

# Multimodal imaging diagnosis for bone fibrous dysplasia malignant transformation: A case report

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**Abstract.** Fibrous dysplasia of bone (FDB) is a rare benign condition in which fibrous tissue replaces normal bone architecture. FDB rarely undergoes malignant transformation, but there are reports of locally aggressive fibrous dysplasia with cortical destruction and soft tissue extension. Diagnosis of FDB malignant transformation is not easy, especially in monostotic form, because of the overlap in imaging features of locally aggressive fibrous dysplasia and fibrous dysplasia with malignant transformation. The present case study reports a rare case of FDB in a 23-year-old man with polyostotic fibrous dysplasia arising in the left side of the pelvis and lower limb bones with partial transformation to fibrosarcoma. This study explored the multimodal imaging features of FDB malignant transformation, to achieve early detection and improve diagnostic accuracy of local FDB aggressiveness and its malignant transformation.

## Introduction

Fibrous dysplasia of bone (FDB) is a non-malignant fibro-osseous lesion that accounts for 5-7% of all benign bone tumors (1), with a low malignant transformation or local aggressive form rate (2,3). FDB may involve single bone (monostotic disease) or multiple bones (polyostotic disease) (3,4). The main pathological changes of FDB are that normal bone architecture and bone marrow are replaced by a large amount of proliferative fibrous tissue, in which there are ill-structured trabeculae (5). A variety of causative factors, including repeated surgical treatment, artificial limb implantation and radiotherapy, are potential factors to stimulate the malignant transformation of FDB (6,7). The age of the patient is another factor that also

correlates to sarcomatous transformation (8). Poorly defined margins, cortical destruction and soft tissue involvement are features on imaging of malignant transformation; however, these features overlap with those of locally aggressive FDB (2,3). Therefore, the diagnosis of malignant transformation of FDB is a clinical challenge. However, the prognosis of patients with FDB malignant transformation is poor as, even if they receive preoperative and/or postoperative chemotherapy and subsequent extensive resection, distant metastasis and death are inevitable (9). Osteosarcoma accounts for more than half of all the malignant transformations of FDB, followed by fibrosarcoma and chondrosarcoma, secondary angiosarcomas and malignant fibrous histiocytoma (4,10). The present case study describes a rare case of FDB that was associated with malignant sarcomatous transformation.

## Case presentation

**Presentation.** A 23-year-old man was referred to the Department of Orthopedics, The Third Affiliated Hospital of Guangzhou Medical University in May 2018 with persistent pain in the left hip for 6 months that had been aggravated for 1 week.

**History of present illness.** The present patient presented with persistent pain in the left hip without obvious inducement that started 6 months before the hospital visit. The pain was obvious in squatting and standing up. The patient was initially admitted to a local hospital, where an X-ray and MRI investigation showed a central intramedullary expansile lytic lesion with a wide zone of transition at the proximal metadiaphysis of the left femur, but the clinical diagnosis was inconclusive, and the patient did not receive any special treatment. On 14 May 2018, the patient was referred to the Department of Orthopedics, the Third Affiliated Hospital of Guangzhou Medical University for further diagnostics and treatment for aggravated pain in the left hip. After admission, multimodal imaging including X-ray, CT, MRI and Technetium 99m-methyl diphosphonate (<sup>99m</sup>Tc-MDP) three-phase bone imaging were performed. It was agreed that these images were consistent with FDB with malignant transformation after a multidisciplinary team discussion. To make a definite diagnosis, the patient underwent a left femur biopsy 4 days after referral to hospital, followed by left femur surgical biopsy and a left tibia percutaneous

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biopsy 10 days later. The pathological analysis showed that the lesions were consistent with malignant mesenchymal tumors of the left femur and it was concluded that they were malignant fibrous histiocytoma of the bone and osteofibrosarcoma. The patient underwent chemotherapy, left femur tumor segment resection and hip joint replacement on 39 days after referral to our hospital. The surgical and postoperative pathological findings confirmed fibrosarcoma of the bone with extraosseous soft tissue involvement.

*History of past illness.* The patient had no relevant previous medical history, such as trauma, falls or tumors.

*Personal and family history.* The patient had no tumor-related family history. The patient had no history of contact with carcinogenic chemical, radioactive or toxic substances, and no history of drug abuse, smoking and drinking.

*Physical examination.* There was no obvious deformity of the left thigh and hip, and no obvious skin redness, swelling and ulceration. Local skin temperature did not increase and the patient had good skin sensation, but obvious local tenderness in the left hip, and longitudinal percussion pain in the left lower limb.

*Laboratory examinations.* Laboratory tests revealed alkaline phosphatase 239 U/l (reference range, 45-125 U/l), erythrocyte sedimentation rate 68 mm/h (reference range, <15 mm/h), C-reactive protein 135.3 ng/l (reference range, <10 ng/l), total neutrophil count  $7.74 \times 10^9/l$  (reference range,  $2.0-6.9 \times 10^9/l$ ) and neutrophil ratio 82.2% (reference range, 37.0-80.0%).

*Imaging and histological examinations.* X-ray and CT of the left femur showed abnormal density of the left femur and the bone marrow cavity of the left hip, upper tibia and sacrum, and bone destruction of the anteromedial cortex of the left femur and formation of surrounding soft tissue masses (Fig. 1A-C). The possibility of malignancy was considered. MRI showed multiple bone destruction areas occupying most of the space of the marrow cavity with hypointensity on T1-weight imaging (T1WI), heterogeneous enhancement on contrast-enhanced T1WI, heterogeneous iso- and hyper-intensity on T2WI, and heterogeneous signal intensity on T2-weight spectral attenuated inversion recovery (T2W-SPAIR).

These features indicated local bone destruction, swelling of surrounding soft tissue and soft tissue invasion (Fig. 2A and B). In the upper left femur, an irregular mass was seen in front of the upper left femur, which broke through the cortex and protruded into the surrounding soft tissue (Fig. 2C).  $^{99m}\text{Tc}$ -MDP three-phase bone imaging was recommended to confirm the blood supply and abnormal uptake of  $^{99m}\text{Tc}$ -MDP. The areas of bone and marrow surrounding the greater trochanter and the neck of the left femur showed increased blood perfusion on the perfusion and blood pool phase, while bone marrow destruction areas in MRI showed higher amounts of blood perfusion in the upper femur (below the greater trochanter) (Fig. 3A and B). However, the levels of tracer uptake of the two areas were reversed in the delayed phase and were clearer on tomography. The other tracer uptake lesions in the left pelvic and lower limb bone

corresponded to an ill-defined radiolucent lesion on X-ray (Fig. 3C and D).

After discussion, it was agreed that this was consistent with malignant mesenchymal tumors. To obtain a definite diagnosis, the patient underwent left femoral and tibial percutaneous biopsy (Fig. 4) and left femoral surgical biopsy (Fig. 5). The pathological analysis (Fig. 5) showed that the lesions were consistent with malignant mesenchymal tumors of the left femur and concluded that they were malignant fibrous histiocytoma of the bone and osteofibrosarcoma. Postoperative histological examination (Fig. 6) confirmed bone tumor tissue and a distal femoral medullary cavity consistent with fibrosarcoma.

*Final diagnosis.* The final diagnosis was made following biopsy and segmental resection, based on a histopathological examination of the resected tumor. The left femur tumor, which destroyed the diaphysis and invaded the soft tissue outside the bone, was confirmed to be osteofibrosarcoma (Figs. 5B and 6). The tumor tissue in the left upper-middle tibia was consistent with fibrous dysplasia without malignant transformation (Fig. 5C and D).

*Treatment and follow-up.* After the final diagnosis, the patient received chemotherapy with epirubicin 50 mg + vincristine 2 mg + methotrexate 10 g, and the process was successful. Subsequently, 2 weeks later (22 June 2018), left femur tumor segment resection and hip replacement were performed (Fig. 7A), and postoperative histological examination confirmed that the bone tumor tissue and distal femoral medullary cavity were consistent with fibrosarcoma. In September 2018, ~3 months after the operation, a surgical biopsy was performed on a mass resected from the surface of the left thigh because of suspicion of local tumor recurrence (Fig. 7B and C). Pathological examination showed recurrence of the left femur fibrosarcoma, and surgical resection and symptomatic treatment were performed again. In March 2019, another operation of the left hip disarticulation was scheduled for tumor resection following further local recurrence. The operation was successful without obvious postoperative acute complications.

*Outcome.* The last operation was performed in March 2019. Subsequently, 1 month later, the condition of the patient deteriorated and the patient died of cachexia caused by extensive metastasis in April 2019.

## Discussion

FDB is commonly found in long bones (proximal femur and tibia), and can be divided into single or multiple bone types (11). It is mostly confined to one limb, but other anatomical sites, such as the jaws, craniofacial bones and sacrum can be also involved (12-14). In the early stage of FDB, patients present with no symptoms, but local aggression to the periosteum or increased bone marrow pressure can cause discomfort, bone pain and movement disorders. Serious cases can lead to stress fracture or pathological fracture (15). When localized osteolytic destruction, soft tissue extension, sudden aggravation of pain or pathological fractures are found, the possibility



Figure 1. X-ray and CT of fibrous dysplasia of bone with malignant transformation. (A) X-ray and (B) bone window CT images showed low-density areas of multiple bone destruction and ground-glass high density in the left hip and upper femur bone marrow cavity. (C) Venous phase (a phase of contrast-enhanced CT) of soft tissue window of the left femur shows destruction of cortical bone with formation of soft tissue masses around the left upper medial femur with heterogeneous enhancement.



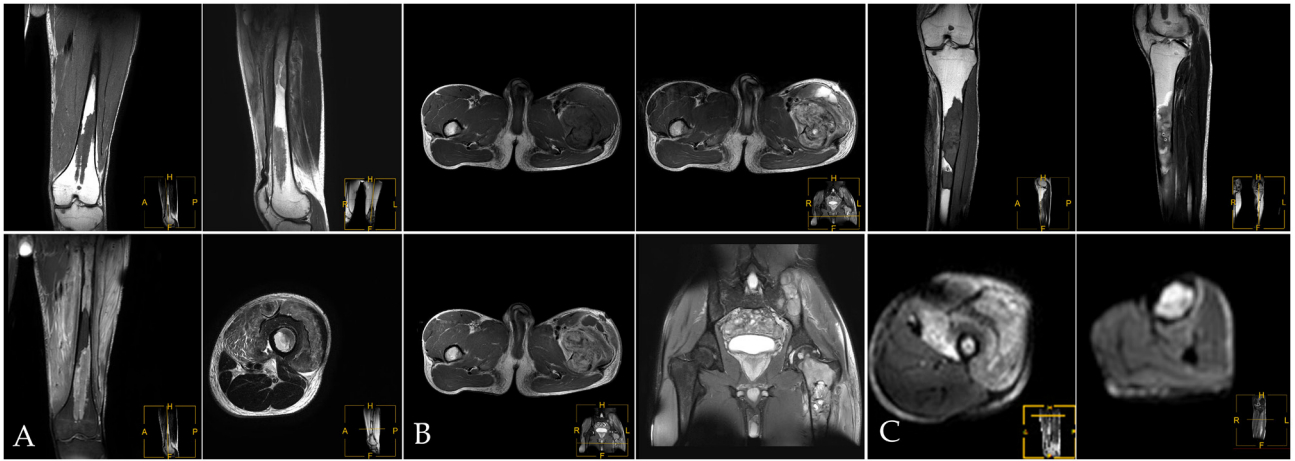


Figure 2. MRI of fibrous dysplasia of bone with malignant transformation. (A and B) Axial T1WI and T2WI and contrast-enhanced coronal T1WI showed destruction of the upper part of the left femur and an irregular soft tissue mass, with hypointensity on T1WI, heterogeneous iso- and hyper-intensity on T2WI, heterogeneous enhancement contrast-enhanced T1WI and heterogeneous signal intensity on T2W-SPAIR. (C) Diffusion of the lesion was limited. The left femur, tibial medullary cavity shows multiple of circular, flaky bone destruction. Diffusion-weighted imaging showed heperintensity. T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; T2W-SPAIR, T2-weight spectral attenuated inversion recovery.

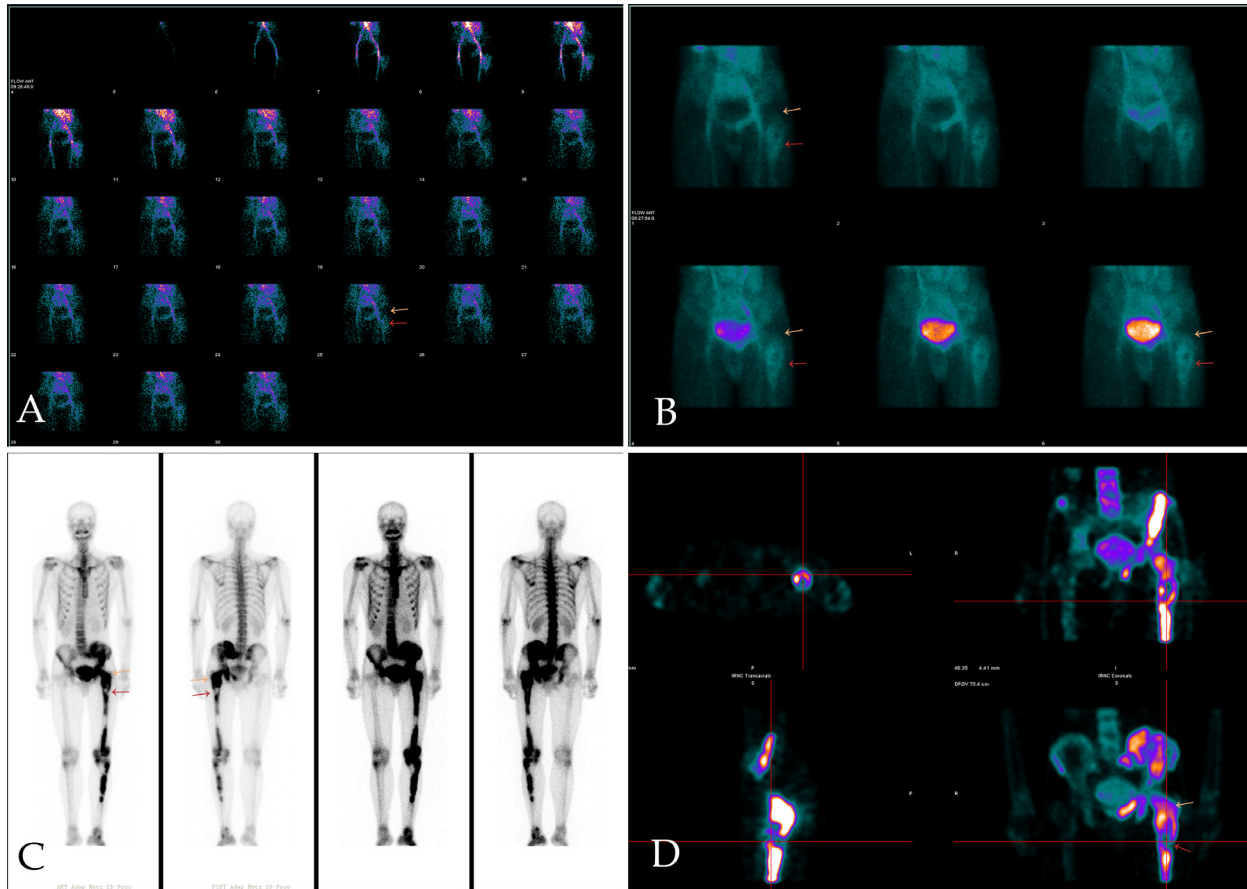


Figure 3.  $^{99m}\text{Tc}$ -MDP three-phase bone imaging of fibrous dysplasia of bone with malignant transformation. (A) Blood perfusion phase showed abnormal high blood perfusion in the right thigh. (B) Blood pool phase showed abnormal radiotracer concentration in the corresponding area of the soft tissue. (C) Whole body bone imaging and (D) tomography showed extensive abnormal concentration of radioactivity in the left pelvis (ilium, pubic bone and ischium) and left lower limb (femur and tibia). By contrast, bone and marrow around the greater trochanter (yellow arrow, about the same height as the bladder) showed less blood perfusion on the perfusion phase but more tracer uptake on the delayed phase, and the opposite is true for the lesion below the greater trochanter (red arrow).

of malignant transformation should be suspected (15,16). However, the treatment and prognosis of malignant transformation are markedly different from locally aggressive FDB.

In the present case, the lesions in the left limb were polyostotic and extensive, including the tibia and femur, and involved the ipsilateral pelvis, with further extrasosseous tissue invasion.



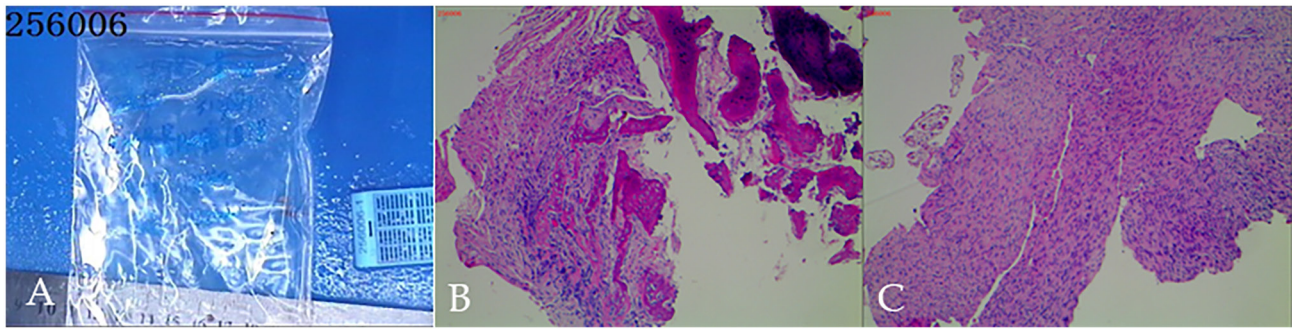


Figure 4. Pathology examination for left femoral percutaneous biopsy. (A) Left femur bone biopsy. The formation of necrotic bone was observed. The fibrous tissue in the residual bone tissue showed signs of proliferation, which was consistent with fibrous dysplasia. No atypia or mitotic figures were seen in the specimens. (B and C) The possibility of malignant transformation could not be excluded (H&E staining; magnification, x100).

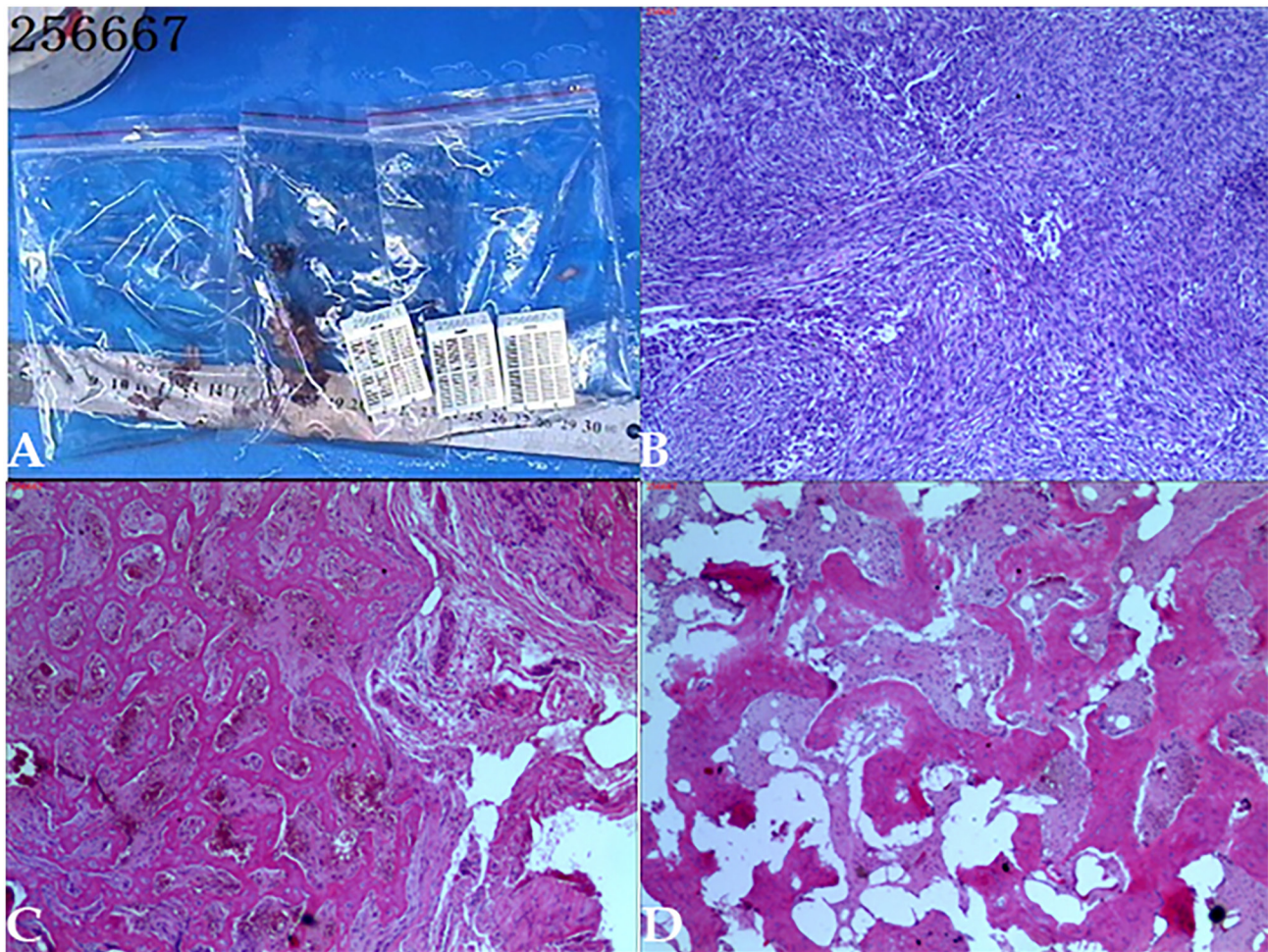


Figure 5. Pathology examination for left femoral surgical biopsy and left tibial percutaneous biopsy. (A) Left femur and tibial biopsies of the tumor tissue of the left femur and surrounding soft tissue. (B) Spindle cells of the tumor tissue were diffused into patches. There was infiltrative destruction of the bone, and dense proliferation of cells. The nuclei were oval or round, with small nucleoli. The chromatin was fine and diffuse and nuclear division was easy to be observed. The pathological features were consistent with those of malignant mesenchymal tumors; fibrosarcoma and malignant fibrous histiocytoma of bone were considered. (C and D) Tumor tissue in the left upper-middle tibia showed that interosseous tissue was composed of moderate spindle cell fibers and collagen-producing fibers. No atypia or mitotic figures were found in the specimens and the pathological features were consistent with fibrous dysplasia (H&E staining; magnification, x100).

The present case study aimed to find the features of malignant transformation of FDB in multimodal imaging.

FDB is most often discovered based on radiographic evidence (1), and radiographic classification for fibrous dysplasia is beneficial to guide treatment planning and evaluation of the

effects of surgery (17). It is recommended that patients with FDB should undergo radiological examinations before pathological biopsy and clinical treatment because malignant transformation and local aggression can usually be distinguished from non-aggressive FDB based on imaging findings (18).



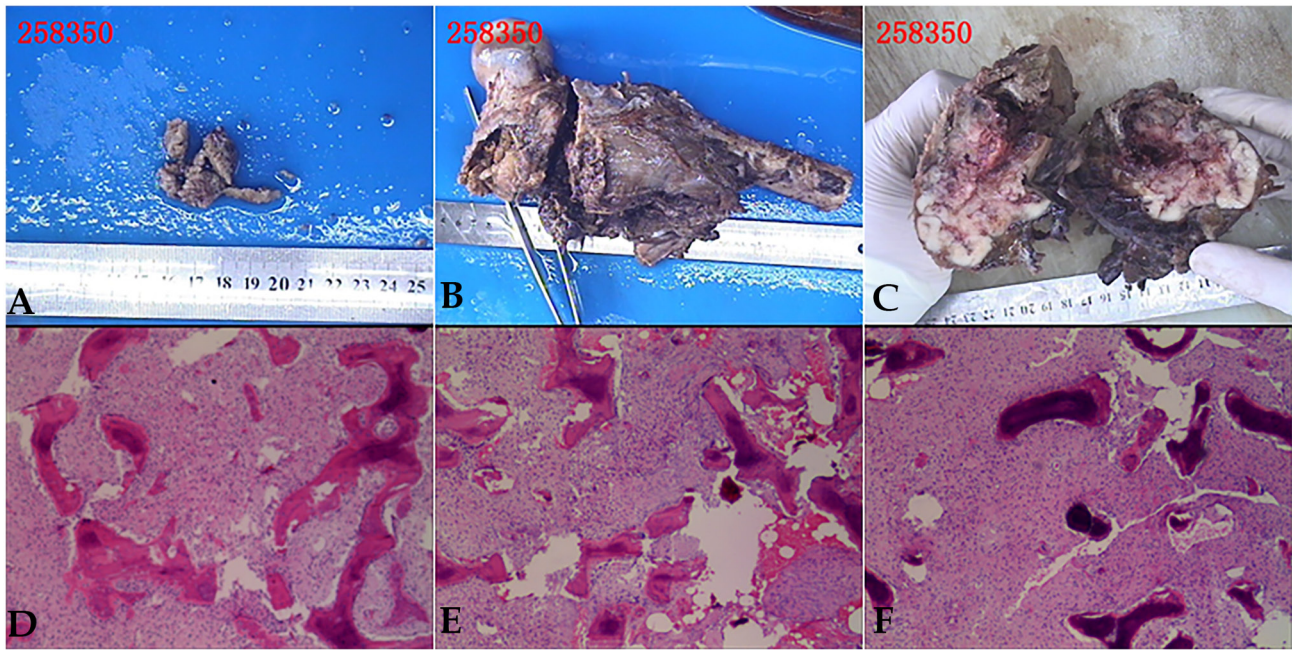


Figure 6. Pathological examination of left femur tumor after segmental resection. (A-C) The gross specimen showed gray-white tumor tissue with local thinning and destruction of the bone cortex. (D-F) The spindle cells in the tumor tissue were diffused into patches. There was infiltrative destruction of the bone and proliferation of the cells was evident; the nuclei were oval or round in shape, the nucleoli were visible, the chromatin was fine and diffuse and cytokinesis was evident. The tumor destroyed the diaphysis and invaded the soft tissue outside the bone, which was consistent with osteofibrosarcoma (H&E staining; magnification, x100).

The specific findings of X-ray and CT depend on the degree of fibrous tissue hyperplasia in the lesion and the content of new and mature bone trabeculae. When the lesion is mainly fibrous tissue, it appears as a cystic clear area. When the lesions are new bone trabeculae and the fibrous tissue of hyperplasia is woven into the bone, it shows a ground glass appearance (2,19), whilst when the lesion area is mature bone tissue, it shows a high-density strip and patchy ossification shadowing. The radiographic features of malignant transformation or local aggression of FDB include poorly defined margins, mineralized osteolytic lesions, cortical destruction and extension into soft tissue (2,15). MRI findings are related to the amount of fibrous tissue, whether there is hemorrhage, cartilaginous island or residual bone marrow fat. FDB is usually featured with homogeneous T1WI hypo-intensity and a surrounding sclerotic rim T1WI and T2WI hypo-intensity (13). T1WI and T2WI hyperintensity is observed in the corresponding areas when cystic degeneration, hemorrhage, cartilage island or residual bone marrow fat are present in the lesion. If the lesion capsule is completely depleted, T1WI hypo-intensity and T2WI hyperintensity are observed (20).

MRI can show cortical destruction and soft tissue extension for locally aggressive FDB which overlaps with malignant transformation (15). A prominent hyper-vascularized soft tissue mass extending from bone may be helpful in the differential diagnosis.  $^{99m}\text{Tc}$ -MDP single photon emission computed tomography (SPECT) directly reflects the calcium/phosphate metabolism of bone tissue and indicates the functionality and number of osteoblasts. The three-phase bone imaging can be used to observe the blood supply and the active state of bone metabolism, which is helpful for the differential diagnosis of benign and malignant bone diseases (21). FDB has distinctive characteristics on  $^{99m}\text{Tc}$ -MDP SPECT/CT; 85.7% of cases show

moderate or high radiotracer uptake on delayed whole-body bone scintigraphy (WBS) (21). This helps identify FDB as the SPECT/CT shows features of ground-glass opacity and expansion in the areas of high radiotracer uptake while without soft tissue occupying lesions in bone marrow. However, a high tracer uptake can be seen on locally aggressive FDB because its tissue type is composed of trabeculae of immature bone and fibers stroma (11). Comparatively low tracer uptake in the delayed phase but high blood perfusion in the perfusion phase and the blood pool phase is considered to have a malignant transformation diagnosis (21,22). In the present case study, the three-phase bone imaging showed that the blood perfusion and blood pool were increased, and the abundant blood perfusion was indicative of malignancy. Delayed phase findings indicated that there were fewer osteoblasts and calcium/phosphate but more interstitial tissue. The corresponding lesions were confirmed through finer anatomic proximity on MRI.

All imaging examinations have their unique functions. The degree of X-ray radiographic density is directly proportional to the degree of mineralization and brighter areas reflect predominantly fibrous zones, which can help with earlier FDB detection. SPECT/CT is important for assessing local function and microscopic components. MRI is an excellent method for assessing cases of complex fibrous dysplasia, reflecting the variable tissue components. CT complements and enhances the interpretation of MRI of bone lesions, especially in cases where MRI shows enhancement that is suspicious of a malignant neoplasm (19,23). However, the presentation of those features is often non-specific, and it is recommended to use multimodal imaging that can show the anatomy, blood supply, molecular components and metabolism of the lesion at the same time to improve the diagnostic accuracy of FDB and its malignant transformation. In

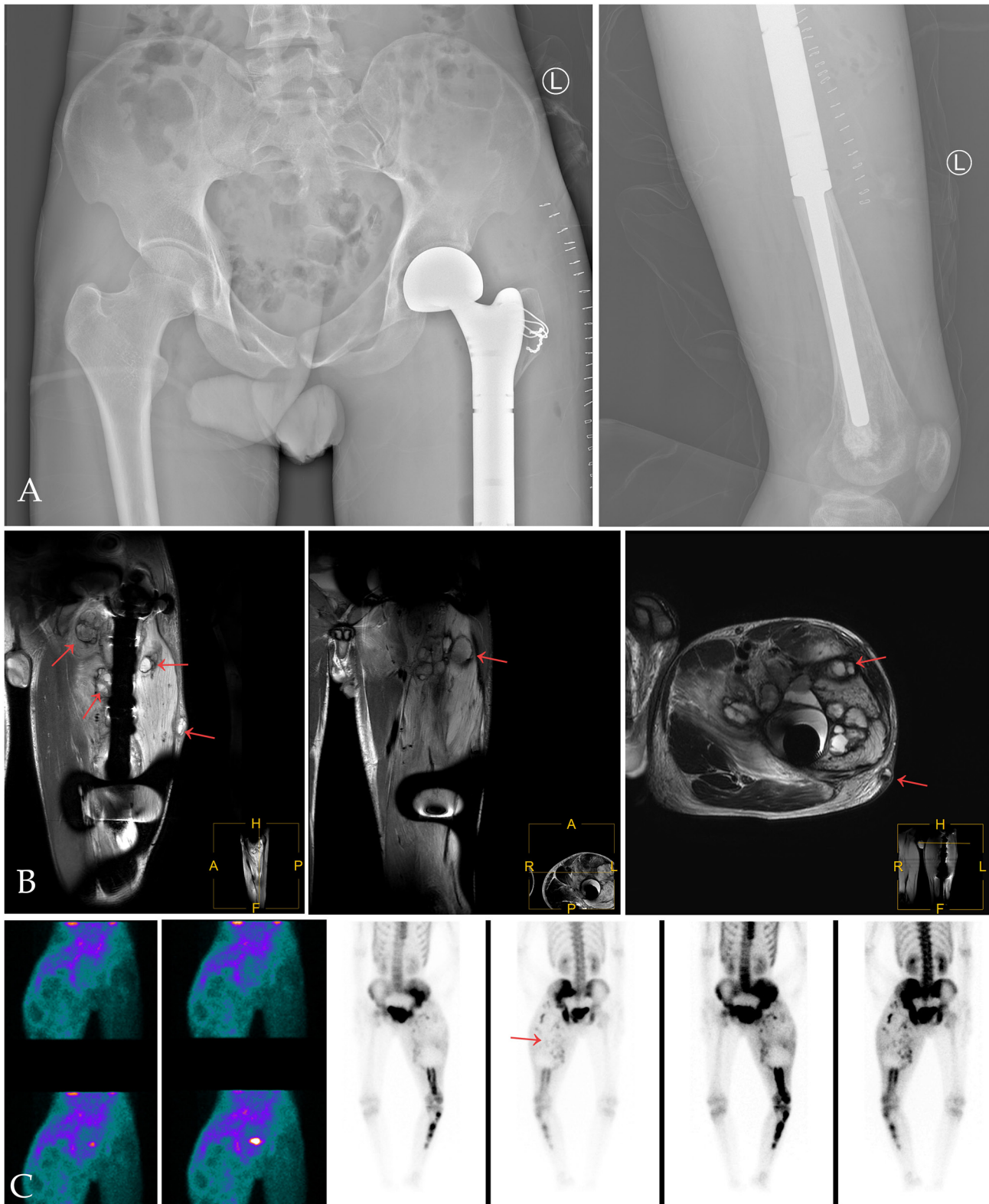


Figure 7. Postoperative and follow-up images. (A) X-ray images showed changes after left femur tumor segment resection and hip replacement. The upper segment of the left femur and surrounding local soft tissue were removed and an artificial femur was fixed internally. (B) MRI at 3 months after surgery showed multiple nodular lesions (red arrows) in the muscle and subcutaneous tissue around the artificial femur. (C)  $^{99m}\text{Tc}$ -MDP three-phase bone imaging showed high blood perfusion and increased tracer uptake of the new soft tissue lesions, although these increases were lower compared with other FDB lesions in the delayed phase.

actual clinical practice, other clinical data need to be considered to make a comprehensive judgment. Consideration of potential factors such as age and history of surgery is important. It is

necessary to combine relevant laboratory indicators, including serum alkaline phosphatase. Wang *et al* showed that FDB with high serum alkaline phosphatase level has a tendency to



progress to severe disease (24). In the present case study, alkaline phosphatase was ~2-fold the upper limit of the normal range, which was significantly higher compared with the normal level. A limitation of the present case study is the lack of imaging data before the malignant transformation.

Although biopsy is often the gold standard for diagnosis, multimodal imaging is useful to define the scope of the lesion and help to guide treatment planning. Comprehensive analysis of multimodal images may improve the detection rate and diagnostic accuracy of local FDB aggressiveness and its malignant transformation, thus guiding clinical diagnosis and treatment decision-making.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

JL, MK, XY and JZ confirm the authenticity of all the raw data. JL, MK and JZ contributed to the conception of the study. JL and MK were responsible for writing the original draft, reviewing and editing the manuscript. XY, JL, MK were responsible for acquisition of clinical data. XY and JZ were responsible for critical revision of the manuscript and the analysis and interpretation of the data. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

This study passed ethical review by the Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University. All the data used were collected from the Third Affiliated Hospital of Guangzhou Medical University with the consent of the patient.

## Patient consent for publication

All the test results, imaging images, and their publication were obtained with written consent from the patient.

## Competing interests

The authors declare that they have no competing interests.

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