Oral squamous cell carcinoma in a patient with keratitis-ichthyosis-deafness syndrome: a rare case

L. Homeida, BDS,[a] R.T. Wiley, DDS,[b] and M. Fatahzadeh, DMD, MSD[c]

Keratitis-ichthyosis-deafness (KID) syndrome is a rare form of ectodermal dysplasia with significant visual and auditory impairment. Pathogenesis involves a mutation in the *GJB2* gene, which encodes connexin-26, a protein in the epithelial gap junctions thought to be involved in the differentiation of ectodermally derived tissues. Affected patients are also at increased risk for the epithelial malignancies. To our knowledge, nearly 100 cases of KID syndrome, including 19 with squamous cell carcinoma (SCC) complications, have been reported worldwide. We report here a patient with KID syndrome who developed an ulcerative oral lesion causing him significant discomfort; he was subsequently diagnosed with oral SCC. We review the clinical presentation and symptomatology, including those affecting the oral cavity for this syndrome and highlight the importance of multidisciplinary collaboration and life-long screening aimed at prevention of the evolving complications. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:e226-e232)

Keratitis-ichthyosis-deafness (KID) syndrome is a rare congenital ectodermal disorder[1] affecting the skin, the corneal epithelium, and the inner ear, with the potential for profound sensory impairment and disability.[2-4] The majority of patients with KID syndrome are neurologically normal, although delayed development and intellectual deficits have been reported.[4-6]

The syndrome is characterized by three distinctive clinical features: erythrokerato-derma, neurosensory hearing deficit, and ocular vascularizing keratitis.[5] The cutaneous signs often present early in life and include hyperkeratosis of the face, scalp, and extremities.[5] Congenital sensorineural hearing loss affects both ears and is not progressive.[5] The majority of patients experience ophthalmologic problems, such as eye irritation, tearing, and photophobia.[5] Neovascularizing keratitis often affects both eyes and can lead to blindness later in life.[7]

Although the hereditary nature of this syndrome is well established, the mode of inheritance is still uncertain.[1,3,5] Pathogenesis is thought to involve a mutation in the *GJB2* gene on human chromosome 13 q11-12, which encodes connexin-26 (Cx26), a membrane protein integral to the formation of gap junctions in a variety of epithelial tissues.[3] The latter include the cochlea, palmoplantar epidermis, hair follicles, corneal epithelium, sweat glands, and ducts.[3]

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[a]Candidate, Master of Dental Science, Rutgers School of Dental Medicine, Newark, New Jersey, USA.
[b]Chief Resident, Oral Pathology, New York Hospital in Queens, New York, New York, USA.
[c]Department of Diagnostic Sciences, Rutgers School of Dental Medicine, Newark, New Jersey, USA.

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Direct cell-to-cell communication via the exchange of small molecules through the gap junctions is critical to the differentiation and hemostasis of ectodermally derived tissues.[3] The substitution of aspartic acid for aspargine at position 50 of the *GJB2* gene (p.Asp50 Asn) or serine for phenylalanine (p.Ser17 Phe) at position 17 may be responsible for defective intercellular channels and ultimately the phenotypic changes associated with KID syndrome.[8] The latter mutation is less common but may be associated with more severe clinical sequelae, including higher predilection for tongue carcinoma.[8] An isolated report of mutation involving the *GJB6* gene coding for connexin-30 protein in one patient has raised the possibility of genetic heterogeneity and variable relative expression of different connexins resulting in specific syndromic and nonsyndromic phenotypes.[3,4,9]

Patients with KID syndrome are also at increased risk for epithelial malignancies of the skin and oral mucosa, especially squamous cell carcinoma (SCC)[1,10,11] This is in line with a higher incidence of mucocutaneous SCC reported in a number of syndromic ectodermal dysplasias in which ectodermal defects and other stigmata are present. This predilection is attributed to the disruption of intercellular communication caused by a connexin-26 mutation.[3] There is no cure for this congenital syndrome, and multidisciplinary interventions primarily aim to prevent evolving complications and provide symptomatic relief. We report a patient with KID syndrome, who developed oral SCC; review the clinical presentation and symptomatology, including those affecting the oral cavity; and highlight the importance of early recognition, multidisciplinary management and life-long surveillance.

CASE REPORT

A 25-year-old white male with KID syndrome was referred to the Oral Medicine service for the evaluation of symptomatic oral sores of several months' duration. Although he had seen a

number of dentists over the years sporadically, he had not received regular dental care. Past medical history was significant for visual impairment, right ear deafness, and significant neurosensory hearing loss in the left ear necessitating the use of a hearing aid. He was not on any medication except multiple antifungals for his skin condition. He was allergic to latex. Social and family histories were noncontributory.

Overall inspection revealed palmoplantar keratoderma; thickened, dystrophic nails; and a fungating mass, diagnosed as a benign neoplasm by his dermatologist, on the dorsum of his left foot (Figures 1A to 1D). Numerous pink papules and deep furrows on his face and neck (Figure 2) and hypotrichosis of the scalp, eyebrows, and eyelashes were clinically evident. He appeared older than his age. Extraorally, there was no cervical lymphadenopathy. Intraorally, he had partial dentition with a few carious lesions. A tender ulceration was clinically visible on the right buccal mucosa contiguous with a nodular, hemorrhagic growth on the lower edentulous ridge extending to the ipsilateral retromolar pad and floor of the mouth. Irregular erosions were also present on the left buccal mucosa (Figures 3A and 3B). Panoramic radiography revealed heavily resorbed mandibular ridges, multiple missing teeth, carious lesions in the right maxilla, bony irregularities related to an extraction socket in lower right jaw, and a periapical radiolucent lesion in the anterior mandible (Figure 4). Differential diagnosis included lesions of traumatic or neoplastic etiology. Histopathologic examination of specimens from the right-sided lesion revealed well-differentiated SCC (Figure 5A). Immunostaining with P16 antibody was positive, suggesting that the tumor was infected by human papillomavirus (HPV) 16 (Figure 5B). He was subsequently referred to a head and neck surgeon for management. Metastatic workup was negative, and the patient underwent right-sided composite resection of malignancy, elective ipsilateral radical neck dissection, and flap reconstruction. Biopsy of the left-sided buccal mucosa lesion revealed squamous mucosa with parakeratosis, chronic inflammation, and no evidence of malignancy. He is now closely monitored by clinicians of various disciplines.

DISCUSSION

The clinical triad of keratitis, ichthyosis, and deafness affecting a 16-year-old boy was first described by Burns in 1915.[12] The term "KID syndrome," which is still in use, was coined by Skinner et al. in1981 after they had reviewed 18 cases with similar presentations to designate a distinct clinical entity.[13] The true nature of skin abnormality (papillomatous hyperkeratosis, rather than ichthyosis), occasional partial loss of hearing (rather than complete deafness), and the absence of keratitis early in the course of disease in some cases, however, have raised concerns about the adequacy of this term to describe the condition.[1,6] In 1996, Caceres-Rios et al. proposed the term *keratodermatous ectodermal dysplasia* to emphasize that the disorder involves cells of ectodermal origin; however, this term is not widely used.[6]

Although the hereditary nature of this syndrome is well established, the mode of inheritance remains uncertain[5] because of reports of both sporadic and familial cases documented in the literature.[1] The majority of cases, however, appear to result from a spontaneous de novo mutation.[1,3,8] The rarity of the syndrome, together with the low likelihood of procreation in those inflicted by the severe cutaneous manifestations, may explain the small number of familial cases reported to date.[5] There is no gender predilection, and the condition has been described in different ethnicities.[6] Although both autosomal dominant and recessive inheritance patterns have been described in the familial cases studied,[1,14] evidence indicates the presence of a dominant gene.[1,3,8] There was no family history of similar conditions in the case described here. The patient's parents were not related and were found not to carry the mutation. The mother reported to have had a normal pregnancy; the patient was the middle child, and his two siblings were unaffected. At birth, this patient had noticeably abnormal (dry, purplish-colored) skin and was diagnosed with ectodermal dysplasia within a few months. Genetic analysis around age 2 years identified a mutation in the *GJB2* gene, more specifically glycine−arginine substitution at nucleotide 34 on the connexin-26 gene responsible for KID syndrome.

The clinical spectrum of the syndrome is heterogeneous, and a variety of major and minor diagnostic criteria have been described, with cutaneous, auditory, and ophthalmologic abnormalities being the most frequent features.[6] Cutaneous abnormalities, such as erythroderma and hyperkeratosis, are often present at birth or manifest within the first 3 months of life.[4,5,15] Patients have thick, coarse-grained skin with deep grooves.[3-6] Hyperkeratotic plaques are erythematous, sharply demarcated, often separated by smooth skin patches, and symmetrically distributed throughout the body, particularly on the face and limbs.[3,6] Reticular palmoplantar keratoderma and cutaneous cysts are also common.[4,6] When the cutaneous changes affect the face, patients appear prematurely old.[16] Hyperkeratotic cutaneous plaques have been managed with mild soaps, keratolytic agents, frequent emollition, and topical or systemic steroids, albeit with limited efficacy.[2,4,5,17,18]

Other reported features include alopecia (congenital, infectious, or cicatricial),[3,5,6] sparse or absent eyebrows and eyelashes,[5,6] eyelid keratosis,[4] nail deformities (thickened, hypoplastic),[3,15,16] and heat intolerance.[3] This patient not only had the characteristic skin changes since birth but also had sparse scalp hair and absent eyebrows and eyelashes, as well as dystrophic nails on his hands and feet. He was also intolerant of heat and required close monitoring in hot environments.

Auditory manifestations in patients with KID syndrome include nonprogressive neurosensory hypoacusia