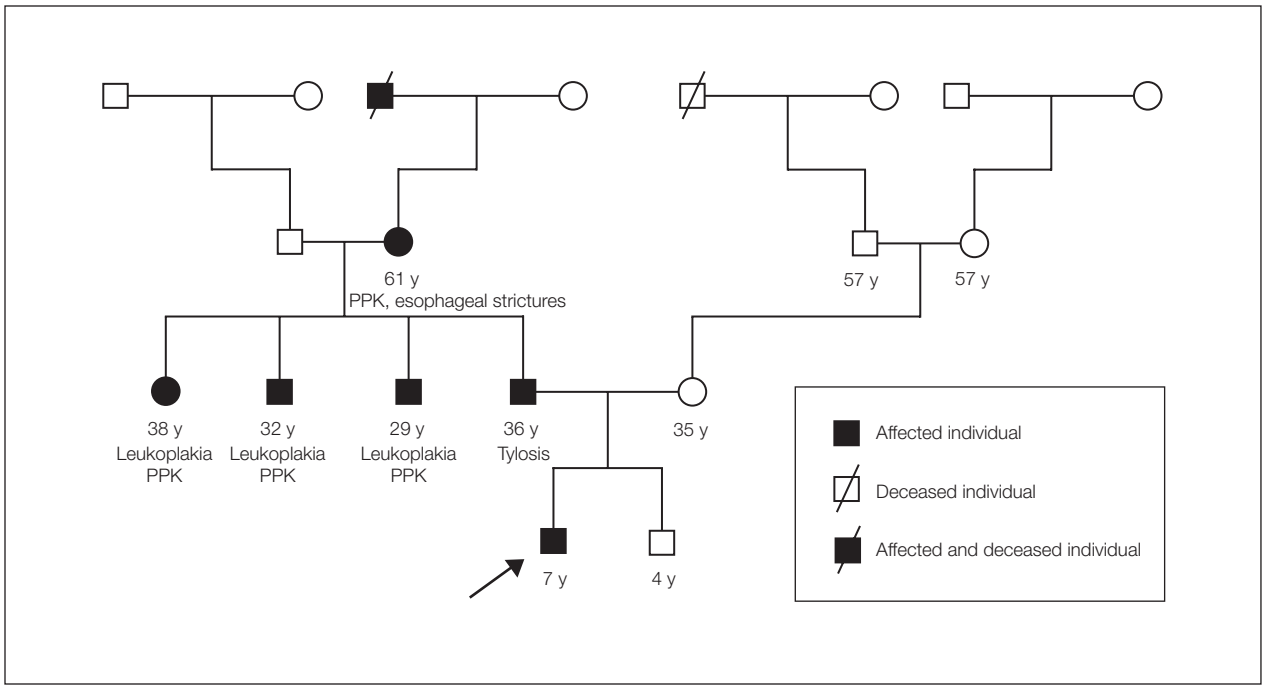

Figure 5. Pedigree for a family with palmoplantar keratoderma (PPK), with the proband indicated by an arrow. A key inside the figure plot explains the symbols.

may represent only a small part of a wider ectodermal defect. We believe that the distinct phenotype of this patient supports a prior proposal by Stevens et al[4] to reclassify Howel-Evans syndrome as a variant of ectodermal dysplasia.

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