

SHORT COMMUNICATION

Squamous Cell Carcinoma Arising from Keratitis–Ichthyosis–Deafness Syndrome

Hiroshi Mayama, Taku Fujimura, Masayuki Asano, Yumi Kambayashi, Yukikazu Numata and Setsuya Aiba

Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, 980-8574, Japan. E-mail: tfujimura1@mac.com

Accepted Oct 18, 2012; Epub ahead of print Feb 6, 2013

Inherited ichthyoses are rare genodermatoses caused by mutations in the genes involved in epidermal development. Keratitis–ichthyosis–deafness (KID) syndrome is a debilitating ectodermal dysplasia that predisposes patients to develop squamous cell carcinomas (SCC) in addition to leading to profound sensory deafness and erythrokeratoderma already present at birth (1–5). Recent reports have provided evidence that KID syndrome is caused by a mutation of connexin 26 (Cx26) (2–5), a gap junction protein, encoded by GJB2, with the majority of patients harbouring the D50N mutation (2–8). Interestingly, a previous review suggested that the missense D50N mutation in patients with KID syndrome is strongly connected with the development of skin SCC (1), although not every case develops malignancies (6, 7). We describe here a case of large areas of SCC arising from KID syndrome after severe infection. Our report also suggests that severe bacterial infection might be one of the reasons for the establishment of this aggressive skin cancer.

CASE REPORT

A 33-year-old man presented with indurated, scaly and infectious plaques on his trunk, limbs and scalp, and severe fever. Immediately after birth, he had had prominent keratitis, ichthyosis and deafness, with later development of mental retardation. He was treated for KID syndrome with oral etretinate, tacalcitol hydrate ointment and anti-bacterial cream at the Department of Dermatology in Kesen-numa City Hospital since 2003. On

19 February 2010, a dermatologist in Kesen-numa performed a skin biopsy from his left heel, which revealed that his lesion was ichthyosis without malignancy. On 11 March 2011, the Great Eastern Japan earthquake occurred and the tsunami struck Kesen-numa City. After this earthquake, the patient had to interrupt his treatment and a severe infection developed on his legs. On his initial visit, physical examination revealed hyperkeratotic plaques with coagulated nodules on his face, buttock and feet (Fig. 1A). Skin ulcers with necrotic degeneration were especially prominent on the bilateral heels (Fig. 1B, C). Biopsy specimens from the buttocks, bilateral heels and leg revealed premalignant fibroepithelial tumour (Pinkus). Microbiological testing from the skin surface was positive for *Corynebacterium* spp. and Methicillin-resistant *Staphylococcus aureus* (MRSA). A full blood count and biochemical profile revealed prominent increases in white blood cells (29,900/ μ l), neutrophils (21,200/ μ l), C-reactive protein (35.9 mg/dl), procalcitonin (5.33 ng/dl) and ferritin (411 ng/dl). In addition, serum SCC antigen (Ag) was increased (116.7 ng/dl). From the above findings, we diagnosed this patient with KID syndrome accompanied by severe skin infection. We treated the patient with doripenem 0.5 mg/day for 10 days, and the serum C-reactive protein gradually decreased and the skin ulcers on the foot improved, although erosive nodules remained on the left lower leg and bilateral soles. To confirm the diagnosis of KID syndrome, we looked for the GJB2 mutations. Following ethics committee approval and informed consent, genomic DNA was extracted from blood leucocytes using standard methods. Primers were designed to amplify individual exons and the flanking intron of the GJB2 gene. PCR-sequencing analysis of the entire coding sequences of GJB2 revealed a c.148G>A substitution at exon 2 (Fig. S1; available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1535>). This variant was predicted to result in an amino acid change from aspartic acid to asparagine at codon 50 (D50N). Because the serum SCC Ag was still 10–20



Fig. 1. (A) Hyperkeratotic plaques with coagulated nodules on the patient's face, (B) lower leg, and (C) feet. (D) Multiple uptakes on the skin detected by positron emission tomography.

times higher than the normal range, we screened for a possible internal malignancy with positron emission tomography and found multiple uptakes on the skin, especially on the bilateral heels and left lower leg (Fig. 1D). A biopsy specimen from the nodules on the left lower leg revealed sheets of small cells with hyperchromatic nuclei extending throughout the dermis (Fig. S2A, B; available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1535>). In addition, tumour-infiltrating lymphocytes contained numerous CD163 M2 macrophages and IL-17-producing cells (Fig. S2C, D). From the above findings, we diagnosed this patient with moderately-differentiated SCC developing from KID syndrome. Because we could not assess the safety margin of this SCC, we palliatively excised the tumour with a 5-mm margin. There was no recurrence of SCC 9 months after the surgical treatment; however, he died of pneumonia at Kesen-numa City Hospital 3 months after his return home.

DISCUSSION

We describe here a case of SCC arising from KID syndrome after severe infection. PCR-sequencing analysis of GJB2 revealed the missense mutation D50N, which was reported to be related to the development SCC from KID syndrome (1). Our present report shed light on the possible mechanisms of the onset of SCC on KID syndrome with severe infection.

Previously, Natsuga et al. (1) reviewed 28 cases of skin malignancy in congenital ichthyoses, including 12 cases of KID syndrome. In their report, 10 cases of KID syndrome with SCC were described and GJB2 mutation was detected in 6 cases; in the other 4 cases, molecular analysis was not performed. Interestingly, the missense mutation of D50N was detected in all 6 cases (2–5). However, previous reports also suggested that some patients with KID syndrome who had the missense mutation D50N did not always develop SCC (6, 7, 10). Therefore other factors must play a role too for developing SCC in KID syndrome. Indeed, strong evidence for an association with bacterial infectious disease, such as chronic osteomyelitis and hidradenitis suppurativa, with oncogenesis has been reported (11). The chronic irritation of the skin and secondary bacterial infection lead to proliferative epidermal changes. From the immunological point of view, bacterial infection strongly induces proinflammatory cytokines, including IL-1 β , IL-6 and PGE2 (12–14). These proinflammatory cytokines induce myeloid-derived suppressor cells, which are known to play a central role in the induction of peripheral tolerance (15). In conclusion, in our present case, severe skin infection might also have triggered the development of large areas of SCC.

REFERENCES

1. Natsuga K, Akiyama M, Shimizu H. Malignant skin tumours in patients with inherited ichthyosis. *Br J Dermatol* 2011; 165: 263–268.
2. van Steensel MA, van Geel M, Nahuys M, Smitt JH, Steijlen PM. A novel connexin 26 mutation in a patient diagnosed with keratitis-ichthyosis-deafness syndrome. *J Invest Dermatol* 2002; 118: 724–727.
3. van Geel M, van Steensel MA, Küster W, Hennies HC, Happel R, Steijlen PM, et al. HID and KID syndromes are associated with the same connexin 26 mutation. *Br J Dermatol* 2002; 146: 938–942.
4. Mazereeuw-Hautier J, Bitoun E, Chevrant-Breton J, Man SY, Bodemer C, Prins C, et al. Keratitis-ichthyosis-deafness syndrome: disease expression and spectrum of connexin 26 (GJB2) mutations in 14 patients. *Br J Dermatol* 2007; 156: 1015–1019.
5. Nyquist GG, Mumm C, Grau R, Crowson AN, Shurman DL, Benedetto P, Allen P, et al. Malignant proliferating pilar tumors arising in KID syndrome: a report of two patients. *Am J Med Genet A* 2007; 143: 734–741.
6. Kelly B, Lozano A, Altenberg G, Makishima T. Connexin 26 mutation in keratitis-ichthyosis-deafness (KID) syndrome in mother and daughter with combined conductive and sensorineural hearing loss. *Int J Dermatol* 2008; 47: 443–447.
7. Bygum A, Betz RC, Kragballe K, Steiniche T, Peeters N, Wuyts W, et al. KID syndrome: report of a Scandinavian patient with connexin-26 gene mutation. *Acta Derm Venereol* 2005; 85: 152–155.
8. Neoh CY, Chen H, Ng SK, Lane EB, Common JE. A rare connexin 26 mutation in a patient with a forme fruste of keratitis-ichthyosis-deafness (KID) syndrome. *Int J Dermatol* 2009; 48: 1078–1081.
9. van Steensel MA, van Geel M, Nahuys M, Smitt JH, Steijlen PM. A novel connexin 26 mutation in a patient diagnosed with keratitis-ichthyosis-deafness syndrome. *J Invest Dermatol* 2002; 118: 724–727.
10. Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryyänen M, et al. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. *Am J Hum Genet* 2002; 70: 1341–1348.
11. Samaras V, Rafailidis PI, Mourtzoukou EG, Peppas G, Falagas ME. Chronic bacterial and parasitic infections and cancer: a review. *J Infect Dev Ctries* 2010; 4: 267–281.
12. Hovden AO, Karlsen M, Jonsson R, Appel S. The bacterial preparation OK432 induces IL-12p70 secretion in human dendritic cells in a TLR3 dependent manner. *PLoS One* 2012; 7: e31217.
13. Fujimura T, Yamasaki K, Hidaka T, Ito Y, Aiba S. A synthetic NOD2 agonist, muramyl dipeptide (MDP)-Lys (L18) and IFN- β synergistically induce dendritic cell maturation with augmented IL-12 production and suppress melanoma growth. *J Dermatol Sci* 2011; 62: 107–115.
14. Ahmed EB, Wang T, Daniels M, Alegre ML, Chong AS. IL-6 induced by *Staphylococcus aureus* infection prevents the induction of skin allograft acceptance in mice. *Am J Transplant* 2011; 11: 936–946.
15. Fujimura T, Mahnke K, Enk AH. Myeloid derived suppressor cells and their role in tolerance induction in cancer. *J Dermatol Sci* 2010; 59: 1–6.