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SHORT COMMUNICATION

Treatment of an Intractable Cutaneous Ulcer in the Right Lateral Malleolus in Fibrodysplasia Ossificans Progressiva

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Fibrodysplasia ossificans progressiva (FOP) is a rare, extremely disabling, autosomal dominant disease of the skeletal system (1). The disease process involves ectopic production of osseous masses in intramuscular and perimuscular connective tissue. The osseous masses form abnormally connected sections of the skeleton, causing disfiguration and inhibiting normal motor functions (1). There is evidence that microtraumas, intramuscular injections and surgical procedures might contribute to the initiation of the disease. The patients need to avoid soft-tissue injuries, contact sports, overstretching of soft tissues and muscle fatigue, biopsies, surgical removal of heterotopic bone and non-emergency surgical procedures (2). Almost all FOP patients have some congenital anomalies, including short great toes, hallux valgus, short thumbs and hypoplasia of digital phalanges (3). Recently, a recurrent mutation in activin receptor 1A/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type 1 receptor, was identified in all sporadic and familial cases of FOP examined, making this one of the most specific disease-causing mutations in the human genome (2).

CASE REPORT

A 35-year-old man was admitted to our department with a skin ulcer on his right lateral malleolus on 4 February 2009. At birth, the patient had bilateral, both hallux valgus, limited anteflexion of thoracic vertebrae, limited flexion of radial and hip joints, and symphalangism of both pollices. At 9 years of age, he had bruised his waist and, subsequently, was unable to bend over. His clinical course led to a diagnosis of FOP by a paediatrician, without genomic analysis. No family members were diagnosed with the disease. At admission, short great toes, a broad femoral neck, and heterotopic calcifications in halluces and tibial bones, seen on X-ray photographs, were noted. A skin ulcer (35×24 mm^2) was observed on the patient's right lateral malleolus. Laboratory data did not reveal any abnormalities. Genomic DNA was extracted from oral mucosa, and exon 4 of the *ACVR 1* gene was amplified by polymerase chain reaction (PCR) after informed consent had been obtained (4). Genomic analysis revealed a heterozygous missense mutation encoding an arginine-to-histidine substitution in the activation domain of the gene product (617G>A; R206H).

Treatment with various ointments was ineffective. A biopsy specimen from the edge of the ulcer revealed ulceration with hyperkeratosis and acanthosis of the epidermis, with proliferation of blood vessels and haemosiderin deposits in the upper dermis. A diagnosis of "stasis dermatitis" was made. The biopsy wound healed without ossification, and we decided to attempt a skin graft. Minimizing the donor site, we obtained an epidermal sheet by the suction blistering method. The ulcer then healed with a pin-hole-like skin defect at the centre of the graft, but, unfortunately, ulceration recurred. Next, we applied a split-skin graft and the ulcer healed completely. However, 8 months later, the ulcer reappeared. No ossification occurred even after repeated skin grafts.

DISCUSSION

Ulceration of the skin over a projecting spur of bone or pressure sores is an occasional feature of FOP (5). During the day, the patient was confined to a motorized wheelchair, in which he sat in an almost upright position. He had often slept in the right lateral recumbent position, and his ulcer was considered to be due to stasis in addition to decubitus. Loss of muscle strength in his legs had reduced the pumping action of his veins. Normal skin perfusion pressure on his dorsal foot suggested that ischaemia had not contributed to formation of the ulcer. We found one case report of a patient with FOP who had a chronic ulcer on his left shin, but treatment was not mentioned (6). To our knowledge, this is the first case report of a skin graft applied to an ulcer in FOP. The surgical procedure, including biopsy and skin graft, was performed without ossification in our FOP patient. However, the ulcer reappeared after successful grafting and has since received only conservative treatment.

One of the disease-causing point mutations in FOP is c.617G>A; p.R206H, in the gene for ACVR1 (7). The R206H mutant has decreased binding affinity for FKBP1A/FKBP12 (12-kDa FK506-binding protein), a molecule that safeguards against leakage of transforming growth factor β (TGF-β) and BMP signalling. Decreased binding affinity of FKBP1A for mutant R206H ACVR1 results in leaky activation of the BMP signal, and decreases steady-state levels of R206H ACVR1 (7). The BMP-Smad pathway includes recruitment and phosphorylation of R-Smad (receptor-activated Smad; Smad 1, Smad 5, and Smad 8) with subsequent formation of their complexes with Co-Smad (heteromeric complexes with Smad 4) and translocation to the nucleus for regulation of transcription (8). Phosphorylation of Smad 1 and Smad 5 is enhanced by the R206H mutation in ACVR1 (4). In BMP-6-overexpressing transgenic mice, re-epithelialization of skin wounds is significantly

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delayed and scar formation is enhanced (8, 9), perhaps explaining the refractory epithelialization of the ulcer in the present case.

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The authors declare no conflicts of interest.

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