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Clinical encounter with a woman with Costello syndrome

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Costello syndrome (MIM number 218040) is a rare genetic disorder caused by mutation in the v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS) gene. Clinically, patients present with distinctive facial features, cutaneous manifestations and skeletal abnormalities. This syndrome is also called facio-cutaneous-skeletal syndrome.

Our patient was a 28-year-old woman, with a deep, hoarse voice, who was referred from the dermatological department for genetic diagnosis. She was a member of the indigenous Amis tribe. There was no knowing family history of consanguinity or other affected members. Her medical history revealed severely delayed developmental milestones and severe mental retardation. Since she was 18 years old, the patient had no social activity and no self care ability in daily life, because she easily became dyspneic. She received a bilateral tympanoplasty at the age of 25 years because of cholesteatomas. She had one episode of paroxysmal supraventricular tachycardia at the age of 26, but a 24 hour Holter monitor revealed no pathological findings.

Physically, the patient had a prominent forehead, a head circumference of 54 cm (−1 SD), short stature (139 cm, −4.5 SD) and an optimal body weight (43.7 kg, -1 SD). She had a coarse face, thick lips, a large mouth, depressed nasal bridge, bulbous nose, coarse voice, and curly, sparse hair. Low-set pinnae with large lobes were also noted (Fig. 1). Cutaneous manifestations include sweaty, oily, hyperpigmented skin, a loose skin texture, very deep palmar/plantar creases, hyperkeratosis with underlying pinkish skin and

Fig. 1. Typical facial features of individuals with Costello syndrome with curly, sparse hair, a long face, sweaty, oily, hyperpigmented skin, thick eyebrows and eyelids, strabismus, a depressed nasal bridge, bulbous nose, large mouth with thick lips, and low-set pinnae with large lobes (with father's consent for publication).

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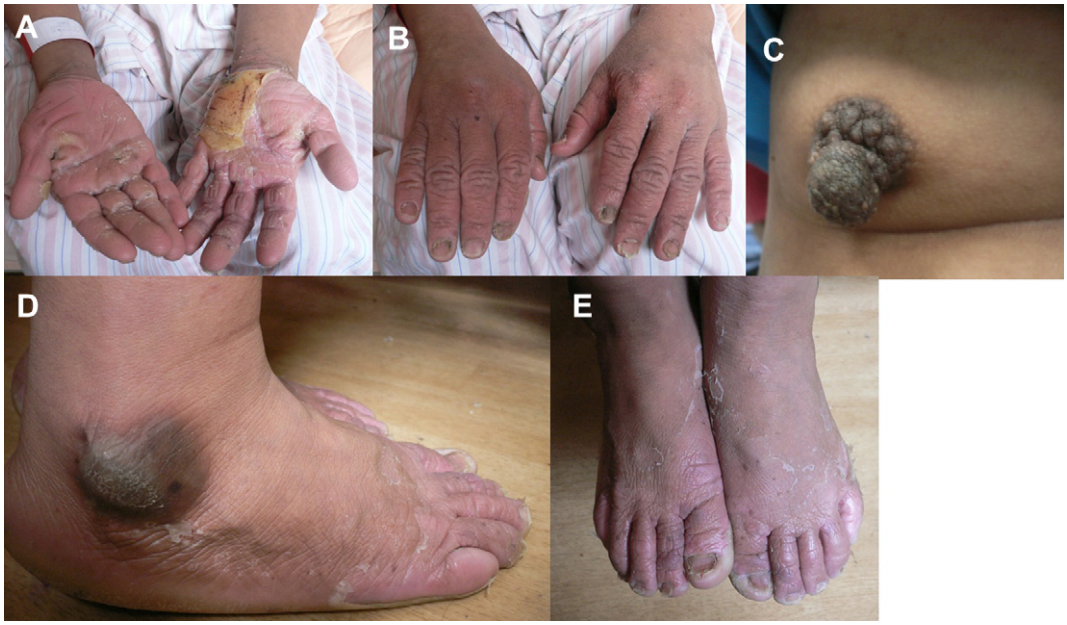

Fig. 2. Cutaneous manifestations of Costello syndrome. (A) and (B) Deep palmar creases and hyperkeratosis. (C) Deep nipple color with papillomas. (D) and (E) Deep plantar creases, pigmented lesions on the ankle, and hyperkeratosis with underlying pinkish skin.

a foul body odor. The nipples were very dark and affected with papillomas (Fig. 2). Skeletal anomalies included hyperextensible joints and thoracolumbar scoliosis shown on an image study. Bone mineral densitometry showed moderate osteoporosis (Z-Score: −3.7 SD, T score: −3.7).

She also had moderate mitral valve regurgitation, pulmonary valve and tricuspid valve insufficiency, hypertrophic cardiomyopathy and severe hypertension (systolic/diastolic blood pressure: 160 ~ 174/107 ~ 130 mmHg). Ophthalmologic examination revealed amblyopia, premature cataracts, partial optic atrophy, nystagmus and high myopia. Her hearing was normal. She also had amelogenesis imperfecta and attrition, hypertrophic gingiva and gingivitis, and heavy calculus deposition. She was malnourished with generally low plasma amino acid levels and a low level of insulin-like growth factor 1 (68.9 ng/mL, normal = 100 ~ 500 ng/mL). A skin biopsy revealed dermatitis with elongation of the rete ridge, and multiple abscess formation in the keratin layer (Fig. 3). HRAS gene sequencing analysis revealed a *de novo* G to A missense mutation in nucleotide 34 (c.34 G→A), leading to an amino acid change from serine to glycine (p.G12S) (Fig. 4). Since the HRAS protein is responsible for regulation of cell growth and division, patients with Costello syndrome are predisposed to both benign and

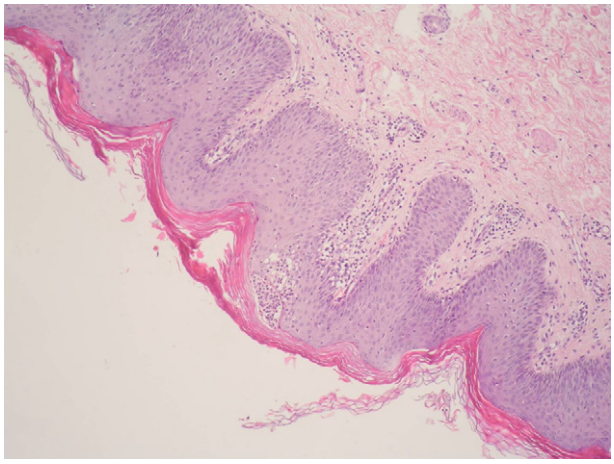

Fig. 3. Skin biopsy. Microscopically, there is chronic dermatitis with elongation of the rete ridge accompanied by microabscess formation in the keratin layer and mild chronic inflammatory cell infiltration in the upper dermis.

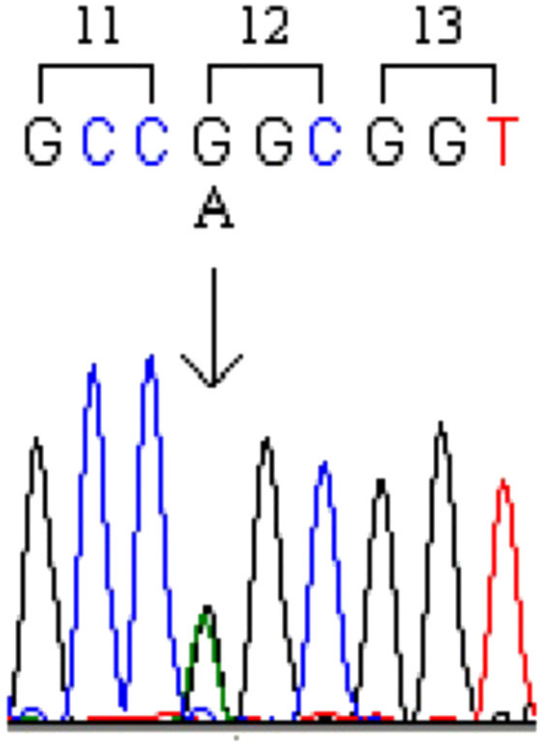

Fig. 4. HRAS gene analysis reveals *de novo* G to A transition in exon 2 (c.34 G→A), leading to an amino acid change from glycine to serine (p.G12S). HRAS: v-Ha-ras Harvey rat sarcoma viral oncogene homolog.

malignant neoplasms. A panel of serum tumor markers revealed mild elevation of the carcinoembryonic antigen level to10.1 ng/mL (normal = 0–3 ng/mL). Abdominal and pelvis computed tomography showed normal results.

Her treatment included dental care, and medications for hypertension and cardiomyopathy. A low salt, low lipid diet, which included adequate calories, was designed, along with a gradual increase in daily physical activity. Treatment of osteoporosis included different strategies, such as bracing for scoliosis, synthetic polypeptide hormone injection, oral bisphosphonate, sun exposure and supplementation with calcium and active vitamin D. Dermatological management included phototherapy, cutaneous application of a keratolytic agent, lubricants, and anti-inflammatory agents. Genetic counseling was offered to the patient and the whole family. Social and medical resources, and a home care project to look after her, were provided. She is now 31 years old, and lives an outgoing and highly sociable life, which is characteristic of patients with Costello syndrome after collaborative interprofessional medical care.

Further reading

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