Keratitis-ichthyosis-deafness syndrome and hidradenitis suppurativa

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INTRODUCTION

First described by Burns in 1915, keratitis-ichthyosis-deafness (KID) syndrome was later characterized and named by Skinner et al in 1981.[1] KID syndrome is a rare ectodermal dysplasia (OMIM #148210). It is caused by heterozygous missense mutations on the connexin-26 gene gap junction beta-2 protein (*GJB2*) and connexin-30 gene gap junction beta-6 protein.[2] The mutations cause a disturbance in the gap junction system which may affect epithelial homeostasis, differentiation, immune response, and carcinogenesis in ectodermal epithelia.[2]

Follicular occlusion occurs in a number of diseases, most notably acne. It is also the connecting sign of follicular occlusion triad (co-occurrence of hidradenitis suppurativa [HS], cystic acne, and dissecting cellulitis of the scalp) and tetrad (triad + pilonidal sinus disease).[3]

The association of HS and KID syndrome has been reported in 6 cases, 4 of which exhibited the triad by also presenting with cystic acne and dissecting cellulitis of the scalp (Table I).[4]

Abbreviations used:

Cx26:	connexin-26
GJB2:	gap junction beta-2 protein
HS:	hidradenitis suppurative
KID:	keratitis-ichthyosis-deafness syndrome

CASE

A 33-year-old male with a history of HS, cystic acne, pilonidal sinus treated surgically, and acanthosis nigricans since the onset of puberty was referred to Department of Dermatology, Zealand University Hospital for diagnosis and treatment at 22 years of age. He had no family history of HS on the maternal branch and no contact with the paternal branch of his family, was overweight (body mass index of 42.4), and smoked. His worst affected area (axillae) reached Hurley stage III with a modified Sartorius score of 59. Other clinical features included keratosis pilaris of his back and limbs, keratotic spiny papules (more white and without inflammation as compared with keratosis pilaris), dystrophic nails, congenital hearing loss, and scoliosis (Fig 1). Patient

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Table I. Associated features of keratitis-ichthyosis-deafness and hidradenitis suppurativa in literature

Reference	KID-cutaneous features	KID-systemic features	HS	Additional features of follicular occlusion and skin disease	Genetic mutation
Current case	Dystrophic nails, follicular hyperkeratosis	Congenital sensorineural hearing loss	Axillary—Hurley Stage III	Severe cicatricial cystic acne, pilonidal cyst, recurrent abscess on posterior neck, keratosis pilaris, acanthosis nigricans, severe atopic dermatitis	Heterozygous missense mutation, 32 G to A transition of exon 2 on GJB2 gene
Bettoli et al[11]	Palmoplantar keratoderma, widespread scales, fingernail and toenail dystrophy, hyperkeratotic plaque of the scalp	Congenital sensorineural bilateral hearing loss	Recurrent inguinal abscesses starting in adolescence, at age 39 developed nodules, abscesses, and fistulas in genital and groin areas	None	D50N on GJB2 gene
Maintz et al[12]	Ichthyosis, transgrediens palmoplantar keratoderma, fine hyperkeratosis and erythrokeratoderma of the hips and thighs, Toenail dystrophy	Congenital sensorineural deafness, vascularizing keratitis	Abscesses in axillae and groin	Dissecting cellulitis of the scalp with cicatricial alopecia, acne conglobata	Heterozygous missense mutation D50N on GJB2 gene
Nyquist et al[13]	Patient 1—dry skin, palmoplantar keratoderma with 'stippled' appearance	Bilateral sensorineural hearing loss, photophobia, corneal vascularization	Groin	Dissecting cellulitis of the scalp with diffuse scarring alopecia, cystic acne, multiple epidermal cysts, moderately differentiated SCC with metastatic tumor nests in 2 inguinal lymph nodes, primary malignant proliferating pilar tumor (PPT) with metastatic spread	Heterozygous missense mutation D50N on GJB2 gene
Prasad and Bygum[14]	Red and dry skin since birth, red-brown hyperkeratotic plaques on face and extremities, and sparse hair	Congenital sensorineural deafness	Axillary and groin	Dissecting cellulitis of the scalp, cystic acne	Heterozygous missense mutation D50N (148 G>A) in GJB2
Montgomery et al[10]	Mild palmoplantar keratoderma, ichthyosis, follicular hyperkeratosis, leukonychia without nail pitting	Congenital deafness, mild keratitis, Leukonychia	Axillae, suprapubic, inguinal and intergluteal areas—interconnected draining sinuses surrounded by macerated nearly verrucous hyperkeratotic skin	Dissecting folliculitis of the scalp with extensive scarring, chronically recurrent cystic acne on face and torso starting at 5 y of age	Novel heterozygous point mutation (C119T) A40V on GJB2 gene

Continued

Table I. Cont'd

Reference	KID-cutaneous features	KID-systemic features	HS	Additional features of follicular occlusion and skin disease	Genetic mutation
Lazic et al[6]	Palmoplantar keratoderma, 20-nail dystrophy, gingival swelling, hyperemia and chronic lip fissuring, soft pedunculated papules on buccal mucosa and lateral edges of tongue	Congenital sensorineural deafness, photophobia, corneal abrasions, scarring, vascularizing keratitis, keratoconjunctivitis sicca.	Recurrent sterile abscesses with sinus tracts and scarring in the axillae, mons pubis and submammary folds.	Dissecting cellulitis of the scalp with diffuse scarring alopecia, partial eyebrow and eyelash alopecia, complete axillary and pubic alopecia, and porokeratotic eccrine ostial and dermal duct nevus (PEODDN), atopic dermatitis	G12R mutation on the GJB2 gene

HS, Hidradenitis suppurativa; *KID,* keratitis-ichthyosis-deafness; *SCC,* squamous cell carcinoma. Adapted from Bettoli et al (2021). KID and HS association features in the literature. Skin Appendage Disord. https://doi.org/10.1159/000509042.

history further revealed that he had keratitis in childhood, and was currently being treated for blepharitis. He had had multiple hospital admissions for treatment of severe atopic dermatitis with fungal and bacterial skin infections. Jobs syndrome was ruled out by normal serum-IgE.

The patient was referred for genetic evaluation and sequencing analysis was performed using the Sanger method. A heterozygous 32G->A transition of exon 2 in the *GJB2* gene was found: *GJB2, NM_004004.5 c.32G>A, p.Gly11Glu*. The missense variant p.Gly11Glu has previously been described as an autosomal dominant form of KID syndrome.[5]

During childhood and adolescence, our patient had numerous skin infections with *Staphylococcus aureus* and *Candida* and had recurrent pneumonia. During his treatment at our institution, he was treated for the skin infections with topical fucidin acid and oral dicloxacillin, amoxicillin-clavulanic acid, and tetracyline.

For the recalcitrant and progressive HS, he was treated with isotretinoin 20 to 40 mg daily for 1.5 years but developed worsening xerosis, dryness of the lips, blepharitis, and cheilitis. Due to these side effects, the dosage was decreased to 20 mg every other day. Metformin was given at a higher than normal dosage of 1g twice a day, combined with topical resorcinol and surgery (pilonidal cyst excision, deroofing, and CO2 laser).

At 30 years of age, our patient was treated for nodular lymphocyte-predominant Hodgkin lymphoma and was also subsequently diagnosed with a microadenoma of the pituitary gland causing pituitary gland dysfunction. He developed a recurrent abscess on his upper back, after the lymphoma treatment was discontinued. The patient was not a candidate for adalimumab because of his history of Hodgkin lymphoma.

DISCUSSION

Syndromes may provide a serendipitous insight into the genetic background of co-occurring diseases. KID syndrome was originally defined by the features implied by the acronym: keratitis causing visual impairment, with fine scale, ichthyosis, and deafness (OMIM #148210). However, this has since been challenged as the skin lesions appear more lichenified than scaly and are therefore not true ichthyoses, hearing loss is only partial, and keratitis develops with a late onset. Furthermore, the usual presentation of KID syndrome includes a variety of symptoms absent in the acronym: erythrokeratoderma, corneal vascularization, photophobia, recurrent bacterial and fungal infections, dystrophic nails, dental abnormalities, and susceptibility

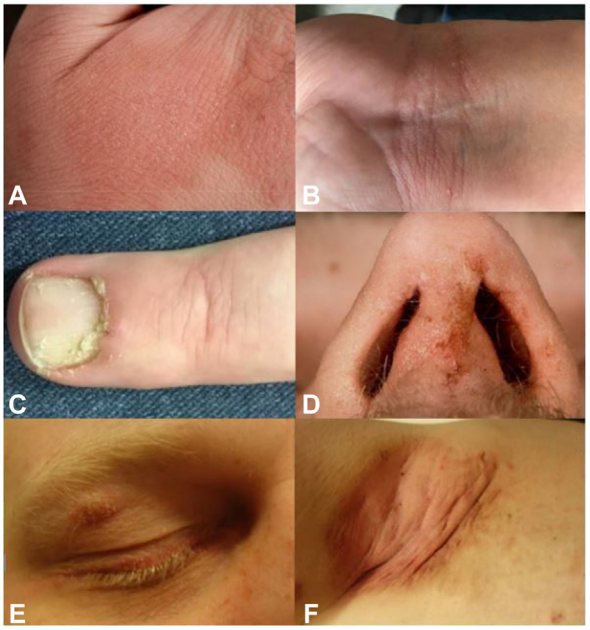

Fig 1. Pictures of our patient's dermatological findings associated with keratitis-ichthyosis-deafness syndrome. **A** and **B,** Lichenified eczematous patches on the dorsal hand and wrist—possible ichthyosis. **C,** Nail dystrophy. **D,** *Staphylococcus* colonization. **E,** Inflamed cyst on the *right* eyelid with overlying impetiginization. **F,** Acanthosis nigricans. Images sourced from Zealand University Hospital, Roskilde, Denmark.

to squamous cell carcinomas and other mucocutaneous tumors.[6,7] Patients with KID syndrome have an increased rate of malignancies, the most common being squamous cell carcinoma. Additionally, KID syndrome has been grouped with other cancer-associated genodermatoses including Cowden syndrome, Gorlin syndrome, and xeroderma pigmentosum.[8]

KID syndrome is caused by connexin-26 gene (*GJB2*) mutations.[5] Connexin is a 4-pass transmembrane protein involved in the assembly of gap junctions and intercellular communication.[9] Connexins have typically been regarded as tumor suppressive proteins. The finding of increased expression and membrane localization of connexins, including connexin-26 (Cx26), in metastases appears relevant.[9] There are several reports of Cx26 abnormalities in different internal malignancies such as breast, lung, prostate, colorectal and hepatic cancer. It is unknown if our patient's nodular lymphocyte-predominant Hodgkin lymphoma is related to his Cx26 mutation.

Multiple epithelial organs including hair follicles, palmoplantar epidermis, sweat glands and ducts, and cochlea have gap junctions which are formed by Cx26. The hyperproliferative tendency of the epidermis of patients with KID syndrome may

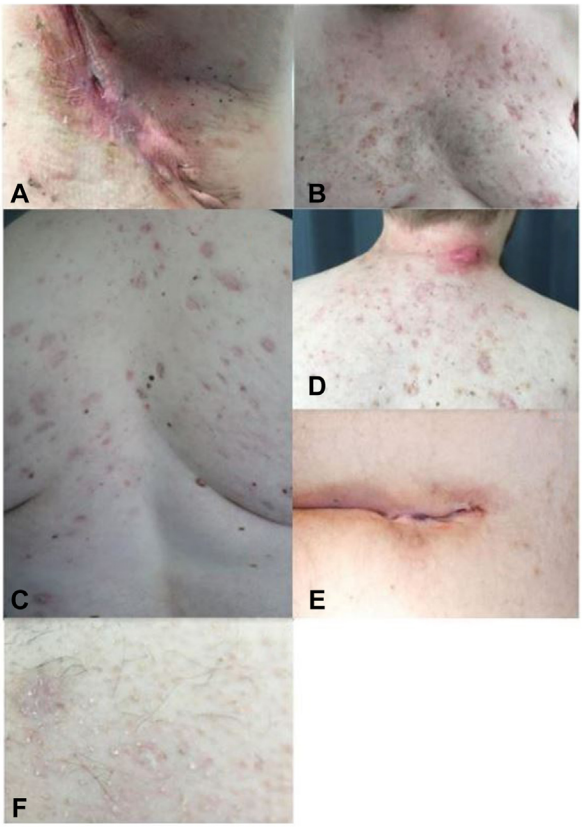

Fig 2. Pictures of our patient's clinical characteristics consistent with follicular occlusion. **A,** Hidradenitis suppurativa of the *left* axillae. **B** and **C,** Cystic acne and subsequent scarring. **D,** Recurrent abscess on the *right* posterior neck. **E,** Pilonidal sinus. **F,** Follicular spiny papules on the back. Images sourced from Zealand University Hospital, Roskilde, Denmark.

contribute to follicular plugging with subsequent cyst formation, rupture, and an inflammatory response seen in HS and the follicular occlusion disorders.[10] Although previous cases have shown variants in Asp50, Ala40, and Gly12 associated with KID syndrome and HS, further studies must be conducted to determine if they play a role in Cx26 function. Our patient has KID syndrome and 3 of the 4 diagnoses of the follicular occlusion tetrad; HS, acne conglobata, and pilonidal disease but not dissecting cellulitis of the scalp. He further presented with keratotic spiny papules on his trunk and upper arms, as shown in Fig 2. In another reported case of KID syndrome with a *GJB2* connexin 26 mutation, the patient developed yellow keratotic spiny papules at the age of 15. This patient was diagnosed with porokeratotic eccrine ostial and dermal duct nevus from biopsies of 3 sites.[4] She was also diagnosed soon after with HS and had a history of atopic dermatitis, similar to our patient. In summary, this case provides further evidence of the link between

KID syndrome and follicular occlusion. The co-occurrence of 2 rare clinical presentations that both link with connexin mutations and the finding of similar mutations in HS implies a new genetic venue for further studies of HS.

Mathias Vig Jakobsen, MD, participated in the early collection of data for this manuscript.

Conflicts of interest

None disclosed.

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