

Case Report

Paget's sarcoma with sarcoma-specific TP53 mutation arising from a Japanese patient

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Abstract: A 71-year-old woman visited our hospital with a feeling of dullness in her left hip joint in March 2012. A plain radiography of her left femur showed irregularly increased density with interspersed radiolucent areas at the left proximal femur. The cortex of the left femur was enlarged. The patient was diagnosed with Paget's disease. She was treated with bisphosphonates (35 mg/week alendronic acid), and the level of alkaline phosphatase (ALP) in her serum gradually improved to within normal levels. A malignant tumor arising from Paget's disease was suspected in September 2014; an increase in serum ALP levels coincided with the malignant transformation. A biopsy of the left distal femur revealed Paget's osteosarcoma. After chemotherapy, the patient underwent a total resection of the left femur; it was replaced with an artificial femur. The surgical specimen was composed of pleomorphic tumor cells with tumor osteoid in the background of the Pagetic bone. Focal tumor necrosis was observed. After surgery, serum ALP levels returned to within normal levels. Furthermore, the patient underwent partial lobectomies for 4 metastatic lung lesions that had been gradually increasing in size over the 9 months following the total femoral replacement. Because of its rarity in Japan, the contribution of *SQSTM1* mutations to Paget's disease in Japanese patients remains unclear. Molecular testing revealed that this case did not contain a somatic *SQSTM1* mutation, but there was a sarcoma component-restricted *TP53* mutation, suggesting a significant role for *TP53* in the malignant transformation of Paget's disease.

Keywords: Paget's disease, sarcoma, TP53

Introduction

Paget's disease is a chronic condition, characterized by disorder of the bone remodeling process, resulting in enlarged and hypertrophic deformed bones. The prevalence of this sporadic disease depends on patient age and country. Paget's disease is frequently found in Europe, the United States, Australia, and New Zealand, but is extremely rare in Asia and Africa [1]. The incidence in Japan is reported to be 4.1 cases per million [2]. Pagetic bone lesions can occur at any skeletal site, and they are polyostotic in approximately 70% of cases. The majority of monostotic skeletal manifestations have been reported in the ilium, followed by the spine and the femur [3]. The incidence of osteosarcomatous transformation in Paget's disease is estimated to be approximately 1% and is most common in patients with polyostotic dis-

ease. It is predominant in men and the peak incidence occurs in the seventh decade of life [3]. This incidence represents an increase in risk that is several thousand-fold greater than that of the general population. Osteosarcoma in Paget's disease accounts for 50% of osteosarcoma cases in patients over 60 years of age.

Although the precise pathophysiology of Paget's disease still remains to be established, mutations in *SQSTM1* on chromosome 5q35, which encodes the p62 protein, has been identified in approximately half of all Paget's disease cases [4, 5]. The most commonly found mutation, C1215T, causes an amino acid substitution of proline [6] to leucine [7] at codon 392 (p62 P392L) and is found in 10% of sporadic, and 30% of familial, Paget's disease cases [4, 5]. Rare syndromes containing Paget's disease can also be caused by mutations in *TNFRSF11A*

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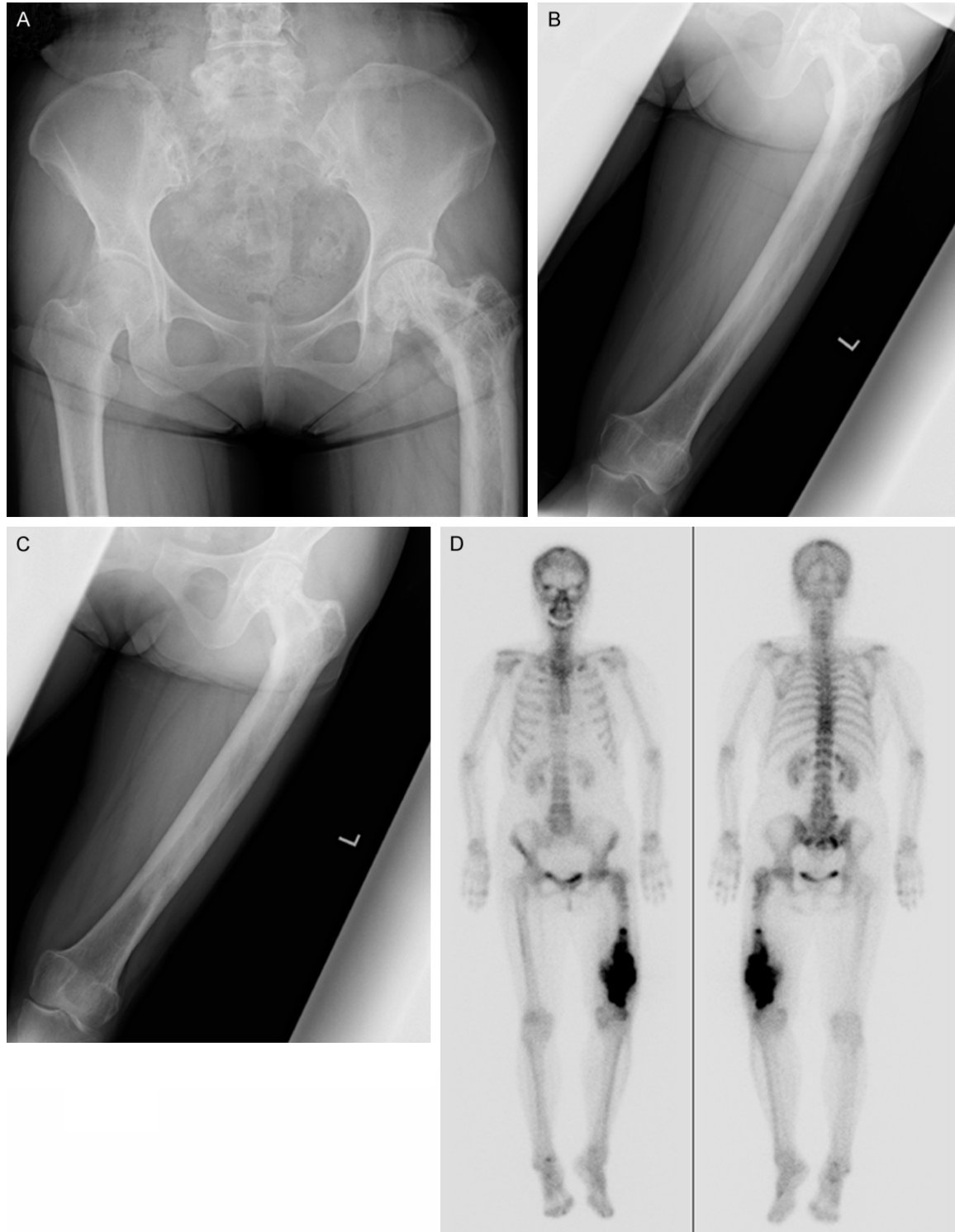


Figure 1. (A) Anterior-posterior view of plain radiograph of both hips taken in March 2012 showing a hypertrophic lesion in the right proximal femur. Anterior-posterior view of plain radiographs of the left femur taken in December 2012 (B) and December 2013 (C) did not indicate any significant sign of tumor. (D) A technetium-99m bone scintigraphy taken in October 2014 revealing strong uptake at the left distal femur suggesting a Paget's sarcoma arising from monostotic Paget's disease.

on chromosome 18q21, which encodes RANK [8], and *TNFRSF11B* on chromosome 8q24,

which encodes osteoprotegerin [9]. Other possible causes of Paget's disease include chronic

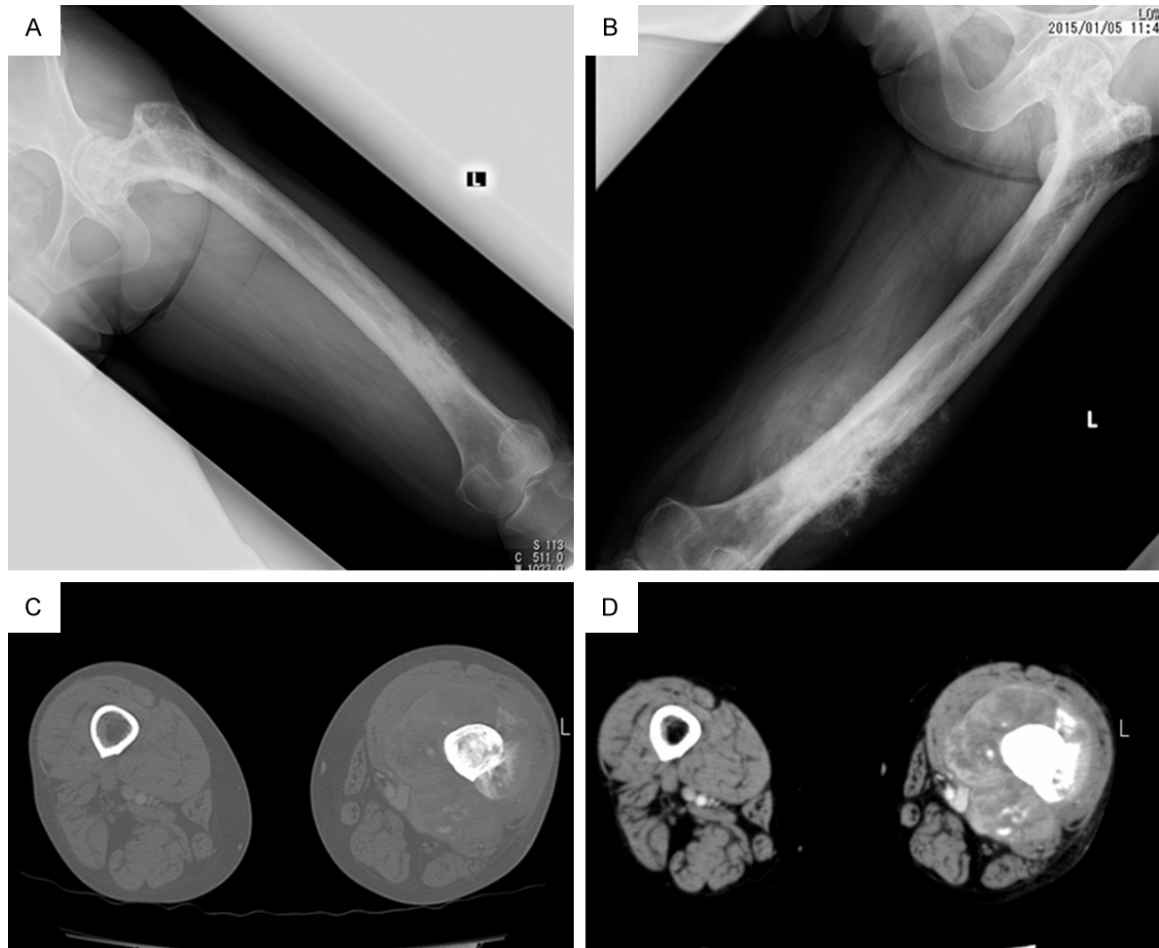


Figure 2. Anterior-posterior view of plain radiograph taken (A) before and (B) after chemotherapy. Spicular formation is clearer after chemotherapy, suggesting progressive disease. (C, D) Computed tomography (CT) scans revealing a bone tumor with calcification extending into the soft tissue.

viral infections, such as the measles virus, as nuclear inclusions of viral components have been observed in osteoclasts from affected patients [7].

We experienced a case of osteosarcoma arising from sporadic monostotic Paget's disease. Because of its rarity in Japan, the contribution of *SQSTM1* mutations in Japanese Paget's disease patients remains unclear. This case did not contain a somatic *SQSTM1* mutation. However, a sarcoma component-restricted *TP53* mutation was present, suggesting a significant role for *TP53* in the malignant transformation of Paget's disease.

Case report

Clinical course

A 71-year-old woman visited our hospital with a feeling of dullness in her left hip joint in March

2012. A plain radiography of her left femur showed irregularly increased density with interspersed radiolucent areas in the left distal femur (**Figure 1A**). The cortex of the left femur was enlarged. She was treated with bisphosphonates (35 mg/week alendronic acid) under the diagnosis of Paget's disease, and the level of alkaline phosphatase (ALP) gradually improved to within normal levels. She was followed up once a year (**Figure 1B, 1C**). In September 2014, she felt an increased dullness and pain in the distal left femur. A bone scintigraphy with technetium-99m revealed strong uptake only at the left distal femur (**Figure 1D**). A plain radiography of her left femur showed an ill-defined calcified lesion extending from the diaphysis to the distal metaphysis; periosteal spicules were also observed (**Figure 2A**). Computed tomography (CT) and magnetic resonance imaging revealed a mass extending into the soft tissue. The level

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Figure 3. (A) The resected total femur shows a mass involving the middle to distal portion of the left femur with soft tissue invasion. The cut surface shows a large yellow to white colored tumor at the distal femur involving the surrounding soft tissue (B).

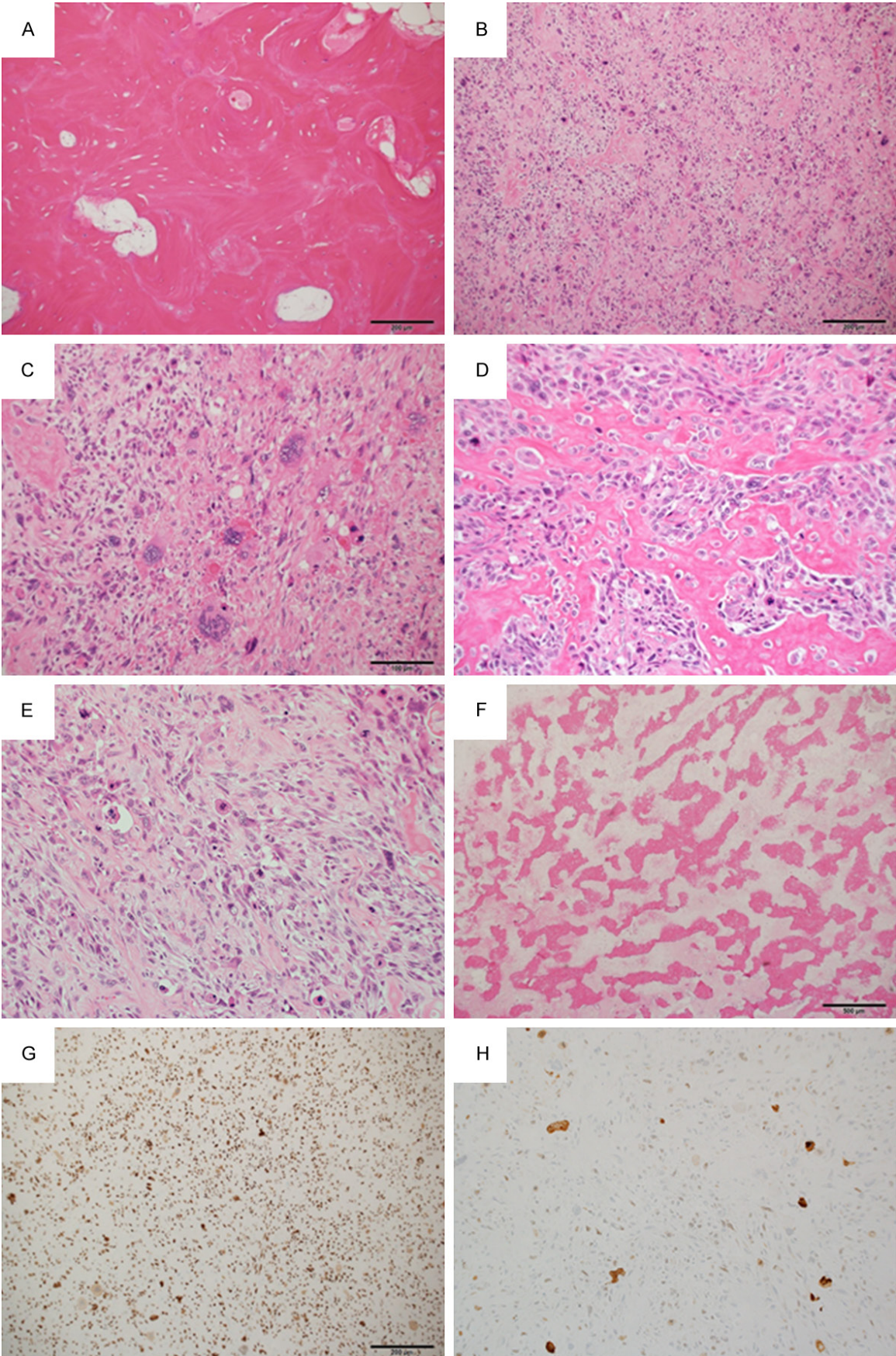
of serum ALP was above the normal level, despite the bisphosphonate treatment.

We performed an incisional biopsy. Histological examination revealed that the specimen was obtained from a transitional area and it showed tumor cell invasion into the Pagetic bone. The tumor was comprised of proliferation of high-grade sarcomatous cells within the irregular dense bone trabeculae; in another area, highly pleomorphic cells had proliferated in the collagenous stroma with less trabecular bone. Part of the bone marrow had also been replaced with fibrovascular connective tissue, leading to the diagnosis of osteosarcoma arising from Paget's disease in the sclerotic phase. The patient received chemotherapy consisting of ifosfamide, cisplatin, and doxorubicin. A plain radiography and CT scan after chemotherapy revealed an ill-defined calcified lesion at the left distal femur with an extra-osseous calcified lesion (Figure 2B-D), identified as progressive disease.

Pathology and molecular testing of surgical specimens

After 2 courses of chemotherapy, the patient underwent a total resection of the left femur, including replacement with an artificial femur. The gross specimen revealed thickening of the cortex (Figure 3A). The cut surface showed coarse medullary bone and thickening of the cortex. The tumor involved the distal portion of the left femur, penetrated the cortex, and invaded into the surrounding soft tissue (Figure 3B). Histologically, the mosaic pattern of the dense trabeculae was prominent in the proximal portion of the left femur, consistent with the sclerotic phase of Paget's disease (Figure 4A). At the distal portion of the left femur, the pleomorphic tumor cells with hyperchromatic nuclei had proliferated with the tumor osteoid formation (Figure 4B-D). Mitotic figures were frequently seen (Figure 4E). Regarding the chemotherapeutic effect, focal necrosis was observed within the tumor, however, most tumor

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Figure 4. Pathology of the resected tumor. (A) The proximal portion of the left femur shows a mosaic pattern of thickened bone trabeculae. The tumor at the distal femur is composed of a proliferation of pleomorphic tumor cells (B) with scattered tumor giant cells (C). (D) Tumor osteoid formation is also present. (E) Mitotic figures are frequently seen. (F) Tumor necrosis is focally observed. Immunohistochemistry shows that (G) the tumor cells were diffusely positive for p53 and (H) the Ki-67 labeling index was approximately 20% (H).

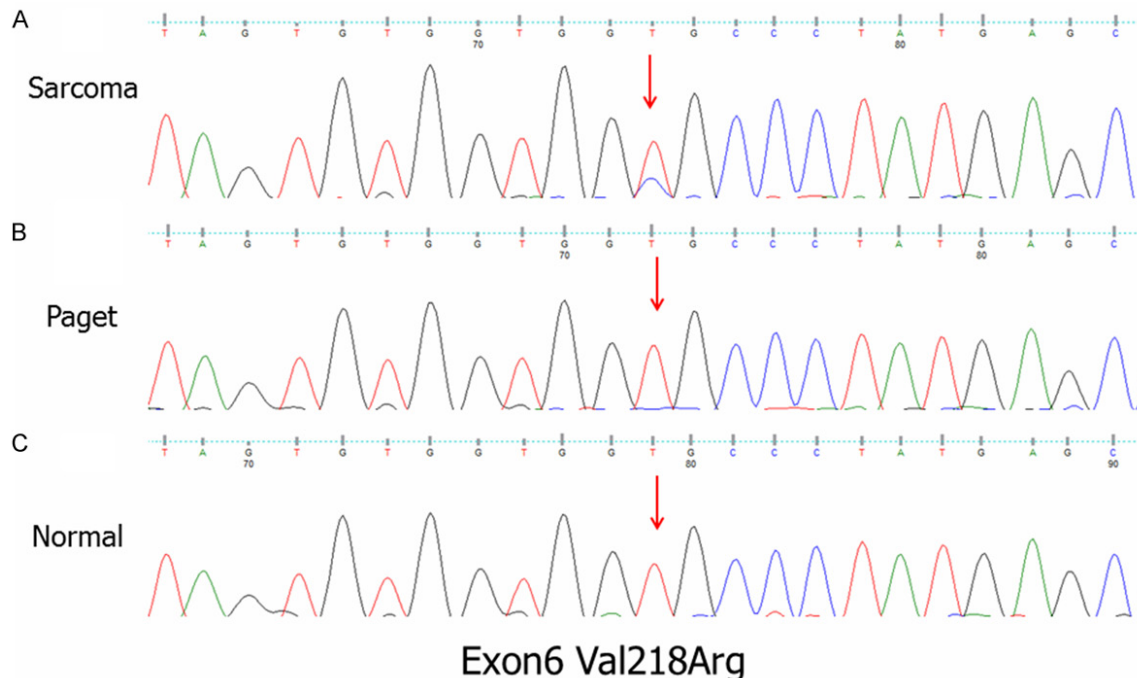


Figure 5. Molecular testing shows a sarcoma component-specific *TP53* mutation. (A) Sarcoma component-derived DNA, (B) Pagetic bone-derived DNA and (C) normal tissue-derived DNA.

cells (>80%) were viable, with no signs of degenerative change (Figure 4F). Immunohistochemically, the tumor cells were diffusely positive for p53, and the MIB-1 labeling index was approximately 15% (Figure 4G, 4H). Molecular testing did not detect any somatic mutation of *SQSTM1*. However, an osteosarcoma component-restricted specific *TP53* mutation was observed (Figure 5A-C). Thus, we histologically diagnosed the lesion as an osteosarcoma arising from Paget's disease. The level of ALP decreased to within the normal range after surgery.

Furthermore, the patient underwent partial lobectomies for 4 metastatic lesions 9 months after the total femoral replacement because these potentially metastatic lesions had been gradually increasing in size (Figure 6A). The lung lesions were histologically confirmed as metastases of the osteosarcoma (Figure 6B-F).

Discussion

We experienced a case of sarcomatous transformation of Paget's disease during the follow-up period. Bone scans have been shown to be more sensitive than radiography in detecting Paget's disease and for the evaluation of monostotic or polyostotic involvement [10]. The bone scintigraphy taken after the diagnosis of Paget's sarcoma revealed a hot spot in the left distal femur only, suggesting that malignant transformation occurred in monostotic Paget's disease. Detection and identification of malignant transformation of Paget's disease during the follow up period is difficult, especially if patients are asymptomatic. Lytic change in the sclerotic Pagetic bone on a plain radiograph is a sign of malignant transformation [11, 12]. Another possible tumor sign in a patient with Paget's disease is pain in a previously painless area. Serum ALP levels have been shown to decline compared with the levels of other meta-

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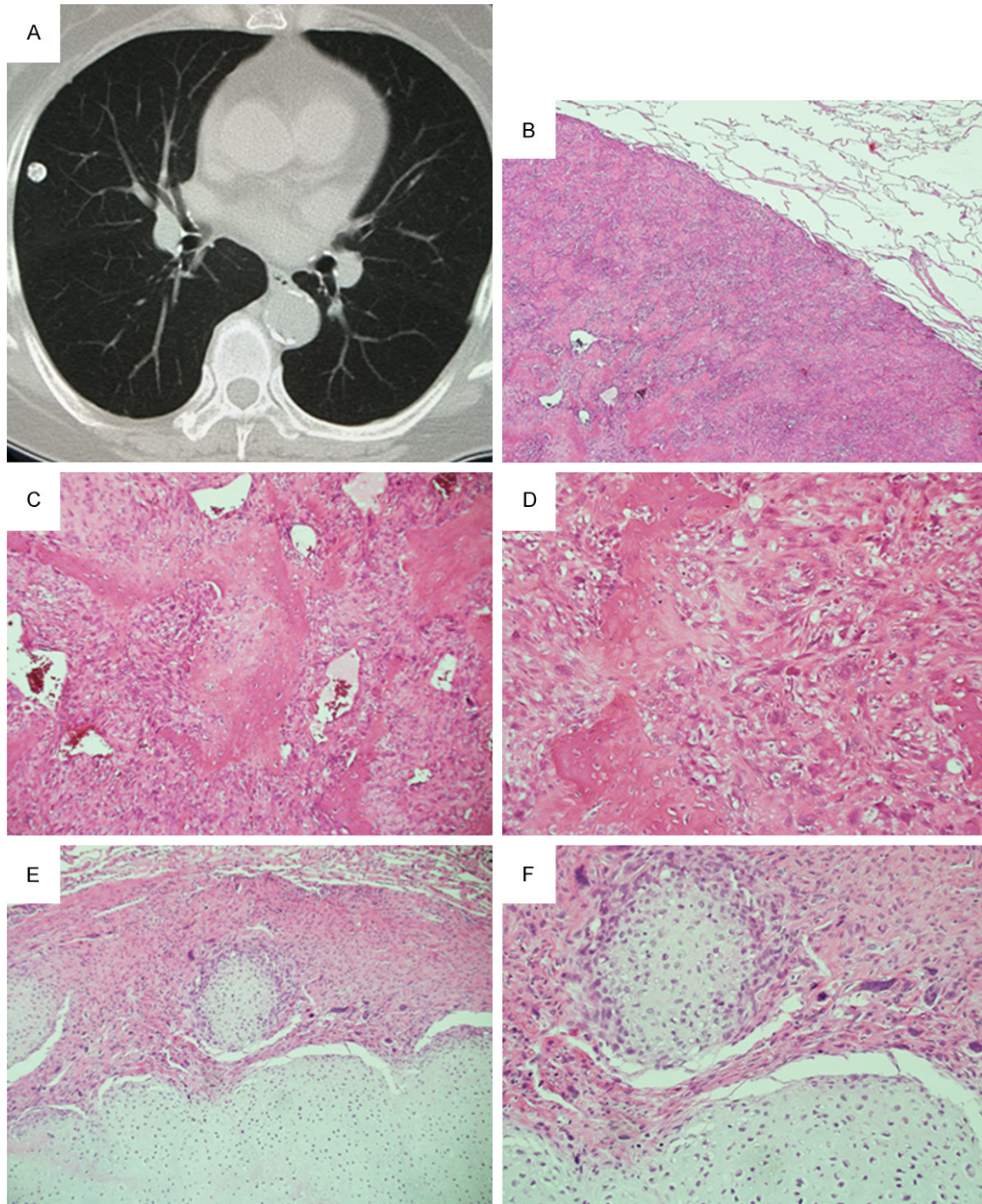


Figure 6. (A) Chest CT shows a nodule with calcification on the right lung. (B-D) The pathology of the resected lung tumors reveals a proliferation of highly pleomorphic cells with massive osteoid formation (B-D). (E, F) Another metastatic nodule predominantly composed of atypical chondroid cells.

bolic bone markers when Paget's disease is treated with bisphosphonates [6]. The elevation of serum ALP has been demonstrated in malignant tumors arising from Paget's disease [11]. However, patients with Paget's disease

may have recently been treated with bisphosphonates [13], similar to the patient in this report; therefore, serum ALP levels may not accurately reflect malignant changes in this disease. In the current case, the serum ALP level

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was slightly higher than normal prior to the surgery, although it decreased to normal levels after the surgery. In addition, it is important for clinicians to recognize the phase in which malignant tumors can arise in Paget's disease. A previous study of 8 Paget's sarcomas demonstrated that 4 sarcomas occurred during the mixed phase and 4 occurred during the sclerotic (blastic) phase [11]. In our case, osteosarcoma occurred during the sclerotic phase.

One study reported that the mean age of patients with p53-positive osteosarcoma was higher than that of patients with p53-negative osteosarcoma, and that 3 out of 4 cases of osteosarcoma arising in Paget's disease showed a p53 accumulation [14]. The impact of *TP53* mutations on the malignant transformation have been reported in various tumors of bone and soft tissue [15, 16], however, the mutation status of *TP53* in Paget's sarcoma has not been described so far. To the best of our knowledge, our finding of a *TP53* mutation in only the osteosarcoma component is the first reported case of its kind. This report suggests a significant role for this *TP53* mutation in the malignant transformation of Paget's disease.

The prognosis of patients with sarcoma arising from Paget's disease is extremely poor and the 5-year survival rates range from 0 to 15% [17-22]; in the most recent study, the survival rate was reported to be approximately 10% [23]. A survival of more than 10 years has been described in a patient with Paget's disease with lymphoma [11]. In the current case, the localized tumor in the distal femur was controlled by the total femoral replacement with arthroplasty, although the patient had multiple lung metastases that were also successfully treated with surgery.

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Disclosure of conflict of interest

None.

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