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

Akimasa SAITO1, Yoshiyuki NAKAMURA1, Ryota TANAKA1, Sae INOUE1, Naoko OKIYAMA1, Yosuke ISHITSUKA1, Hiroshi MARUYAMA1, Rei WATANABE1, Kenji YOSHIDA2, Akira ISHIKO1, Manabu FUJIMOTO1, Satoru SHINKUMA3 and Yasuhiro FUJISAWA1

1Department of Dermatology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, 2Department of Dermatology, Toho University School of Medicine, Tokyo, and 3Divisions of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Some bone lesions are reported to mimic bone metastases 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.

Accepted Aug 26, 2019; E-published Aug 27, 2019
Acta Derm Venereol 2019; 99: 1166–1169.
Corr: Yoshiyuki Nakamura, Department of Dermatology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. E-mail: ynakamura-tuk@umin.ac.jp

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 on the 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. 1a). 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 cutaneous squamous cell carcinoma lesion and 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.

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.
Fig. 1. (a) A large tumour with ulceration in the left lower extremity. (b, c) Poikilodermia 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 healthy 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/m²) and 5-fluorouracil (800 mg/m²) for 5 consecutive days and repeated every 4 weeks for up to 3 cycles. Then, 60 mg/m² of TS-1®, a combination capsule containing tegafur, 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 MRI, 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.

ACKNOWLEDGEMENTS

The authors thank Ms Flaminia Miyamasu (Medical English Communications Center, Faculty of Medicine, University of Tsukuba) for useful comments. We also thank Ms Emi Takatsu (Divisions of Dermatology, Niigata University Graduate School of Medical and Dental Sciences) for the technical support of sequencing analysis of COL7A1.

The authors have no conflicts of interest to declare.

REFERENCES

1. Kim M, Li M, Intong-Wheeler LRA, Tran K, Marucci D, Murrell DF. Epidemiology and outcome of squamous cell carcinoma in epidermolysis bullosa in Australia and New Zealand. Acta Derm Venereol 2018; 98: 70–76.
2. Ng YZ, Pourreyron C, Salas-Alanis JC, Dayal JH, Cepeda-Valdes R, Yan W, et al. Fibroblast-derived dermal matrix drives development of aggressive cutaneous squamous cell carcinoma in patients with recessive dystrophic epidermolysis bullosa. Cancer Res 2012; 72: 3522–3534.
3. Bratu AM, Raica VP, Sălcianu IA, Zaharia C, Popa VB, Lupu AR, et al. MRI differential diagnosis: bone metastases versus bone lesions due to malignant hemopathies. Rom J Morphol Embryol 2017; 58: 1217–1228.
4. Ciray I, Aström G, Sundstrom C, Hagberg H, Ahlstrom H. Assessment of suspected bone metastases. CT with and without clinical information compared to CT-guided bone biopsy. Acta Radiol 1997; 38: 890–895.
5. Chow LT, Ng AW, Wong SK. Focal nodular and diffuse haematopoietic marrow hyperplasia in patients with underlying malignancies: a radiological mimic of malignancy in need of recognition. Clin Radiol 2017; 72: 265 e267–265 e223.
6. Hubbard LD, Mayre-Chilton K. Retrospective longitudinal study of osteoporosis in adults with recessive dystrophic epidermolysis bullosa. Clin Case Rep 2019; 7: 58–63.
7. Horikawa A, Miyakoshi N, Shimada Y, Kodama H. The relationship between osteoporosis and osteoarthritis of the knee: a report of 2 cases with suspected osteonecrosis. Case Rep Orthop 2014; 2014: 514058.
8. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32: 94–124.
9. Mont MA, Baumgarten KM, Rifai A, Bluemke DA, Jones LC, Hungerford DS. Atraumatic osteonecrosis of the knee. J Bone Joint Surg Am 2000; 82: 1279–1290.
10. Samara S, Kollia P, Dailiana Z, Chassanidis C, Papatheodorou L, Koromila T, Malizos KN. Predictive role of cytokine gene polymorphisms for the development of femoral head osteonecrosis. Dis Markers 2012; 33: 215 e223.
11. An F, Du J, Cao Y et al. MMP8 polymorphism is associated with susceptibility to osteonecrosis of the femoral head in a Chinese Han population. Oncotarget 2017; 8: 21561–21566.
12. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res 2014; 2014: 149185.
13. Küttner V, Mack C, Rigbolt KT, Kern JS, Schilling O, Busch H, et al. Global remodelling of cellular microenvironment due to loss of collagen VII. Mol Syst Biol 2013; 9: 657.
14. Patel S, Maheshwari A, Chandra A. Biomarkers for wound healing and their evaluation. J Wound Care 2016; 25: 46–55.
15. Kotwal GJ, Chien S. Macrophage differentiation in normal and accelerated wound Healing. Results Probl Cell Differ 2017; 62: 353–364.