Clinical Report

Malignant Proliferating Pilar Tumors Arising in KID Syndrome: A Report of Two Patients

Gurston G. Nyquist,1 Christina Mumm,2 Renee Grau,2 A. Neil Crowson,2 Daniel L. Shurman,3 Paul Benedetto,4 Pamela Allen,2 Kelli Lovelace,2 David W. Smith,4 Ilona Frieden,5 C. Patrick Hybarger,6 and Gabriele Richard3,7*

1Department of Otolaryngology, Head and Neck Surgery, Kaiser Permanente, Oakland, California
2Department of Dermatology, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
3Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania
4Department of Pathology, Head and Neck Surgery, Kaiser Permanente, San Rafael, California
5Department of Dermatology, University of California San Francisco, California
6Department of Otolaryngology, Head and Neck Surgery, Kaiser Permanente, San Rafael, California
7GeneDx Inc., Gaithersburg, Maryland

Received 1 May 2006; Accepted 17 November 2006

We report on two young adults with KID syndrome and follicular hyperkeratosis, hidradenitis suppurativa of the groin, progressive development of proliferative pilar cysts and dissecting cellulitis of the scalp, who developed metastatic malignant pilar tumors. Based on our findings, we believe that cancer surveillance in patients with KID syndrome should include screening for pilar tumors and their early removal to avoid development of malignant proliferating pilar tumors with poor prognosis.

Key words: KID syndrome; skin cancer; squamous cell carcinoma; malignant pilar tumor; proliferating trichilemmal tumor; hidradenitis suppurativa; cystic acne; connexin; Cx26


INTRODUCTION

Keratitis–Ichthyosis–Deafness (KID) syndrome is a rare ectodermal dysplasia (OMIM 148210) characterized by sensorineural hearing loss (SNHL), photophobia and corneal vascularization, hyperkeratosis of the palms and soles (palmoplantar keratoderma, PPK), erythrokeratoderma, follicular hyperkeratosis (keratosis pilaris) and recurrent bacterial and fungal infections. Since the first description by Burns [1915], more than 90 KID syndrome cases have been reported worldwide. The disorder can be transmitted as autosomal dominant, albeit nine out of ten cases are sporadic due to a very high rate of new mutations. KID syndrome is caused by missense mutations in the connexin (Cx) 26 gene, GJB2. Almost 80% of patients with KID syndrome harbor a common, recurrent mutation, which replaces the highly conserved aspartic acid residue at position 50 of the polypeptide with asparagine (D50N). Cx26 is a gap junction protein involved in intercellular communication and control of cellular differentiation in ectoderm-derived stratifying epithelia of cochlea, cornea, palmoplantar epidermis and sweat glands and ducts. In addition, Cx26 is highly expressed in the hair follicle inner and outer root sheath (ORS) in human hair follicles [Arita et al., 2004]. Cx26 expression...
pattern and function overlaps with that of Cx30 in ectodermal epithelia and in one patient with KID syndrome and congenital atrichia, a missense mutation of the Cx30 gene, GJB6, was reported [Jan et al., 2004].

Remarkably, KID syndrome is also associated with an increased susceptibility for squamous cell carcinoma (SCC) of the skin and tongue, which have been observed in at least 10% of patients [Lancaster and Fournet, 1969; Baden and Alper, 1977; Madariaga et al., 1986; Morris et al., 1991; Hazen et al., 1992; van Steensel et al., 2002]. We report here on two young patients with KID syndrome who developed hundreds of proliferating pilar (trichilemmal) scalp cysts transforming into metastatic malignant pilar tumors and make recommendations for cancer surveillance and treatment of these tumors in KID syndrome.

**CLINICAL REPORTS**

**Patient 1**

A 31-year-old African American woman presented with a history of KID syndrome and recalcitrant hidradenitis suppurativa. Family history revealed that the patient’s paternal aunt had been also tentatively diagnosed with KID syndrome and passed away in her young adulthood. The patient did not have a relationship with this aunt and, therefore, did not know her clinical course or her cause of death. There were no vision, hearing, or skin disorders, including follicular tumors or skin cancers in other family members. The patient’s father is estranged and was unavailable for physical exam, thus the segregation of KID syndrome in this family could not be confirmed.

The patient had bilateral SNHL first diagnosed in infancy, photophobia and corneal vascularization, which were slowly progressing since adolescence. Her skin was dry. She had PPK with a ‘stippled’ appearance typical for KID syndrome (Fig. 1) and deep atrophic scars on both cheeks from previous cystic acne. Seven years earlier she was diagnosed with hidradenitis suppurativa of her groins as well as dissecting cellulitis of the scalp. Both were recalcitrant and progressive and were aggressively yet unsuccessfully treated with multiple courses of antibiotics and a 5-month course of isotretinoin (80 mg/day). By age 28, the dissecting cellulitis had finally resolved with diffuse scarring alopecia involving the occipital, parietal, and frontal scalp (Fig. 1). The hidradenitis remained a therapeutic challenge and eventually a surgical en bloc resection as performed, which lead to the discovery of a moderately differentiated SCC upon histological examination. The tumor mass was surgically excised and a lymph node dissection was performed. The resection showed a moderately differentiated SCC extending into the subcutis with clear surgical margins. Uninvolved skin at the borders of the tumor showed multiple epidermal cysts, chronic inflammation and marked dermal scarring. Two superficial inguinal lymph nodes contained metastatic tumor nests. The patient was treated with adjuvant radiation and chemotherapy and was free of local recurrence 3 years later.

At age 32, the patient presented with another significant, ulcerating skin tumor on the left occipital scalp draining serous fluid (Fig. 1). The fungating tumor was 12 cm × 10 cm in size and the suboccipital lymph nodes were enlarged. A superficial shave biopsy of the skin, which did not include the deeper pilo-sebaceous structures, showed full-thickness epidermal keratinocytic dysplasia and hence was interpreted as a primary, well-differentiated SCC. Computerized tomography (CT) scans showed a large skin and subcutaneous lesion extending into the skull bone with erosion of the posterior aspect of the mastoid air cells. There were several enhancing lymph nodes inferior to the left parotid gland suspicious for metastases. Staging CT of the chest, abdomen and pelvis were negative for disease involvement. The magnetic resonance imaging (MRI) of the brain was negative. The patient underwent a complete surgical excision of the skin tumor and draining lymph nodes. Final histological examination of the entire resected tumor demonstrated morphological hallmarks of a primary malignant proliferating pilar tumor (PPT), clearly originating from the pilosebaceous unit but reaching the epidermis. There were sheets of fully transformed malignant squamous cells with extensive areas of abrupt tricholemmal keratinization lacking a granular cell layer (Fig. 1). In several foci, the malignant epithelial sheets arose in continuity with cystic structures lined by banal squamous epithelium showing pilar differentiation, in continuity with areas of progressive dysplasia of the ORS epithelium, held to be further morphologic evidence of derivation from cysts arising from the deep components of the hair follicle apparatus. There was perineural invasion. Metastatic deposits were identified in 3 of 25 sampled lymph nodes. Within the excised scalp skin, the hair follicle density was greatly reduced; residual hair follicles were dilated and plugged with keratin material and the dermis was sclerotic, consistent with her history of scarring alopecia secondary to dissecting cellulitis. After a hiatus of 4 months, during which the patient did not receive radiation or chemotherapy, she returned for a dermatological follow up visit with a 4 cm × 4 cm tumor mass along the left anterior cervical chain. She was immediately referred back to otorhinolaryngology and oncology and is currently undergoing chemotherapy.

Mutation analysis of the Cx26 gene was performed to confirm the clinical diagnosis of KID syndrome. The
The patient was heterozygous for a G to A nucleotide change resulting in the missense mutation D50N (Asp50Asn) commonly associated with KID syndrome.

**Patient 2**

This 24-year-old man of mixed Japanese/African-American background was born with generalized, red and thickened skin and follicular hyperkeratosis. There was no family history of skin abnormalities, skin cancer, eye disorder or hearing loss. Since infancy, he has had PPK with a reticulate, pitted surface and interrupted dermatoglyphs. At age 2 years bilateral SNHL was diagnosed and serial audiograms from the age of 3–17 years revealed a stable mild-moderate hearing loss in the right ear and profound hearing loss in the left. MRI of the brain and CT of the temporal bones did not show any brain, internal auditory canal, or bony inner ear malformations. Mild, punctate keratitis developed by the age of 3 years but was stable and did not lead to subjective symptoms or visual decline. Based on these findings, a clinical diagnosis of KID syndrome was made.

The patient’s skin condition worsened with age, especially during puberty. Besides PPK, he had spiny, verrucous, hyperkeratotic plaques on the extremities. Recurrent episodes of bacterial skin infections necessitated treatment with oral antibiotics. The patient’s nails were thickened and showed longitudinal ridging. He had malalignment of the left great toenails and thinning of the lateral eyebrows. He also

---

**FIG. 1.** Patient 1: Female with KID syndrome. **A** Large, exophytic, ulcerated tumor mass and numerous small cystic tumors on the scalp at age 32 y. **B** Typical ‘stippled’ appearance of the palmar surface of the digits. **C** Depicted are the remnants of a cyst containing amorphous eosinophilic debris. The cyst wall shown on the left demonstrates abrupt keratinization indicative of a proliferating trichoepithelial tumor. The cyst wall shows progressive neoplastic transformation. Tumor cells radiate from the wall into the stroma, 40× magnification. **D** Fully transformed malignant neoplastic cells grow as tongues through the stroma, provoking a proliferative fibroblastic reaction. In concert with the features shown in (C), the atypical mitoses, fully transformed malignant cytology and the infiltrative growth pattern indicate a malignant pilar tumor, 600× magnification.
developed severe cystic acne with hard, erythematous papules and pustules in typical distribution. In addition, there were multiple small, hard or cystic nodules on the back, shoulders and scalp, which evolved into large, fluctuant, boggy masses of 1–8 cm in diameter. The cystic nodules intermittently became infected but responded well to systemic antibiotic treatment. Several of these scalp tumors proliferated and grew explosively leading to ulceration, necrotization and widespread plaques of scarring alopecia on his scalp with intermittent bunches of hair. At age 13 years, the patient began a 20-week course of oral isotretinoin to treat severe facial acne, and the scalp nodules became less active during this regimen. However, another course of isotretinoin was aborted secondary to cheilitis, epistaxis, and fear of skeletal toxicity.

At age 19, the patient presented with a fleshy, ulcerated, 5 cm × 4 cm nodule on the right temporal scalp that was larger then any of the multiple scalp cysts. The nodule had a soft consistency and released a white exudate when punctured. No cervical lymphadenopathy was present. Results of a shave biopsy showed features of a SCC. Micrographic, margin-controlled excision was performed and resulted in a 6 cm × 9 cm defect, which was reconstructed with a large rotation flap. As discovered during surgery, the scalp contained hundreds of small and larger cysts.

Six months later, enlarging nodules of the right and left sides of the scalp appeared and were excised (Fig. 2). Histopathological examination showed a spectrum of disease from pilar (trichilemmal) cysts, to PPTs, to areas showing fully transformed malignant changes of the associated squamous epithelia with an infiltrative pattern of growth and a desmoplastic stromal reaction indicating a primary malignant PPT (Fig. 2).

Over the next several years, the patient developed multiple masses of the scalp that were treated with intralesional methotrexate. While some lesions resolved, those that did not respond to this regimen were excised with Mohs technique. Because of disease progression, the patient ultimately required subtotal full-thickness scalp resection. It was successfully reconstructed with a split-thickness skin graft (STSG) after an Integra bilayer dermal substitute scaffolding was placed and given 3 weeks to heal (Fig. 2). On each occasion, histopathological examination showed SCCs arising in a field of multiple proliferating trichilemmal tumors. Despite the radical surgical treatment, the patient suffered a local recurrence of the tumors through the STSG with transcalvarial dural spread and compression of the superior sagital sinus on MRI. A work-up revealed pulmonary metastases, and the patient developed later also new metastases to the base of the skull and cavernous sinus. He underwent cyberknife radiation

![Fig. 2. Patient 2. Male with KID syndrome. A: Large, fungating and ulcerated malignant pilair tumor and hundreds of proliferating trichilemmal cysts of the scalp at age 23 years. Note the scarring alopecia. B: Postoperative status after subtotal full-thickness scalp resection and interim placement of an Integra bilayer dermal substitute scaffolding, which was later successfully constructed with a split-thickness skin graft. C: Shown is a dermal tumor characterized by proliferating lobules of neoplastic squamous epithelia that show abrupt (i.e., tricholemmal) keratinization without a granular cell layer. Tongues of tumor infiltrate the stroma, which shows fibroplasia and a granulation tissue reaction. There are areas of dystrophic calcification (indicated by their deep purple stain) in both the tumor lobules and in the stroma, 100× magnification. D: Depicted toward the left is the wall of a tricholemmal cyst lined by squamous epithelium with a glassy, eosinophilic appearance. In the lower levels of the canal cyst wall, the epithelial cells show typical features of malignancy. The adjacent stroma contains an infiltrating component with tongues of tumor and a sheet-like pattern of growth. Numerous mitoses are evident, 200× magnification.](image-url)
treatment to treat the sagittal sinus metastases, and later whole brain radiation therapy in conjunction with multiple cycles of systemic chemotherapy; however, the patient ultimately succumbed to the disease.

Mutation analysis of the Cx26 gene revealed a homozygous A-to-G nucleotide substitution leading to replacement of the highly charged glutamic acid residue at position 114 with a small, neutral glycine (E114G). In addition, the patient was heterozygous for another sequence variant of Cx26 with codons present for both valine and isoleucine (V27I). Both variants are common among individuals of Asian descent and are can be found together on the same Cx26 allele (in cis) [Posukh et al., 2005]. A pathogenic dominant mutation could not be identified in GJB2. Similarly, no mutation was found in several other connexin genes that are expressed in the skin and ectodermal epithelia, including GJB3, GJB4, GJB5, and GJB6.

Results of immunostaining of the patient's acanthotic, tumor-free scalp epidermis with antibodies against 10 different gap junction proteins, including Cx26, was comparable to normal human epidermis with exception of Cx26. Normally, this connexin is expressed in the epithelial cells of the eccrine sweat glands and ducts as well as in the hair follicle but not in interfollicular epidermis. The patient skin showed, however, an ectopic punctate plasma membrane staining in the granular layer (Fig. 3), similar to a previous report [Richard et al., 2002]. In a malignant cystic pilair tumor, immunoreactivity for Cx26 was limited to a few clusters of tumor cells, while no Cx30 staining was found. Cx43 staining was detected in a typical punctate plasma membrane pattern as well as in an aberrant diffuse cytoplasmic distribution. Positive connexin staining of cell clusters for Cx31 and Cx36 was seen in the malignant tumor, but not in surrounding skin, and showed an unusual cytoplasmic pattern (Fig. 3). These observations are consistent with an upregulation and shift in the expression of connexins in malignant pilair tumors in a patient with KID syndrome. The abnormal cytoplasmic distribution of these gap junction proteins could be the result of a failure in intracellular trafficking or, alternatively, reflect a different function of connexins in tumor cells.

**DISCUSSION**

KID Syndrome belongs to a diverse group of genetic connexin disorders with disturbed gap junction function. Nonetheless, it appears to be the only connexin defect that is associated with an increased susceptibility for SCC. The first patient with KID Syndrome and cutaneous SCC was reported in 1969 [Lancaster and Fournet, 1969]. Since then, at least nine additional cases have come to light, including six patients with SCC of the skin and three patients with SCC of the tongue and oral mucosa, which translates to an incidence rate of about 10%. In some of the cases with epidermal SCC, preexisting hyperkeratosis of the skin was noted [Richard et al., 2003]. When considering also the young age of KID syndrome patients at time of tumor development, (age range between 6 and 55 years, mean: 25 years) [Baden and Alper, 1977; Madariaga et al., 1986; Morris et al., 1991; Hazen et al., 1992; Richard et al., 2003; van Steensel et al. 2002; Grob et al. 1987; Lancaster et al., 1969] it seems evident that the underlying genetic cause of KID syndrome, namely mutations in the Cx26 gene, are directly or indirectly responsible for the increased SCC risk. The pathogenesis of SCC in KID syndrome patients remains unclear, especially since none of the other known Cx26 disorders, that is, non-syndromic SNHL and PPK and SNHL, including Vohwinkel syndrome and Bart-Pumphrey syndrome, apparently do not
convey an increased risk of malignant tumors [Richard 2005]. However, these allelic disorders also lack other features of KID syndrome, such as involvement of cornea and pilosebaceous units and abnormalities of the immune system, suggesting that those Cx26 mutations leading to KID syndrome have unique detrimental consequences.

We report here two patients with KID syndrome who developed primary malignant proliferating pilar tumors (PPT) of the scalp. Both patients shared a constellation of features that has not been previously recognized as an entity: (1) history of severe cystic acne, hidradenitis suppurativa and/or dissecting cellulitis of the scalp with scarring alopecia; (2) progressive development of a large number of pilar cysts with onset in early teens; (3) sudden onset of rapid tumor growth and transformation into malignant pilar tumors with (4) highly invasive and metastatic behavior leading to a poor prognosis. Benign and malignant pilar (tricholemmal) tumors on the buttocks, elbows and knees have been reported once before in a Korean patient with KID syndrome, albeit in this case no clear history of a follicular inflammatory processes was reported, [Kim et al., 2002]. In contrast, two unrelated KID syndrome patients from the USA and Germany exhibited features of a ‘follicular occlusion triad’ characterized by follicular plugging, chronic follicular inflammation and scarring (dissecting folliculitis), hidradenitis suppurativa, and cystic acne but without malignant tumors [Montgomery et al., 2004; Maintz et al., 2005].

The mounting number of KID patients with follicular occlusion syndrome strongly suggests that the underlying genetic defect in KID syndrome results in a perturbed keratinization not only of the epidermis but also of the hair follicles and thus predisposes to follicular occlusion triad and follicular tumors. Montgomery et al. [2004] hypothesized that abnormal epidermal and follicular keratinization in KID syndrome leads to plugging of the follicular orifices with subsequent cyst formation, rupture and spillage of keratin and glandular secretions into the subcutaneous tissue, which in turn causes an inflammatory response. It is conceivable that recurrent and chronic inflammation and scarring may be one additional factor in triggering transformation of benign pilar cysts to malignant PPTs during a multistep carcinogenesis process as demonstrated for other subtypes of SCC and many other malignant tumors.

Pilar (tricholemmal) cysts of the scalp are common and arise from the ORS of the hair follicle isthmus. They are characterized histologically as a nodule formed by an outer wall of keratinizing epithelium without a granular layer at the base of the hair follicle. Most nodules are solitary and less than 5 mm, but it is not unusual for them to be greater than 5 cm. Transformation into a PPT, also referred to as proliferating trichilemmal cyst/tumor, is possible when extensive keratinocyte proliferation occurs in the basal cell layer. Microscopically, the well-circumscribed tumors are formed by proliferating lobules of squamous cells showing multiple central areas of trichilemmal keratinization (without the presence of a granular layer) and formation of homogeneous keratin cysts. Typically, the transition from pale, enlarged peripheral cells to a densely packed keratin layer is abrupt and there is some cellular atypia and increased mitotic activity [Mehregan and Lee, 1987; Park et al., 1997; Lopez-Rios et al., 2000]. These histological characteristics may overlap with those of epidermis-derived SCC, in particular since in up to 24% of PPT the epidermis may be involved [Sau et al., 1995], also illustrated in Patient 1. The classification of pilar tumors is debated [see Cassarino et al., 2005], some consider pilar (tricholemmal) cysts and proliferating pilar (tricholemmal) cysts/tumors benign in nature, others believe they represent low-grade SCC as a review of the literature in 2002 showed 30 cases of PPT’s transforming into malignant PPT/SCC [Folpe et al., 2003]. Nevertheless, it has been recognized that once transformation into malignant PPT (aka malignant proliferating tricholemmal tumor) has occurred, these tumors behave more aggressively with respect to local invasiveness and distant metastasis than many other more common subtypes of epidermal SCC. Recently, Cassarino et al. [2005] proposed a classification of SCC based upon their malignant potential into those with low (<2% metastatic rate), intermediate (3–10%), high (greater than 10%), and indeterminate behavior. Malignant PPTs were grouped as high-risk tumors, similar to Bowen disease, adenosquamous and desmoplastic carcinoma. Based on our experience, we support the viewpoint that malignant PPT represent a distinct form of SCC arising from the deep component of the hair follicle apparatus, which have a very high malignant potential.

The current management of PTT is excision with clear margins of those tumors that have grown rapidly and begin to ulcerate. This treatment strategy proved insufficient for the presented KID syndrome patients. Both required extensive and repeated surgical excision of the scalp tumors due to invasion into local structures and lymph node metastases. The invasion into the calvarium and dura in Patient 2 resulted also in neurological abnormalities and a high morbidity. Based on our experience in the cases reported here, we believe that the surgical treatment in KID syndrome patients must be especially aggressive with wide local excision of proliferating tumors and, ideally, Mohs micrographic surgery because of the apparent high potential for malignant transformation and metastatic progression. It has to be considered that the presence of many adjacent proliferating tricholemmal cysts can make the precise margin analysis difficult and that an early
removal of the entire scalp with preliminary ligation of feeding vessels and Integra/split-thickness skin grafting may be beneficial.

Considering the increased SCC risk, the early age of tumor onset, and aggressive behavior of tumors in some KID syndrome patients, KID syndrome belongs to the list of cancer-associated genodermatoses, such as Gorlin syndrome, Cowden syndrome, Xeroderma pigmentosum and others [Brose et al., 2003]. The guidelines for dermatologic surveillance in patients with KID syndrome should be most stringent for those patients with clinical evidence of follicular occlusion. We recommend that these patients perform monthly self-examinations of the skin and oral cavity and be fully examined by a dermatologist at 3- to 6-month intervals with a low threshold for biopsy of proliferating, ulcerating or otherwise suspicious lesions. In particular, circular cysts should be removed in toto (if possible) to avoid proliferation malignant transformation. Similarly, regular full oral examination should be included in the surveillance program because of the reported KID syndrome cases with SCC of the tongue and mouth. Such a regimen is expected to lead to early cancer detection and might therefore be of major importance for the survival of KID syndrome patients.

Gap junctions formed by Cx26 are found in many epithelial organs, including the cochlea, palmar/plantar epidermis, hair follicles, and sweat glands and ducts. In the hair follicle, Cx26 expression is found in the ORS and inner root sheath (IRS) but most pronounced in the outermost layer of the ORS in contrast to Cx43, which shows predominantly staining in the inner part of the ORS, IRS, cortex and medulla [Arita et al., 2004]. Connexin 26 has been considered a tumor suppressor gene, which can modulate development, growth and differentiation in epithelial modules [Lee et al., 1991] and its upregulation has been linked to epidermal hyperplasia, for example, in psoriasis and viral warts [Lucke et al., 1999]. Based on the strong follicular expression of Cx26 in keratinizing cells and the observation of follicular occlusion syndrome and cystic pilartumors in patients with KID syndrome, we suspect that hyperplasia in the isthmus of the hair follicle may cause proliferation and subsequent increased incidence of malignant transformation resulting in SCC mimicking or arising from PPTs. Cx26 has been also tight to different steps during carcinogenesis and several recent reports have described abnormalities in Cx26 structure and regulation in various internal organ malignancies, such as breast, lung, prostate, colorectal and hepatic cancer [Muraiaw, 2002; Momiyama et al., 2003; Tanaka and Grossman, 2004; Kanczuga-Koda et al., 2005, 2006; Ito et al., 2006]. For example, upregulation of Cx26 was found in cells of 15 out of 27 invasive breast carcinoma tumors, although the staining was usually cytoplasmic and heterogeneous in contrast to the normal plasma cellular localization of gap junction proteins [Jarjeson et al., 1998]. Similarly, we also observed intense and abnormal cytoplasmic immunostaining for Cx26 as well as three other connexins (Cx31, Cx31.1, and Cx36) in a malignant pilartumor in Patient 2. Since connexins are usually localized at the plasma membrane, where they form hemichannels and intercellular gap junction channels, the predominantly cytoplasmic localization of Cx26 in tumor cells suggests that gap junction communication is reduced. Indeed, a decrease of gap junction communication has been correlated previously with stepwise progression of benign papillomas to SCC in a mouse carcinogenesis model [Budunova et al., 1996]. Moreover, this finding implies that Cx26 plays a role in tumorigenesis, tumor progression and/or metastasis independent of gap junction communication. This hypothesis is supported by recent studies demonstrating that Cx26 suppresses tumor growth and induces apoptosis in tumor cells via association with apoptotic, cell cycle control and focal adhesion proteins [Tanaka and Grossman, 2004; Kanczuga-Koda et al., 2005]. It is feasible that KID syndrome associated mutations in Cx26 selectively alter any of these interactions with Bax, Bcl2, focal adhesion kinase and others, thus promoting tumor growth and metastasis. However, this hypothesis remains to be investigated. Based on the co-existence of benign, proliferating and malignant pilartumors in patients with KID syndrome, it is conceivable that tumor development follows a two- or multihit model similar to other genetic cancer syndromes. Chronic festering inflammations, such as recalcitrant hidradenitis suppurativa or dissecting cellulitis of the scalp could represent crucial local factors contributing to malignant transformation.

In summary, a subset of patients with KID syndrome develops multiple cystic pilartumors, which are prone to malignant transformation and metastasis. The sheer number and aggressive malignant behavior of these tumors is a therapeutic challenge and results in considerable morbidity and mortality. We suggest including pilary (tricholemmal) cysts and proliferative pilartumors in the cancer surveillance of KID syndrome patients and recommend their early excision to prevent malignant transformation and metastatic disease.

ACKNOWLEDGMENTS

We like to extend our special thanks to the patients who so generously supported our work and research on KID syndrome. We are grateful to Dr. Jason Lee and Dr. David Cassarino for helpful comments and stimulating discussions. This work was partly supported by the National Foundation for Ectodermal Dysplasias and NIH/NIAMS grants K08-AR02141 and P01-AR04923 (GR).
REFERENCES


