INTRODUCTION

There are growing numbers of reports of atypical femoral fractures (AFFs) in the subtrochanteric or shaft region that are characterized by unique radiographic and clinical features that make them distinct from osteoporotic femoral fractures. AFFs are atraumatic or minimally traumatic, refractory, and often associated with prodromal symptoms, transverse or oblique fracture patterns, medial spiking, and focal cortical thickening (Table 1). We report a case in which a patient undergoing hemodialysis with a history of AFF developed a contralateral AFF after starting denosumab treatment.
On June 6, 2016, her walking cane slipped on the kitchen floor, and she fell down "after hearing a snapping sound.” She was transferred to our department, and radiographs taken on admission revealed a left AFF. After a period of time to wash out the oral anticoagulant clopidogrel sulfate that the patient was taking at the time of admission, intramedullary nail fixation was performed on June 15, 2016 under spinal anesthesia (Fig. 2). After the surgery, alendronate was replaced with calcitonin for the treatment of osteoporosis. On September 21, 2017, the patient started hemodialysis due to advanced kidney failure. Subsequently, she developed multiple compression fractures of the thoracolum-
bar spine, which led to the start of denosumab administration once every 6 months on January 12, 2018. Around July 2019, after 4 cycles of denosumab injections, she began to feel pain in her right femur for no explicit reason. On October 13, 2019, she was doing household chores in the garden, and as she was trying to turn around, she heard a "snapping sound" and fell to the ground. She was transferred to our department, and radiographs taken on admission revealed a right AFF. Bone turnover markers were normal: total procollagen I intact N-terminal propeptides of 319 ng/mL and tartrate-resistant acid phosphatase 5b of 127 mU/dL. The lumbar vertebrae (L2-L4) had a bone mineral density of 0.902 g/cm², which was 89% of the young adult mean. Because the patient had deep vein thrombosis, heparin-bridging therapy was conducted to substitute for clopidogrel sulfate. On October 30, 2019, intramedullary nail fixation was performed under spinal anesthesia (Fig. 3). Although the femoral pain dissipated nearly completely postoperatively, neither of the femoral fractures were fully healed, and the patient was on regular follow-up at the time of writing.

DISCUSSION

Based on the 2018 nation-wide registry survey by the Japanese Orthopaedic Association’s Osteoporosis Committee (Table 2), 116,453 patients aged 35 years or older had new cases of AFFs, with a rate of 0.49% relative to new cases of proximal femoral fractures. Of the patients with AFF who were newly registered in 2018, 21.5% had prodromal symptoms of dull or aching pain in the groin or thigh. Bisphosphonate use was reported in 58.5% of patients, of whom 78.2% had used bisphosphonate for 3 or more years. These statistics were similar from 2014 to 2018, although the use of anti-RANKL antibodies was reported in 6.9% of new cases of AFF registered in 2018, reflecting the growing popularity of this treatment in recent years. Bisphosphonates strongly inhibit bone resorption by inducing osteoclast apoptosis. However, this
eventually leads to low bone turnover and suppression of bone formation. Consequently, bisphosphonate therapy should be administered on a short-term basis (1 to 3 years), as longer durations may result in cumulative overdose. The therapeutic effects of the bisphosphonate alendronate persist for many years after treatment termination. Specifically, in women with osteoporosis who received alendronate daily for 5 years, bone mineral density at the lumbar spine and other regions remained significantly above the baseline levels 5 years after termination. Our patient had been on bisphosphonate therapy for approximately 3 years before experiencing the first left AFF. Although the patient had prodromal dull pain in the groin and thigh, the absence of radiographic abnormalities (X-ray and MRI) did not warrant precautionary measures for AFF, such as termination of bisphosphonate therapy. Although bisphosphonate therapy was discontinued after the left AFF, another antiosteoporotic agent (calcitonin) was initiated to treat the multiple spinal compression fractures that occurred after the start of hemodialysis for chronic renal failure. In a study of fractures in patients with dialytic and predialytic chronic kidney disease, 3-year cumulative risks of hip fracture (intertrochanteric and femoral neck) significantly increased in a graded manner for both sexes with an estimated glomerular filtration rate of <45 mL/min per 1.73 m². Interventions to prevent fracture in patients with chronic kidney disease should focus primarily on correcting mineral metabolism disturbances, and the use of antosteoporotic agents may be considered to address bone mass reduction. Most antosteoporotic drugs are contraindicated or should be administered with caution in patients with renal failure, and denosumab should be administered with monitoring for signs of hypocalcemia. Hypocalcemia can be more easily managed in patients with chronic kidney disease undergoing dialysis than in patients with predialytic chronic kidney disease due to dialytic correction of serum calcium levels and the ease of active vitamin D and calcium carbonate supplementation. Denosumab is a fully human monoclonal antibody against RANKL. By binding specifically to osteoblast-produced RANKL, this antosteoporotic agent prevents RANKL’s interaction with its receptor RANK, a key pathway in osteoclastic bone resorption, thereby helping to increase bone mineral density. Whereas bisphosphonates act primarily on mature osteoclasts, denosumab can affect both precursor and mature osteoclasts. Denosumab is administered subcutaneously once every six months, and therefore is associated with less patient adherence burden than conventional oral bisphosphonate therapies. Moreover, whereas bisphosphonates are renally cleared and consequently accumulate in patients with chronic renal failure, no dose adjustments are required for denosumab in patients with chronic renal disease because its pharmacokinetics...

| Table 2 | Results of Atypical Femoral Fracture Registry Survey by the Japanese Orthopaedic Association Osteoporosis Committee |
|---------|---------------------------------------------------------------------------------------------------------------|
| Year    | 2014       | 2015       | 2016       | 2017       | 2018       |
| No. of patients registered | 420        | 359        | 462        | 529        | 603        |
| No. of patients analyzed  | 406        | 352        | 448        | 505        | 574        |
| BPNs  | 259 (63.8%) | 234 (66.5%) | 292 (65.2%) | 332 (65.7%) | 336 (58.5%) |
| Anti-RANKL antibodies | 8 (2.0%)   | 13 (3.7%)  | 25 (5.6%)  | 26 (5.1%)  | 40 (6.9%)  |
| Corticosteroids   | 57 (14.0%) | 40 (11.4%) | 67 (14.9%) | 66 (13.1%) | 92 (16.0%) |
| PPIs   | 43 (10.5%) | 40 (11.4%) | 50 (11.2%) | 44 (8.7%)  | 67 (11.7%) |

BPNs, bisphosphonates; RANKL, receptor activator of nuclear factor kappa-B ligand; PPIs, proton pump inhibitors.
are not influenced by renal function\textsuperscript{5}.

AFFs often require a long recovery time. After intramedullary nail fixation, recovery of a femoral fracture typically takes approximately 3 months, whereas intramedullary nailing of AFFs requires a mean of 8.3 months\textsuperscript{5}. To prevent AFFs in patients receiving bisphosphonates, denosumab, and other bone resorption inhibitors, it is important to monitor for prodromal symptoms (e.g., thigh or groin pain) and radiographic lesions. Patients receiving bisphosphonate therapy for 3 years or more are at an elevated risk of AFF. Our patient experienced an AFF 1.5 years after starting denosumab therapy. For clinical management of denosumab-treated patients with an AFF, the diagnostic and treatment guidelines published by the Japanese Orthopaedic Association recommend diagnostic imaging of the contralateral femur, discontinuation of bone resorption inhibitor use, and calcium and vitamin D supplementation\textsuperscript{8}. In our case, the patient’s regular hemodialysis visits to our hospital provided many potential opportunities to monitor for clinical and imaging signs and prodromal symptoms of a contralateral AFF. However, the patient’s frequent complaints of malaise and discomfort after dialysis discouraged us from proposing additional medical procedures after 4-hour dialysis sessions. In our case, delayed union was noted after surgery of the right AFF, although the low-intensity pulsed ultrasound treatment, a procedure for accelerating fracture healing, was administered during postoperative hospitalization\textsuperscript{1}. A retrospective study reported that teriparatide decreased the mean postoperative time to AFF healing from 8.6 to 5.4 months and reduced the risk of delayed union and nonunion\textsuperscript{6}. Because teriparatide therapy requires careful consideration when administered to patients with chronic kidney disease, this option was not used in this case. This therapy may represent a viable option in future cases of AFF.

**CONCLUSIONS**

We reported a case in which a patient undergoing hemodialysis with a history of an AFF experienced a contralateral AFF after the start of denosumab therapy. Denosumab may be administered with caution for hypocalcemia in patients with chronic renal failure or dialysis. The decision to recommend this option to a patient should be based on careful assessments of its risks and benefits, and administration of this agent should be accompanied by frequent follow-up, particularly in patients with a history of an AFF.

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(和文抄録)

デノスマブ投与後の比較的早期に非定型大腿骨骨折を生じた1例

末 永 英 慈・住 吉 康 之・高 田 真 一

血液透析患者へのデノスマブ治療中、比較的早期に非定型大腿骨骨折を生じた1例を経験した。75歳女性、60歳時に重症筋無力症と診断され、以降ステロイドを使用している。2013年よりアレンドロン酸内服を開始したが、2016年6月左非定型大腿骨骨折を生じ、骨接合術を行った。アレンドロン酸投与は中止した。2017年腎機能悪化のため、血液透析導入。胸腰椎の多発圧迫骨折を生じたため2018年1月よりデノスマブ投与を開始したところ、2019年7月より誘因なく右大腿痛出現。2019年10月右非定型大腿骨骨折を生じたため、骨接合術を行った。腎不全時は骨粗鬆薬のほとんどが禁忌もしくは慎重投与となっているが、デノスマブは低カルシウム血症に注意をしながら投与可能とされる。非定型大腿骨骨折の既往がある場合は、使用に際し十分な検討および慎重な経過観察が必要と思われた。