Letter to the Editor

Visualization of hidden soft-tissue recurrence of giant cell tumor of bone enabled by preoperative denosumab treatment: a case description

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Case presentation

An 18-year-old Japanese female presented to prior hospital with a 3-month history of pain in the right proximal lower leg and gradually progressive muscle weakness of the ankle dorsiflexion. A radiological examination suggested a bone tumor of the fibular head (*Figure 1A,B*), and the patient was then referred to our hospital. Magnetic resonance imaging (MRI) showed an expansile and osteolytic lesion in the proximal fibula with extraosseous extension (*Figure 1C,D*). After a needle biopsy, the lesion was diagnosed as a giant cell tumor of bone (GCTB), Campanacci grade III (1), and we performed a tumor resection.

The intraoperative gross findings revealed an extraosseous tumor involving the common peroneal nerve, and we dug out and preserved the nerve from the tumor (*Figure 1E,F*). The histopathological examination showed typical numerous osteoclast-like multinuclear giant cells and mononuclear neoplastic stromal cells (*Figure 1G*). Mononuclear neoplastic stromal cells showed immunopositivity for H3.3 G34W, characteristics of GCTB, but multinuclear giant cells were negative (*Figure 1H*). The patient was finally diagnosed as a GCTB. Although common peroneal nerve palsy temporarily occurred after the operation, it spontaneously recovered within approx. 6 months.

Nineteen months after the surgery, plain radiographs of the right lower leg showed a tiny ossification in the soft tissue of the posterior to fibula stump (*Figure 2A,B*), MRI demonstrated a mass in the soft tissue anterior to the fibula stump (*Figure 2C,D*), and the lesions observed were considered a latent recurrence. Considering the intraoperative findings, we suspected that there was a possibility that spread recurrent tumors that were not visible to the naked eye were present around the preserved common peroneal nerve. Therefore, before the resection of the recurrent lesion, the patient underwent nine courses of preoperative denosumab treatment, injecting 120 mg of subcutaneous denosumab every four weeks with loading doses on days 8 and 15, for the purposes of visualizing the hidden recurrent tumors by mineralization and shrinking the recurrent tumor.

Six months later, the recurrent lesion had shrunk in size and eggshell-like ossification appeared, and another ossification appeared in the surrounding soft tissue inferior to the fibula stump on plain radiographs (*Figure 2E,F*) and MRI (*Figure 2G,H*). We performed a marginal resection of

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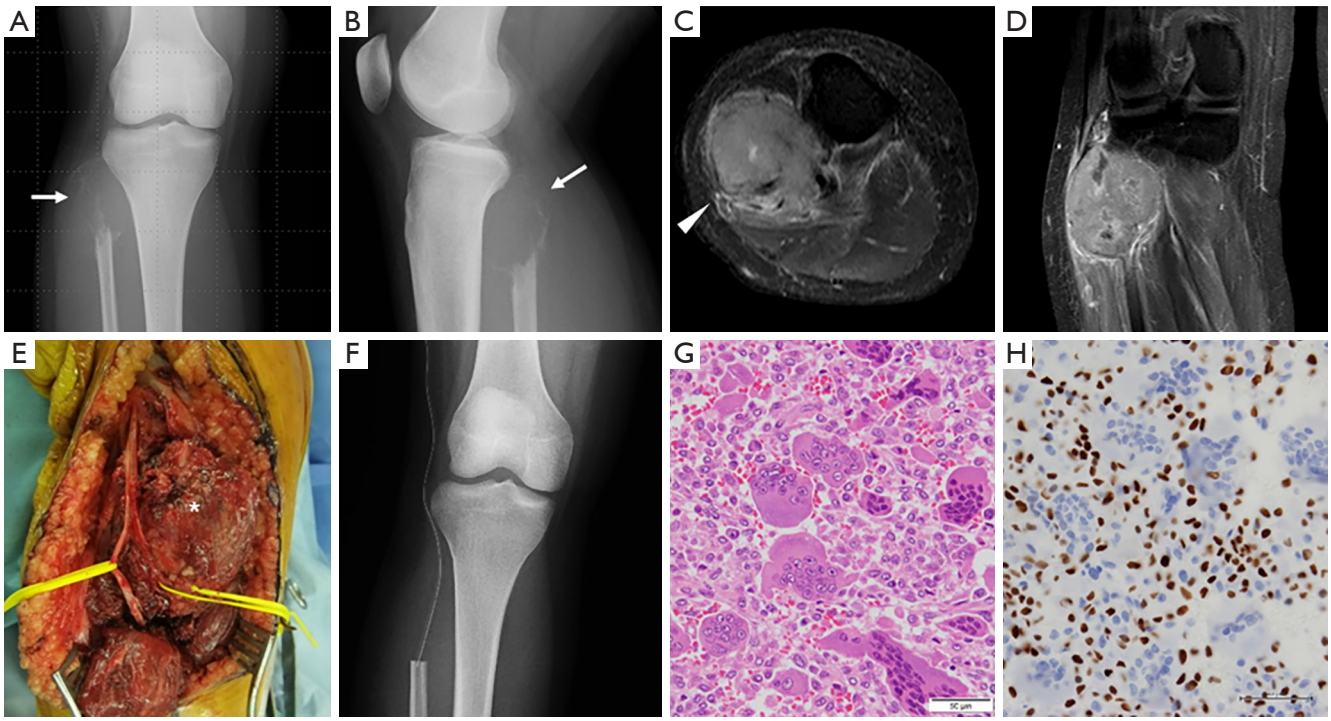

Figure 1 Imaging of primary giant cell tumor of the fibular head. Plain anteroposterior (A) and lateral (B) radiographs showing an expansive osteolytic lesion localized in the right proximal fibula (arrow). Axial MRI showing a proximal fibular tumor, displaying high intensity on short-tau inversion recovery (C). Coronal gadolinium-enhanced T1-weighted fat-suppressed imaging showing a homogeneously enhanced extensive tumor (D). Intraoperative findings showing the bone tumor extending extraosseously and involving the common peroneal nerve (E). Postoperative plain radiograph showing the bone defect caused by the fibular head resection (F). Histopathological examination of a resected specimen showing numerous osteoclast-like multinuclear giant cells and mononuclear neoplastic stromal cells. Hematoxylin-eosin (HE) staining, high-power field (×400) (G). Immunohistochemistry for H3.3 G34W showing positivity in mononuclear neoplastic stromal cells and negativity in osteoclast-like multinuclear giant cells (×400) (H).

these two lesions (*Figure 3A*,*B*,*C*). The histopathological examination showed eggshell-like ossification on the periphery of the tumor and mononuclear cells and foamy cells on the central area, but no giant cells were observed (*Figure 3D*,*E*). Since mononuclear cells were positive for H3.3 G34W (*Figure 3F*), we judged that the cells are neoplastic. There was no tumor cell outside the peripheral ossification. Four years after the second surgery, there is no sign of local recurrence or distant metastasis.

Discussion

GCTB is an intermediate (locally aggressive) primary bone tumor with a high recurrence rate (2,3). In particular, in the Campanacci grade III (1) cases that extend into circumferential soft tissue with cortical destruction, postoperative local recurrence in the surrounding soft tissue as well as in the bone is an issue of great concern.

GCTB is histologically characterized by the diffuse growth of RANKL [receptor activator of nuclear factor-κB (RANK) ligand]-positive mononuclear neoplastic stromal cells and RANK-positive osteoclast-like giant cells. RANKL is a key mediator, which orchestrates the recruitment of monocyte cells to their milieu, incites the production of the multinuclear giant cells and activates osteoclasts. The RANK-RANKL interaction in GCTB is thought to participate in the production of multinuclear giant cells which express mediators degrading the organic and hydroxyapatite component of bone, leading to bone resorption (4). Based on this mechanism, denosumab, the

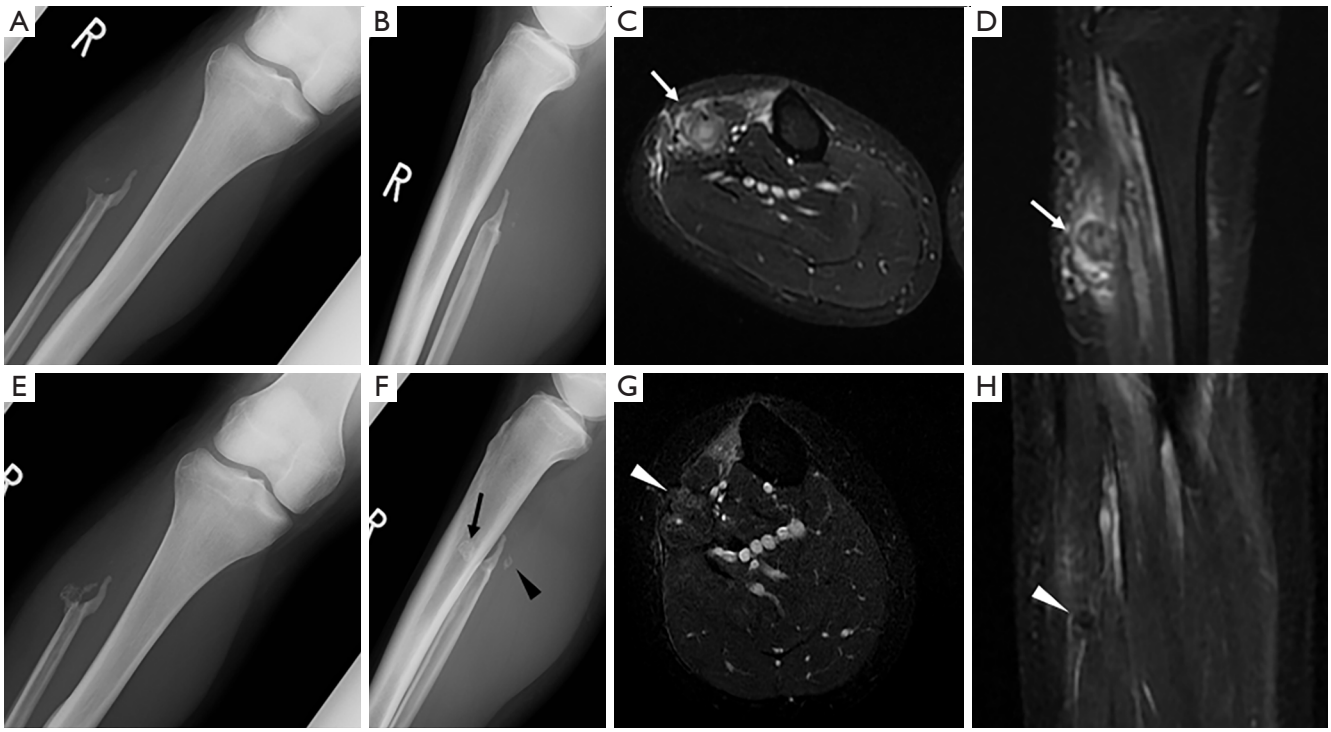

Figure 2 Radiological findings of before and after the denosumab treatment for recurrent GCTB. At 19 months after the initial operation, plain radiographs of the right lower leg show a tiny ossification in the soft tissue of the posterior to fibula stump (A,B). MRI demonstrating a soft tissue mass considered a recurrent lesion (arrow), displaying heterogeneously high intensity on STIR images (C, axial; D, coronal). After 6 months of preoperative denosumab treatment, the recurrent lesion is reduced in size and eggshell-like ossification appears (black arrow), and another ossification appeared in the surrounding soft tissue inferior to the fibula stump (black arrowhead) on plain radiographs (E,F). MRI showing the shrunken low-intensity mass on STIR (G, axial; H, coronal). GCTB, giant cell tumor of bone.

monoclonal antibody against RANKL, has been used to treat patients with GCTB (5).

Recently, a mutation of the histone family member 3A gene (H3F3A) was identified as the driver mutation of GCTB. Behjati *et al.* (6) reported that the H3F3A mutation was found in 92% of GCTB. This mutation was also observed in spindle cells and mononuclear cells appeared following denosumab treatment (7). Thus, H3F3A-mutated tumor cells survive after denosumab treatment and related to bone formation.

Our patient had a GCTB of the fibular head. Following the fibular head resection, this tumor visibly and invisibly recurred in the circumferential soft tissue, but it was visualized and easily resected following preoperative denosumab treatment. Preoperative denosumab treatment for GCTB has been reported to induce disappearance of osteoclast-like multinuclear giant cells microscopically, as well as morphological changes including eggshell-like ossification and shrinkage of tumor (7,8). Akaike *et al.* (9) and Niu *et al.* (10) reported cases of soft-tissue recurrent GCTB treated surgically with the support of preoperative denosumab treatment, and they suggested that eggshell-like mineralization makes the surgical resection easier. Our present experience also indicates that preoperative denosumab treatment for a soft-tissue recurrence of GCTB is beneficial for a subsequent surgical resection by enabling the visualization of the recurrent lesion for patients in whom extraosseous recurrence is strongly suspected. The eggshell-like mineralization following preoperative denosumab treatment made the marginal resection easier, too. Although local recurrence of GCTB after three years from initial treatment is reported to be rare, late recurrence more than four years and malignant transformation more than ten years after treatment were reported (11). Therefore, a long-term, meticulous follow-up is essential.

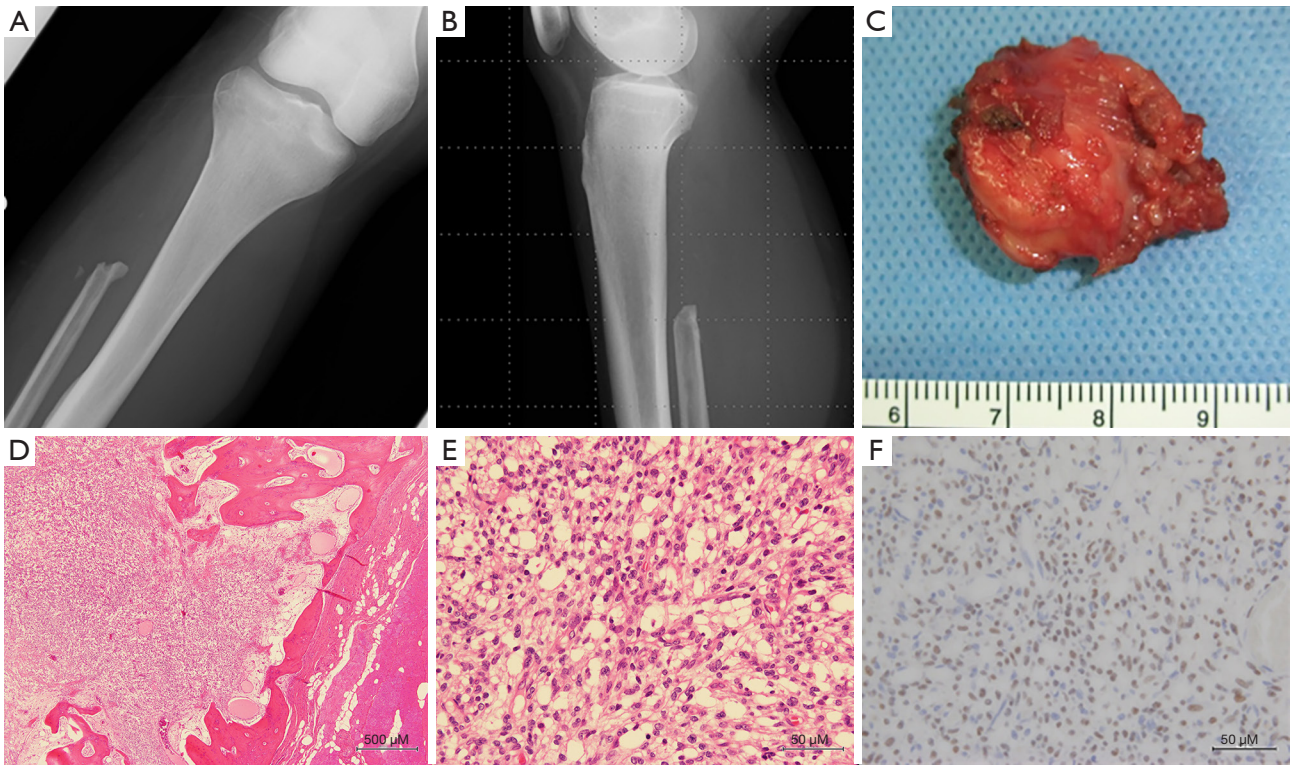

Figure 3 Plain anteroposterior (A) and lateral (B) radiographs taken after the second operation show no ossification lesion. The resected specimen as 28×23 mm^2 in size (C). Histopathological examination of the resected lesion showing peripheral bony shell surrounding the tumor tissue consisting of mononuclear neoplastic stromal cells and foamy cells (D, HE staining ×40, low-power field), but osteoclast-like multinuclear giant cells are absent (E, HE staining, high-power field). Mononuclear neoplastic stromal cells showing immunopositivity for H3.3 G34W (F, ×400, high-power field).

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1157). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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