INVESTIGATIVE REPORT

Unusual Bone Lesions with Osteonecrosis Mimicking Bone Metastasis of Squamous Cell Carcinoma in Recessive Dystrophic Epidermolysis Bullosa

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Some bone lesions are reported to mimic bone metastasis on imaging tests. Herein, we report a case of a 55-year-old Japanese man who presented with a skin tumour on the left lower extremity. He also had a history of recurrent generalized cutaneous blister and erosion formation since childhood. His skin lesions were diagnosed as cutaneous squamous cell carcinoma complicated by recessive dystrophic epidermolysis bullosa. Magnetic resonance imaging of the left lower extremity detected multiple focal bone lesions mimicking bone metastases in the left femur and tibia. However, bone biopsy revealed that the bone lesions were osteonecrosis without tumour cells. We suggest that cancer-induced osteonecrosis should be included in the differential diagnosis of bone lesions suspected of being metastases on magnetic resonance imaging.

Key words: osteonecrosis; bone metastasis; squamous cell carcinoma; recessive dystrophic epidermolysis bullosa.

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SIGNIFICANCE

We report a case of unusual bone lesions with osteonecrosis mimicking bone metastases of cutaneous squamous cell carcinoma in a patient with recessive dystrophic epidermolysis bullosa. In our case, it was speculated that various humoral factors carried by the feeder arteries from the primary cutaneous squamous cell carcinoma lesion and surrounding the multiple chronic wounds and scars associated with recessive dystrophic epidermolysis bullosa might be involved in the development of osteonecrosis. Our case suggests that cancer-induced osteonecrosis should be considered for the differential diagnosis of bone lesions suspected of being metastases on imaging tests.

Whilst bone metastases may occur in various types of cancer, some bone disorders may mimic bone metastases on imaging tests. We report here a case of unusual bone lesions with osteonecrosis mimicking bone metastases of cutaneous squamous cell carcinoma (cSCC) in a patient with recessive dystrophic epidermolysis bullosa (RDEB).

CASE REPORT

A 55-year-old Japanese man was referred to our department with a 4-month history of a rapidly growing skin tumour in his left lower extremity. He had a history of recurrent generalized cutaneous blister and erosion formation since childhood. His brother had experienced similar recurrent symptoms, but his parents had not. Physical examination revealed a 20 × 18-cm, ulcerated tumour with a bad odour and grossly abnormal discharge around the left knee (**Fig. 1**a). Poikiloderma, hypopigmentation and erosions were present on the face, neck, trunk, and extremities, as were some blisters on the trunk (Fig. 1b, c). Skin samples from the blisters demonstrated decreased expression of collagen VII on immunohistochemical staining, and hypoplastic anchoring fibrils on electron microscopy compared with a healthy control skin sample (Fig. 1d–g). Direct sequencing analysis of *COL7A1* revealed that the patient was compound heterozygous for the splice-site (c.2440G>A (p.Gly814Ser)) and recurrent frameshift (c.5819delC (p.Pro1940fs)) mutations (Fig. 1h). RDEB was diagnosed from these findings. Histological analysis of the skin tumour revealed proliferation of atypical squamous cells with frequent dyskeratosis and mitoses, although the atypia was weak and destructive invasion was not observed (Fig. 1i, j). cSCC was diagnosed from the combined findings of the histological analysis and clinical features showing a significantly large and rapidly growing tumour.

Magnetic resonance imaging (MRI) of the left lower extremity revealed that the primary tumour may have extended to near the tibia (**Fig. 2**a). In addition, multiple focal bone lesions with hypointense signals on the T1-weighted images and hyperintense signals on the T2-weighted images of the left femur and tibia were observed (Fig. 2a, b). Dynamic contrast-enhanced MRI revealed enhancement of the bone lesions with multiple feeder arteries from the primary tumour to the focal bone lesions

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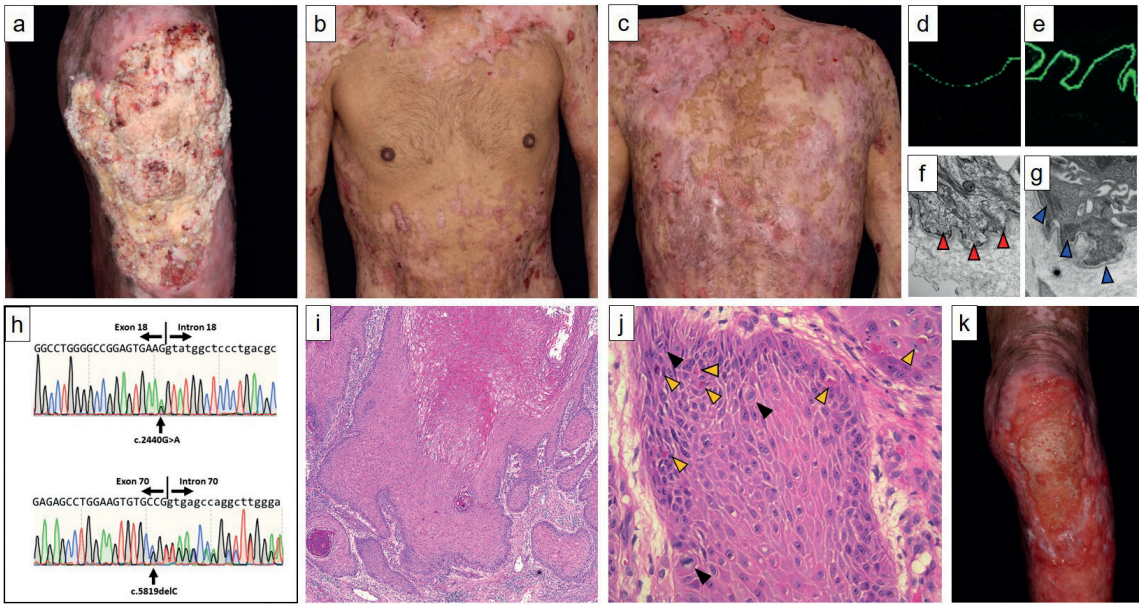

Fig. 1. (a) A large tumour with ulceration in the left lower extremity. (b, c) Poikiloderma and hyperpigmentation were observed over most of the body. Some blisters were present on the trunk. (d, e) Decreased expression of collagen VII shown on immunohistochemical staining (d) compared with a heathy control skin sample (e). (f, g) Electron microscopy revealed hypoplastic anchoring fibrils (f, red triangles) compared with a healthy control skin sample (g, blue triangles). (h) DNA sequence of the proband. Compound heterozygous mutations (c.2440G>A and c.5819delC) were detected. (i, j) Histology revealed atypical squamous cell proliferation with relatively frequent dyskeratosis and mitoses (haematoxylin and eosin (H&E): h, 40×; i, 400×). The yellow triangles and black triangles show dyskeratosis and mitoses, respectively. (k) The skin tumour had regressed after the chemoradiotherapy.

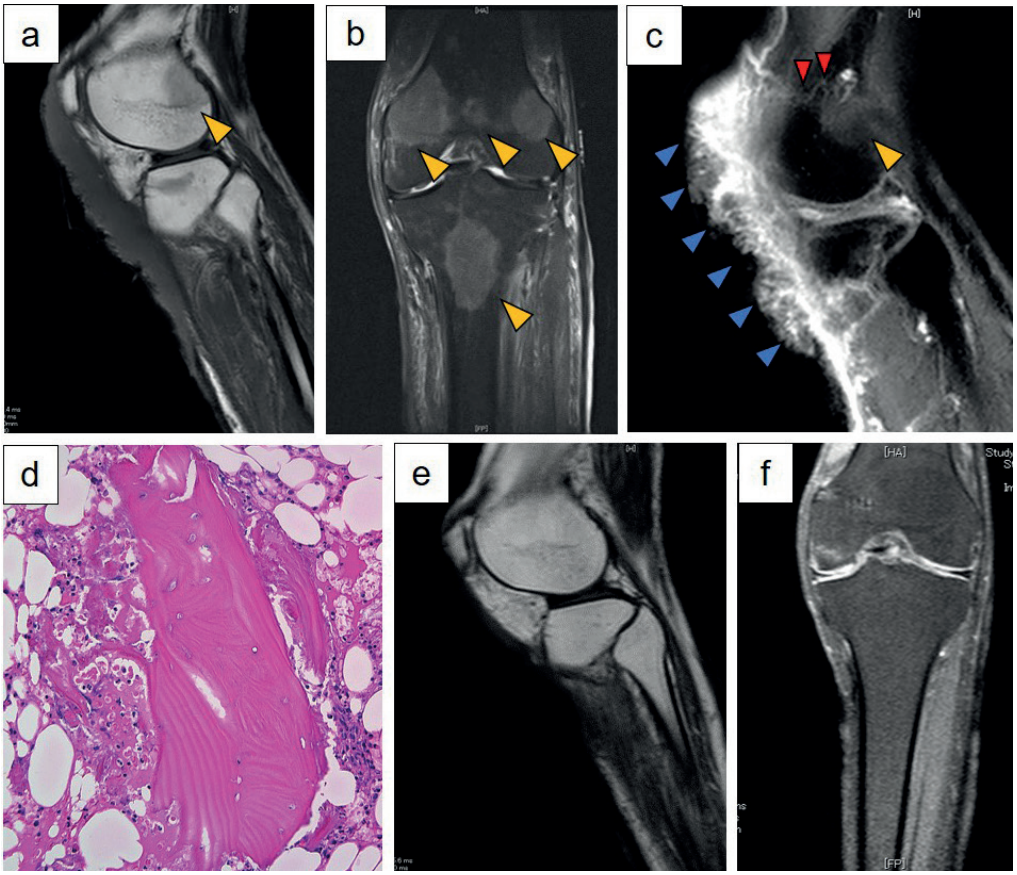

Fig. 2. (a, b) Multiple focal bone lesions (yellow triangles) shown on magnetic resonance imaging (MRI) of the left femur and tibia. (a) A T1-weighted image and (b) T2-weighted image with fat saturation are shown. (c) Feeder arteries (red triangles) from the primary tumour (blue triangles) to the bone lesions (yellow triangle) shown on dynamic contrast-enhanced MRI. (d) Non-viable trabecular bone with empty cellular lacunae (haematoxylin and eosin (H&E), 200×). (e, f) The multiple bone lesions shown on MRI were no longer visible after the chemoradiotherapy. (T1-weighted image [e] and T2-weighted image with fat saturation [f]).

(Fig. 2c). Computed tomography (CT) from the chest to the inguinal regions did not show metastatic lesions or abnormal bone findings. Whole-body bone scintigraphy demonstrated no abnormal uptake. Dual-energy X-ray absorptiometry (DXA) of the lumbar spine revealed normal bone density. On the basis of these findings, the bone lesions were suspected to be metastases of the cSCC. Then, open bone biopsies from the medial lesion of the femur were performed. Consistent with the MRI findings, a fragile bone lesion was observed. The lesional tissues were harvested, along with their surrounding non-lesional tissues as a negative control. Histological analysis revealed non-viable trabecular bone with empty cellular lacunae scattered throughout the lesional tissues, whereas such findings were not seen in the non-lesional tissues (Fig. 2d). Although a substantial amount of the tissues were harvested, no tumour cells were found in the lesion. From these findings, the bone lesions were diagnosed as osteonecrosis. The patient refused surgical treatment, and the primary skin lesion was treated with radiotherapy (total 70.2 Gy) and chemotherapy consisting of cisplatin (15 mg/m^2) and 5-fluorouracil (800 mg/m^2) for 5 consecutive days and repeated every 4 weeks for up to 3 cycles. Then, 60 mg/m^2 of TS-1®, a combination capsule containing tegaful, gimeracil, and oteracil potassium, was given orally for 4 weeks, followed by a 2-week rest, which was repeated for up to 4 cycles. After the chemoradiotherapy, the size of the primary tumour decreased rapidly, although the ulcer remained (Fig. 1k), and repeated biopsies confirmed no residual tumour cells in the lesion. In addition, the multiple bone lesions were no longer visible 7 months after the chemoradiotherapy (Fig. 2e, f). Four years after the chemoradiotherapy, no recurrence or metastases have occurred.

DISCUSSION

RDEB is a blistering skin disease caused by mutations in the *COL7A1* gene encoding keratinocyte-secreted type VII collagen, which functions as an anchoring fibril. It is well known that cSCC frequently develops in patients with RDEB, whereas other inherited chronic blistering diseases do not show significant association with cSCC occurrence (1). cSCC associated with RDEB is characterized by invasive lesions, and a recent countrywide study showed that metastasis occurred in 68% of patients with cSCC with RDEB, a rate that is higher than that in patients with cSCC without RDEB (1). Although the mechanism of the rapid progression of cSCC in RDEB remains unclear, a previous study suggested that down-regulation of type VII collagen alters gene expression in dermal fibroblasts toward a cancer-associated fibroblast phenotype, leading to the promotion of invasion and progression of cSCC (2).

In our case MRI detected unusual multiple focal bone lesions under the primary cSCC lesion; to our knowledge, such cases have not been reported previously. Although MRI is sensitive to the early detection of bone metastases, which generally show hypointensity or isointensity on T1-weighted images without a specific signal on T2-weighted images (3), the specificity of this method is limited (4, 5). Since some disorders may mimic metastases on MRI, bone biopsies are recommended for the definitive diagnosis (4, 5). Although bone metastases were also suspected in our case on the basis of the MRI findings, open bone biopsies, which show a high accuracy for metastases, revealed osteonecrosis without tumour cells.

Previous reports have revealed that children with RDEB may show osteoporosis, characterized by low bone mass and density value, owing to the slower growth and stature and to the frequent periods of immobilization (6). However, it has been reported that attainment of puberty can lead to an improvement in the osteoporosis (6). Although osteoporosis might be associated with osteonecrosis (7), our case showed no abnormal findings suggestive of osteoporosis on CT from the chest to the inguinal regions and the lumbar spinal DXA, indicating that osteoporosis was not involved in the osseous lesions.

The exact pathogenesis of osteonecrosis is unknown, but it can be associated with trauma, use of steroids or bisphosphonates, or alcohol abuse (8). Most cases of atraumatic osteonecrosis are characterized by progressive bone destruction and require surgical intervention, whereas cases of osteonecrosis with spontaneous radiological resolution have also been reported (9). Although the suspected causes of osteonecrosis include ischaemia, MRI of our case revealed hypervascularity, presumably due to the newly formed feeder arteries from the primary cSCC lesion. In contrast, many kinds of factors, such as matrix metalloproteases (MMPs), transforming growth factor beta (TGF-β), interleukin (IL)-1, tumour necrosis factor alpha (TNF-α), and interferon alpha (IFN-α), are suggested to be involved in osteonecrosis through various effects, including inhibition of osteoblast differentiation and proliferation and promotion of bone cell death (10, 11). Most of these factors could be produced in the tumour environment (12). In addition, these factors could also be produced in chronic wounds and scars, and fibroblasts obtained from patients with RDEB manifest increased amounts of MMPs and TGF-β (13–15). Therefore, although the precise mechanism underlying the unusual bone lesions in the current case remains unclear, we speculate that various humoral factors carried by the feeder arteries from the primary cSCC lesion and surrounding the multiple chronic wounds and scars might be intricately involved in the development of osteonecrosis. This case suggests that cancer-induced osteonecrosis

should be considered in the differential diagnosis of bone lesions suspected of being metastases on MRI.

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The authors have no conflicts of interest to declare.

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