Monostotic Fibrous Dysplasia in the Femur Strongly Expressing RANKL With Concomitant Osteoporotic Vertebral Compression Fracture: A Case Report

EDELYN S. AZURIN1,2, NORIO YAMAMOTO1, KATSUHIRO HAYASHI1, AKIHIKO TAKEUCHI1, SHINJI MIWA1, KENTARO IGARASHI1, TAKASHI HIGUCHI1, HIROTAKA YONEZAWA1, SEI MORINAGA1, YOHEI ASANO1, SHIRO SAITO1 and HIROYUKI TSUCHIYA1

1Department of Orthopaedic Surgery, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan; 2Department of Orthopaedics, Jose B. Lingad Memorial General Hospital, Pampanga, the Philippines

Abstract. Background/Aim: This study aimed to present a rare case of fibrous dysplasia (FD) in a healthy young adult man with a concomitant osteoporotic vertebral compression fracture. FD is a benign lesion of the bone characterized by replacement of the medullary component with fibro-osseous tissue that contains abnormally arranged trabeculae of immature woven bone. Recently it has been reported that several bone tumors including FD express the receptor activator of nuclear factor-kappa B (RANK) and its ligand (RANKL). Therefore, we hypothesized that FD contributed to osteoporosis, linked by the RANK-RANKL pathway of osteoclastogenesis. Case Report: We report the case of a healthy man with monostotic femoral fibrous dysplasia (FD) with concomitant 7th thoracic vertebra compression fracture due to osteoporosis [young adult mean (YAM) was 79% in bone mineral density (BMD)]. After curettage of the FD, artificial bone grafting in the cavity, and administration of alendronate sodium, BMD improved considerably within 9 months. FD is a benign bone condition in which abnormal fibrous tissue replaces normal bone. The axis of the receptor activator of nuclear factor-kappa B (RANK) and its ligand (RANKL) has been implicated in osteoporosis pathogenesis. RANKL immunohistochemical staining was performed, and strong staining of stromal cells was observed compared to other FD cases that showed weak to moderate staining. Conclusion: The presence of FD might have contributed to the low BMD due to the RANK-RANKL axis acting as osteoclastogenesis stimulator.

Fibrous dysplasia (FD) is a benign lesion of the bone characterized by replacement of the medullary component with fibro-osseous tissue that contains abnormally arranged trabeculae of immature woven bone. It may exist as an isolated lesion (monostotic form) or it may involve multiple skeletal sites (polyostotic form) (1-4). In monostotic FD, lesions are usually asymptomatic, and most are discovered incidentally on radiographs obtained for unrelated reasons (3, 4).

Osteoporosis is a systemic skeletal disease characterized by decreased bone mineral density (BMD), which leads to bone fragility and increased fracture risk (5, 6). It arises when bone resorption exceeds bone formation, causing destruction of bone tissue, leading to a fragile skeleton (7, 8). The receptor activator of nuclear factor-kappa B (RANK) and its ligand (RANKL) axis have been implicated in osteoporosis pathogenesis (8). RANKL is a potent stimulator of osteoclastogenesis and promotes osteoclast differentiation, leading to increased bone resorption (1-4, 9), and it has recently been reported to be expressed by several bone tumors (10).

We present a case of monostotic FD in the proximal femur with concomitant osteoporotic vertebral compression fracture. We hypothesized that the bone lesion contributed to osteoporosis, linked by the RANK-RANKL pathway of osteoclastogenesis. Therefore, we aimed to analyze RANKL expression through the immunohistochemical staining of
seven samples of histologically proven FD, including a sample taken from the patient described in this study.

**Case Report**

A 46-year old man was referred to our Institution because of an incidental finding of a well-defined osteosclerotic lesion in his right proximal femur. Three months prior to referral, he had experienced sudden back pain after carrying a miniature shrine during a festival. He consulted a local hospital and was diagnosed with a compression fracture of the 7th thoracic vertebra. Until the occurrence of this acute back pain, the patient was free of complaints and was active in daily living and work. The patient had no known comorbidities. His family history was unremarkable. He was a non-smoker and an occasional alcoholic beverage drinker. Apart from the clinical findings associated with vertebral fractures, the physical examination was unremarkable.

Computed tomography (CT) of the thoracic spine revealed a compression fracture at the level of the 7th thoracic vertebra (Figure 1a and b). Plain radiography showed a well-defined lytic lesion with a sclerotic rim (Figure 2a), without any periosteal reaction or cortical break at the right proximal femur. A united right clavicular fracture could be seen on plain chest radiography (Figure 2b). Magnetic resonance imaging of the right hip showed an isointense lesion spanning the femoral neck and proximal femur on a T1-weighted image (Figure 3a), a heterogeneous hyperintense lesion on a T2-weighted image (Figure 3b), and enhancement of the lesion on a contrast-enhanced image (Figure 3c). CT of the thoracic spine showed no abnormal findings or compression fractures (Figure 1a and b).

Bone scintigraphy showed high uptake at the fractured 7th thoracic vertebra and a united right clavicular fracture. It also showed a low uptake at the 11th thoracic vertebra for the minor compression fracture and at the right femoral neck for the osteosclerotic lesion (Figure 4a). A fluorodeoxyglucose-positron emission tomography/computed tomography (FDG PET/CT) scan revealed abnormally high FDG accumulation in the right thyroid gland (SUVmax=30.7), whereas weak FDG accumulation was observed in the 7th thoracic vertebra (SUVmax=4.3) and right proximal femur (SUVmax=3.8) (Figure 4b, c and d).

Bone densitometry revealed low BMD at the lumbar spine (0.942g/cm²), a T-score of -2.1, and a young adult mean (YAM) of 79%. In contrast, the left femur showed normal values and the right femur showed elevated values because of the presence of an osteosclerotic lesion. In light of these results, laboratory examinations were requested to rule out...
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Figure 2. Pelvic radiographs showing a well-defined lytic lesion with a peripheral sclerotic rim without any periosteal reaction or cortical break at the right proximal femur (a). United fracture of the right clavicle (white arrow) (b). Immediate post-operative radiographs showing internal fixation using a compression hip screw with a 135-degree 4-hole side plate and a 100 mm lag screw (c). Plain radiogram 60 months after showing no recurrence and a good incorporation of the grafted substitute (d).

Figure 3. Magnetic resonance imaging of the right hip. A T1-weighted image (TR 205 ms, TE 2.484 ms) showing an isointense lesion spanning the femoral neck and proximal femur (a), a T2-weighted image (TR 6816.67 ms, TE 107.436 ms) showing a heterogenous hyperintense lesion (b), and a contrast-enhanced image (TR 4.32 ms, TE 2.06 ms) showing an accumulation of contrast causing hyperintensity of the lesion (c).
the possibility of secondary causes that might be contributing to the low BMD of the patient.

Blood and biochemical test results (Table I) were normal, except for elevated levels of serum uric acid, elevated liver enzymes (AST, ALT, and γ-GTP), and thyroglobulin. Because of the abnormal FDG accumulation in the right thyroid gland (as shown by FDG-PET/CT) and elevated thyroglobulin levels, further investigations were warranted to rule out the possibility of malignancy. The patient underwent thyroid biopsy, revealing normal thyroid cells without any malignant cells, and was diagnosed with a benign thyroid lesion.

After exclusion of all possible secondary causes of osteoporosis based on radiologic and laboratory studies, the patient was diagnosed with primary idiopathic osteoporosis. He underwent an open biopsy of his right proximal femur, and the postoperative histopathological results concluded that the lesion was fibrous dysplasia (Figure 5a). The patient underwent another surgery with curettage, bone augmentation using a synthetic bone substitute (β-tricalcium phosphate: Osferion® Olympus, Tokyo, Japan), and internal fixation using a compression hip screw (JAPAN MDM, Tokyo, Japan) (Figure 2c). Postoperatively, the patient was started on alendronate sodium hydrate 35 mg/tablet, one tablet once a week, and vitamin D 1,000 mg/tablet, 1 tablet daily. Medical management was continued for 39 months. Conservative management through observation was performed for osteoporotic vertebral compression fractures (Figure 1c).

To evaluate RANKL expression in this case, we performed immunohistochemical staining and analysis. A rabbit polyclonal antibody raised against RANKL (1:200; ab9957; Abcam, Cambridge, UK) was used as the primary antibody. We used an anti-rabbit immunoglobulin G (IgG) conjugated with peroxidase-labeled polymers (EnVision, Dako, Carpinteria, CA, USA) as the secondary antibody. We included six specimens of histologically-proven FD to evaluate RANKL expression. Staining intensity was graded as weak, moderate, or strong (11). Strong RANKL

Figure 4. Bone scintigraphy. High uptake at the fractured 7th thoracic vertebra and united right clavicular fracture. Low uptake at the right femoral neck for the osteosclerotic lesion (a). FDG-PET/CT scan (b). High FDG accumulation in right thyroid gland with an SUVmax of 30.7 (c). Weak FDG accumulation in 7th thoracic vertebra with an SUVmax of 3.8 (d). Right proximal femur with an SUVmax of 3.8 (e).
expression was detected in this case (Figure 5b and c), whereas weak to moderate expression was observed in the other six cases (Figure 5d and e) (Table II). This study was approved by the Ethics Committee of the Kanazawa University Hospital (no. 3283) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient using the opt-out method.

The patient had an unremarkable postoperative follow-up. He continued to be asymptomatic with no evidence of recurrence at the right proximal femur (Figure 2d) and no further vertebral collapse on the latest imaging taken at 60 months after surgery. Continuous improvement of the patient’s BMD was also noted by serial bone densitometry (Table III), even after the discontinuation of bisphosphonates and vitamin D supplementation.

**Discussion**

Monostotic FD is a benign lesion in the bone that is usually asymptomatic and discovered incidentally on radiographs obtained for other reasons. The polyostotic form may also be accompanied by extra-skeletal abnormalities, such as single or multiple endocrinopathies and cutaneous hyperpigmentation (café-au-lait spots) in the classical triad of McCune–Albright syndrome. FD accounts for 2.5% to 7% of all benign bone tumors (4), and the monostotic form is more common and accounts for approximately 80% of patients with these bone lesions (3).

FD is caused by a mutation in the α-subunit of the stimulatory G protein (Gso), leading to excessive cyclic adenosine monophosphate (1-4). This mutation creates bone marrow stromal cells with an impaired capacity to differentiate into mature cells (3). Hence, the normal bone and bone marrow are replaced by disorganized fibro-osseous tissues (9).

Osteoporosis is a skeletal disorder characterized by decreased BMD, which leads to bone fragility and increased fracture risk (5, 6). It arises when bone resorption exceeds bone formation, causing the destruction of bone tissue and leading to a fragile skeleton (7, 8). In osteoporosis, the interaction of RANK and RANKL has been identified as the final common pathway through which bone resorption is regulated (8). RANKL is a potent stimulator of osteoclastogenesis that promotes osteoclast differentiation and leads to increased bone resorption (1, 9). In our case, because it is uncommon for a healthy young adult male to be diagnosed with osteoporosis, work-ups were performed and an osteosclerotic lesion was incidentally found in the right proximal femur. Because of the presence of this bone lesion, there was a need to analyze whether the two bone pathologies correlated with each other.

Laboratory tests were performed to determine the possibility of a systemic disorder or other bone-related diseases. Most of the laboratory test results were within normal levels, including those for bone metabolic markers. Although levels of serum uric acid and liver enzymes were elevated, they did not produce any derangement of bone density. The elevated thyroglobulin levels required further investigation because they were accompanied by high FDG accumulation in the right thyroid gland (as determined by an

### Table I. Blood biochemistry values.

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<tr>
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<th>Result</th>
<th>Reference interval</th>
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<tr>
<td>Hemoglobin</td>
<td>14.8 g/dl</td>
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<td>Hematocrit</td>
<td>43.7%</td>
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<td>WBC</td>
<td>6.45×10⁴</td>
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<td>Platelet</td>
<td>350×10⁴</td>
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<td>PT</td>
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<td>PT-INR</td>
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<td>APTT</td>
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<tr>
<td>CRP</td>
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<td>TRACP-5b</td>
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<td>SII-2R</td>
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<tr>
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<tr>
<td>Albumin</td>
<td>64.3%</td>
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</table>

WBC: white blood cell; PT: prothrombin time; PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; CRP: C-reactive protein; 1, 25 VD3: 1, 25 vitamin D3; BUN: blood urea nitrogen; UA: uric acid; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase; HbA1c: hemoglobin A1c; FBS: fasting blood sugar; Intact P1NP: intact amino-terminal propeptide of type I procollagen; TRACP-5b: tartrateresistant acid phosphatase-5b; SII-2R: soluble interleukin-2 receptor; FT3: free triiodothyronine 3; FT4: free triiodothyronine 4; TSH: thyroid stimulating hormone; PTH: parathyroid hormone; CK: creatine kinase; T-Bilirubin: total-bilirubin; D-Bilirubin: direct-bilirubin
FDG-PET/CT scan). It is vital to rule out the possibility that this was the primary cause of the bone abnormalities; hence, thyroid biopsy was performed and revealed benign findings. A previous study suggested that levels of male sex hormone should be determined because low testosterone levels can produce hypogonadism and cause secondary osteoporosis (5). Although we were not able to determine this, our patient did not present any signs or symptoms of hypogonadism during examination and system review, ruling it out as a probable cause.

Radiological studies showed no osteolytic lesions nor any aggressive features of the fractured 7th thoracic vertebra. A previous study suggested that biopsy is recommended for lesions that appear morphologically aggressive in radiologic studies (12), therefore biopsy of the spine was not considered. The patient bone densitometry results showed a YAM of 79% in the lumbar spine. In the Japanese 2011 guidelines for the prevention and treatment of osteoporosis, primary osteoporosis is diagnosed according to these criteria in the absence of diseases causing low bone mass or secondary osteoporosis: 1) fragility fracture (sites including the spine, proximal femur, and distal radius) is a nontraumatic bone fracture that is caused by a slight external force to a bone with low BMD (less than 80% of the YAM); and 2) BMD is less than 70% of YAM with evidence of radiographic osteopenia of the spine (13). The patient had normal laboratory results, no osteolytic lesion or aggressive features in his vertebra by radiologic studies, and a YAM of 79%; therefore, he fulfilled the first criteria for osteoporosis with a vertebral fracture. Overall, it was concluded that the vertebral compression fracture originated from primary osteoporosis.

It has been recently reported that RANKL is expressed in several bone tumors, proven by real-time PCR and immunohistochemistry (10), and that there is a 16-fold increase in serum RANKL levels in FD patients compared to healthy volunteers, which strongly correlate with the burden of the disease (9). However, this pathway has not yet been proven and fully understood in FD pathophysiology. It has also been reported that RANKL inhibition might be a therapeutic target of FD (9, 14), and the expression of RANKL in FD might influence the situation of osteoporosis, which caused a fragility fracture in our patient.

A study using alendronate sodium to manage osteoporosis concluded that administration of 75 mg once a week, 35 mg twice a week, and 10 mg daily for 24 months increased the BMD of the lumbar spine by 6.8%, 7.0%, and 7.4%, respectively, with the greatest gain occurring after 6 months of intake (15). In contrast, our patient was started postoperatively on alendronate 35 mg/tablet once a week, and his repeat bone densitometry after 9 months of intake showed an increase in BMD at the lumbar spine by 16.5% (from 0.942 g/cm² to 1.097 g/cm², T-score from -2.1 to -0.8, and YAM from 79% to 92%). This was a considerable increase compared to the alendronate study. We hypothesized that the surgery might have decreased the tumor burden, decreasing the possible increase of RANKL levels in our patient, which might have contributed to the primary osteoporosis.
The primary osteoporosis in our patient was linked to the FD lesion and, therefore, both disease entities can be linked to the RANK-RANKL axis. In this study, we performed RANKL immunohistochemical staining of seven specimens of histologically proven FD cases, including one taken from our patient. The results showed that our patient had strong staining of stromal cells for RANKL compared to the other cases. These results suggest that FD with high RANKL expression might induce osteoporosis. Although we were unable to prove that the patient had elevated serum RANKL levels, it was determined instead by the presence of strongly stained stromal cells for RANKL by immunohistochemistry.
Moreover, we did not perform BMD analysis except for in the case of our patient; therefore, the effect of the degree of RANKL expression on BMD has not been clarified. Further prospective and large-scale analyses are required.

In conclusion, we present a case of FD concomitant with primary osteoporosis, with all secondary causes of osteoporosis excluded. The patient drastically recovered after FD removal alendronate sodium administration; therefore, FD might have contributed to the low BMD of the patient due to the RANK-RANKL axis acting as a osteoclastogenesis stimulator.

Conflicts of Interest
The Authors declare that they have no conflicts of interest.

Authors’ Contributions
Conceptualization: Edelyn S. Azurin and Akihiko Takeuchi. Data curation: Akihiko Takeuchi, Katsuhito Hayashi, Shinji Miwa, Kentaro Igarashi, Takashi Higuchi, Hirotaka Yonezawa, Sei Morinaga, Yohei Asano, Shiro Saito. Investigation: Edelyn S. Azurin and Akihiko Takeuchi. Project administration: Akihiko Takeuchi. Writing – original draft: Edelyn S. Azurin and Akihiko Takeuchi. Writing – review and editing: Norio Yamamoto, Akihiko Takeuchi, and Hiroyuki Tsuchiya. All Authors approved the final version of the manuscript.

Acknowledgements
We would like to thank Editage (www.editage.com) for English language editing.

References

Received July 23, 2021
Revised October 17, 2021
Accepted October 18, 2021