

Malignant Transformation Of Fibrous Dysplasia In Combination With Bone Cyst: A Case Report.

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Case report

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Abstract

Background: Fibrous dysplasia and Simple bone cyst are all common benign lesions. A case of osteosarcoma developing from fibrous dysplasia in combination with unicameral bone cyst will be discussed. The radiologic, histologic characteristics and clinical prognostic of the patient will be described. As far as we know, this is the first case report of malignant transformation secondary to fibrous dysplasia in combination with unicameral bone cyst, which is extremely rare and worthy of clinical attention or vigilance.

Case presentation: This study describes a case of a 20-years-old male who suffered a 7-years history of intermittent pain in his right proximal tibia, obvious after activity and progressively worsening. Clinical symptoms and imaging examination were consistent with the characteristics of benign primary bone tumor. He underwent a successful curettage operation. Pathological diagnosis was fibrous dysplasia in combination with unicameral bone cyst. After the curettage surgery, the pain in his right knee quickly disappeared and function activities returned to normal during a regular follow-up postoperative. However, He was diagnosed with a recurrence of fibrous dysplasia in combination with unicameral bone cyst and osteosarcoma malignant transformation by chief complaint symptoms of pain and swelling in the right proximal tibia, adequate imaging examination, and pathological diagnosis at 2 years follow-up. Then the patient undergo a limb salvage with tumor prosthesis reconstruction of the right knee. Unfortunately, multiple and unresectable lymph nodes distant metastases happened even with two weeks localized inguinal radiotherapy treatment and one course of neoadjuvant chemotherapy monthly. He eventually received cancer hospice care and died eight months after the diagnosis as malignant transformation and systemic multiple organ metastasis.

Conclusions: Although malignant transformation of fibrous dysplasia in combination with unicameral bone cyst is very rare, patients with this disease should be monitored and received lifelong follow-up to obtain early detection, diagnosis and treatment to maximize the efficacy of treatment and survival time. The histological and immunohistochemical findings is very important but not enough. Further research is required to clarify the pathogenesis and prevent malignant transformation.

Background

Fibrous dysplasia (FD) is a common benign bone lesion, representing 5%-10% of benign bone tumors according to World Health Organization (WHO) 2013 edition classified, characteristic with monostotic or polyostotic forms and constitute 2.5% of all bone tumors [1]. Unicameral bone cysts also is a common benign lesion about 2 or 3 to 1 male predominance and 80% of patients are in their second decade including unicameral bone cyst (UBC) or partially separated. Unicameral bone cysts make up 3% of the primary bone lesions but the actual incidence is not known as many of these are never discovered [2]. Rarely malignant transformation occur in fibrous dysplasia with very low risk at less than 1 % in the monostotic form, but up to 4 % in the polyostotic form [3]. Although malignant transformation has been reported for aneurysmal bone cysts (ABCs) in literature [4], there are no reports of malignant

transformation of UCB following surgical intervention in human. Berger B, et al. first reported a unicameral bone cyst in the proximal humerus of a 3-year-old Norwegian forest cat was malignant transformation to osteosarcoma at 17 months postoperative of the curettage and bone cement incorporation surgery with Pulmonary metastasis [5]. As far as we know, this is the first case report of malignant transformation secondary to fibrous dysplasia in combination with unicameral bone cyst patient, which is extremely rare and worthy of clinical attention or vigilance.

This study describes the case of a osteosarcoma malignant transforming secondary to fibrous dysplasia in combination with unicameral bone cyst in the lower limb in his right proximal tibia of a 20-year-old male patient.

The study was approved by the Institutional Ethics Review Board of the First Affiliated Hospital at Third Military Medical University. Written informed consent was obtained from the patient and his guardians and retrospectively registered.

Case Presentation

A 20-years-old male presented to our Department of Orthopaedics with a complaint for a 7-years history of intermittent pain in the right proximal tibia in November 2009, obvious after activity and progressively worsening. Clinical examination revealed no apparent local tenderness or soft tissue mass, without swelling and ulceration, no limited motion of the right knee. Also, no lymph nodes swollen were found in the inguinal area of the patient. The patient had no previous history of radiation therapy and local infection of the right knee. Complete blood count, serum biochemistry panel, alkaline phosphatase, lactate dehydrogenase levels, serum calcium, phosphorus were all normal.

Adequate imaging examinations were performed that on the plain X-ray of the right knee revealed a mixed-density lesion, expansile ground-glass lesion, radiotransparent, well-contoured, centered and oblong along the longitudinal axis of the tibia, without periosteum reaction (Fig. 1-a). Axis view of a computed tomography (CT) showed a ground-glass lesion involving the right anterolateral proximal tibia with radiotransparent and pseudo-septum, consistent with fibrous dysplasia in combination with unicameral bone cyst (Fig. 1-b). The benign lesion was further characterized by magnetic resonance imaging (MRI) on T1-weighted and T2-weighted sagittal image which showed no soft tissue mass, edema and periosteal reaction outside the lesion (Fig. 1-c).

According to the clinical and imaging features of the patient, it seems obvious a benign bone tumor consensus of expert meeting without performing preoperative biopsy. No surgical indications of bone grafting or internal fixation for this 2cm diameter benign lesion with complete tibial cortex and very low risk for pathologic fracture. A simple intracapsular curettage and decompression of tumor lesions was adequate and performed soon after signed informed consent from the patient. In the operation, the lesion revealed about 5ml light yellow fluid in the cystic cavity, mixed a small amount of silt-like bone tissue and proliferative fibrous granulation tissue. After intracapsular curettage and decompression, the cyst wall of the lesion was treated with electric coagulation, intraoperative irrigation careful, and alcohol-inactivated

furthermore. The initial samples from the lesion was scraped off for pathological examination and confirmed FD in combination with UBC one week after the intracapsular curettage surgery (Fig. 2-a) (Fig. 2-b). After the curettage surgery, Pain of the right knee quickly disappeared, the incision healed normally and function activities returned to normal during a regular follow-up postoperative after the curettage surgery. Review of X ray film showed 3 days postoperative (Fig. 2-c), progressive sclerosis of the lesion at six months after intracapsular curettage surgery (Fig. 2-d).

At two years follow – up after the initial curettage and decompression operation, the patient developed pain again and even worse at the original surgical area, accompanied by a 3*2cm soft tissue mass and tenderness locally. Radiography, CT and MRI of the right knee were immediately examined (Fig. 3-a), (Fig. 3-b), (Fig. 3-c). The radiological features were consistent with the obvious and typical appearance of osteosarcoma. CT-guided puncture biopsy on the recurrent lesion was performed immediately, but the pathological diagnosis reported fibrous tissue hyperplasia with hyalinosis in the upper segment of the right tibia. A further open biopsy seemed obviously necessary after expert meeting with great suspected whether the malignant transformation happened. Written informed consent was obtained from the patient. Post of the open biopsy, the histopathological evaluation revealed that the solid tumor section of soft tissue mass showing pleomorphic spindle cells, consistent with high-grade osteosarcoma, including hyperchromatic pleomorphic nuclei and numerous scattered mitotic figures (Fig. 3-d). Combined with definite clinical, imaging, histological and immunohistochemical findings, it was consistent with the diagnosis of osteosarcoma malignant transformation secondary to FD in combination with UBC.

The patient requested a limb salvage operation as soon as possible, neoadjuvant chemotherapy before surgery or radical surgical treatment of amputation was rejected. The patient underwent radical proximal tibial resection with tumor type endoprosthesis for the defect reconstruction (Fig. 4-a) (Fig. 4-b). Satisfactory limb function was obtained immediately after limb salvage operation. One course of neoadjuvant chemotherapy monthly was received postoperative with the cisplatin, ifosfamide and Adriamycin (DIA) chemotherapy regimen.

At two months follow – up after the limb salvage, there was a local recurrence of the right knee with a soft tissue mass, even multiple and unresectable lymph nodes distant metastases of the patient was certified in the right groin and pelvic cavity by Positron Emission Tomography-Computed Tomography (PET - CT) examination (Fig. 4-c). Two weeks of vitro radiotherapy in the groin region was received then. The patient developed multiple osteosarcoma metastases to his right lung, intrapulmonary lymph nodes, and right inguinal lymph nodes by re-examined PET – CT diagnosis at six months follow – up after the limb salvage. Unfortunately, the left frontal bone with soft tissue mass, invasion of the skull, intracranial invasion, and compression of brain parenchyma were found by cranial CT examination after eight months of the limb salvage (Fig. 4-d). During the last chemotherapy, the patient developed severe intracranial hypertension and was forced to stop the chemotherapy. After an successfully emergency brain edema and neurological functional recovery, the patient's vital signs recovered. Cancer hospice care eventually received and died eight months after the diagnosis of fibrous dysplasia in combination with

unicameral bone cyst, its systemic multiple organ osteosarcoma metastasis was the leading cause of death for this young man.

Discussion

As benign tumors and tumor-like lesions, fibrous dysplasia (9, 1.3%) and simple bone cyst (7, 1.0%) can affect children and adults of all ages with epidemiological characteristics of 1385 primary sacral tumors in one institution in China [6]. Bone resorption may play a key role in FD progression with high level of osteoclastogenesis, manifested as the neoplastic fibro-osseous tissue replaces normal medullary bone with typical imaging findings like "Ground-Glass" changes. Craniofacial bones and femur are the most common sites of involvement in both forms [7]. Patients of FD are always found to be complain of pain or swelling in clinical usually with good prognosis. As the FD history prolongs, local cystic lesions may develop changes with edge hardening, irregularly shaped and partial cortical destruction, but rarely present with pathological fracture [8]. FD is formed by oval to spindle-shaped fibroblasts with no cytological atypia in histopathologically. The common symptomatic of UBC including pain, swelling, deformity and pathologic fracture, but the treatment is usually limited to large bone cyst, deformity or symptoms, or an impending fracture [9, 10]. Overall, the majority lesions of UBC are clinically insignificant, and patients do well [11].

Treatment of patients with FD by clinical observation, patient education, bisphosphonate therapy and surgery is the current mainstream [12]. Traditional surgical treatments including deformity correction, pathologic fracture prevention, symptomatic lesions. Because of the development of effective therapies for FD has been limited by large gaps in knowledge of its pathogenesis [13]. There is no cure for FD and no way to prevent malignant transformation at the present. Malignant transformation of FD is rare. FD may be accompanied with mutation of G-nucleotide binding protein alpha sub unit (GNAS). Although GNAS detection in osteosarcoma with secondary malignant transformation may be helpful to determine whether it is the differentiation from FD [14], the association between mutation and malignant transformation has not been established [15]. Diagnosis is still based on pathological examination as the gold standard of tumours and the immunostaining is very important but not decisive and enough for the diagnosis, which analysis based on any single factor or incomplete information may easily lead to arbitrary conclusion [16]. Clinical picture, imaging examination and regular follow-up is as important as the assessment and guide value of pathological diagnosis for a neoplastic disease with potentially malignant progression. In this case, possibility of malignant transformation was presented in the immediate clinical symptoms and supported imagings, but negative results of CT-guided biopsy pathological diagnosis, although the needle trajectory was considered carefully and the approach was discussed when planning a percutaneous biopsy [17]. Requiring an open biopsy for definitive diagnosis of osteosarcoma was necessary. The pathological diagnosis confirmed that major histopathologic characteristics of the malignant transformation tumor segment was composed of a large amount of round epithelioid cells and spindle cells proliferation, disperse and disorderly in sheets or fascicles, along with intercellular bone-like matrix and collagen fiber components. Those tumor cells are large, abundant eosinophilic cytoplasm and the nucleus of the cells are mild atypical, divided and moderate mitotic

activity. Immunohistochemical analysis of the excision malignant transformation tumor segment from limb salvage surgery showed negative for CK, EMA, but positive for P53 and Ki67 positive cells accounted for 15%. According to the above findings, the diagnosis of osteosarcoma secondary to FD with UBC of the the right proximal tibia was clearly and finally confirmed.

Osteosarcoma is the most common histologic type of FD malignant transformation, fibrosarcoma, chondrosarcoma and undifferentiated pleomorphic flesh tumor is the next [18]. Local treatment options for sarcomatous depends on the location of the lesion and the type of malignant transformation, radical resection if the tumor location is amenable to surgical excision has been suggested [19], including amputation or limb salvage and radiotherapy. Whether amputation or limb salvage surgery is the main treatment of choice with high local control rate, the efficacy of radiotherapy used to be regarded as uncertainty exists. In particular, it needs to be emphasized that patients with FD received radiation therapy will increases the risk of malignant transformation [12]. Radiotherapy is an important and definite option as local treatment of unresectable tumors, following intralesional resection, or as palliation of symptomatic metastases, but survival prognosis of such patients is poor [20]. In our case, multiple and unresectable lymph nodes distant metastases in the right groin and pelvic cavity had happened two month after limb salvage surgery. Two weeks localized inguinal radiotherapy treatment was carried out, but quickly developed multiple metastases throughout the body in the next six months even in combination with one course of neoadjuvant chemotherapy monthly. It was a painful subject that diagnosis as malignant transformation to osteosarcoma, radiotherapy is likely to exacerbate and accelerate malignant transformation events [12], but with the high degree of osteosarcoma malignant transformation, limited systemic treatment of unsensitive chemotherapy or radiotherapy, incredibly challenging to control rapid progression of metastasis resulted in very poor clinical outcomes.

Pain was the mainly specific symptoms of the malignant transformation and rapidly worse in a relatively short period [21], accompanying symptoms with mass or pathological fracture should be taken great suspected whether the malignant transformation happened when evaluating. Although the mechanism of malignant transformation secondary to FD with UBC remains unclear, the early close follow-up should be performed clinically to make an effort to ensure timely diagnosis and prevent rapid progression of deterioration or peripheral metastasis.

Conclusions

we reported this unusual case of osteosarcoma malignant transformation after curettage and decompression of a monostotic fibrous dysplasia in combined with a unicameral bone cyst of the limb. Although malignant transformation secondary to fibrous dysplasia and unicameral bone cyst is very rare, patients with this disease should be monitored and received lifelong follow-up to obtain early detection, diagnosis and treatment to maximize the efficacy of treatment and survival time. The histological and immunohistochemical findings is very important but not enough. Further research is required to clarify the pathogenesis and prevent malignant transformation.

Declarations

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Availability of data and materials

All data used in the study are available at the request of the editors and reviewers.

Authors' contributions

Meitao Xu and **Jiajia Wang** contributed equally to this work and should be considered co-first authors; they reviewed this case and wrote this article. **Xi Zhang** and **XuQuan Wang** are both corresponding authors; they were responsible for performing the study. All authors are familiar with the contents of the final draft and take responsibility for the authenticity of the data used in the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Review Board of the First Affiliated Hospital at Third Military Medical University. Written informed consent was obtained from the patient and his guardians and retrospectively registered. Patients' privacy is strictly and fully protected and respected. A copy of this document is available for review by the editor in chief of this journal.

Consent for publication

All patients consented to the publication of the results of this study.

Competing interests

The authors declare that they have no competing interests.

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Figures

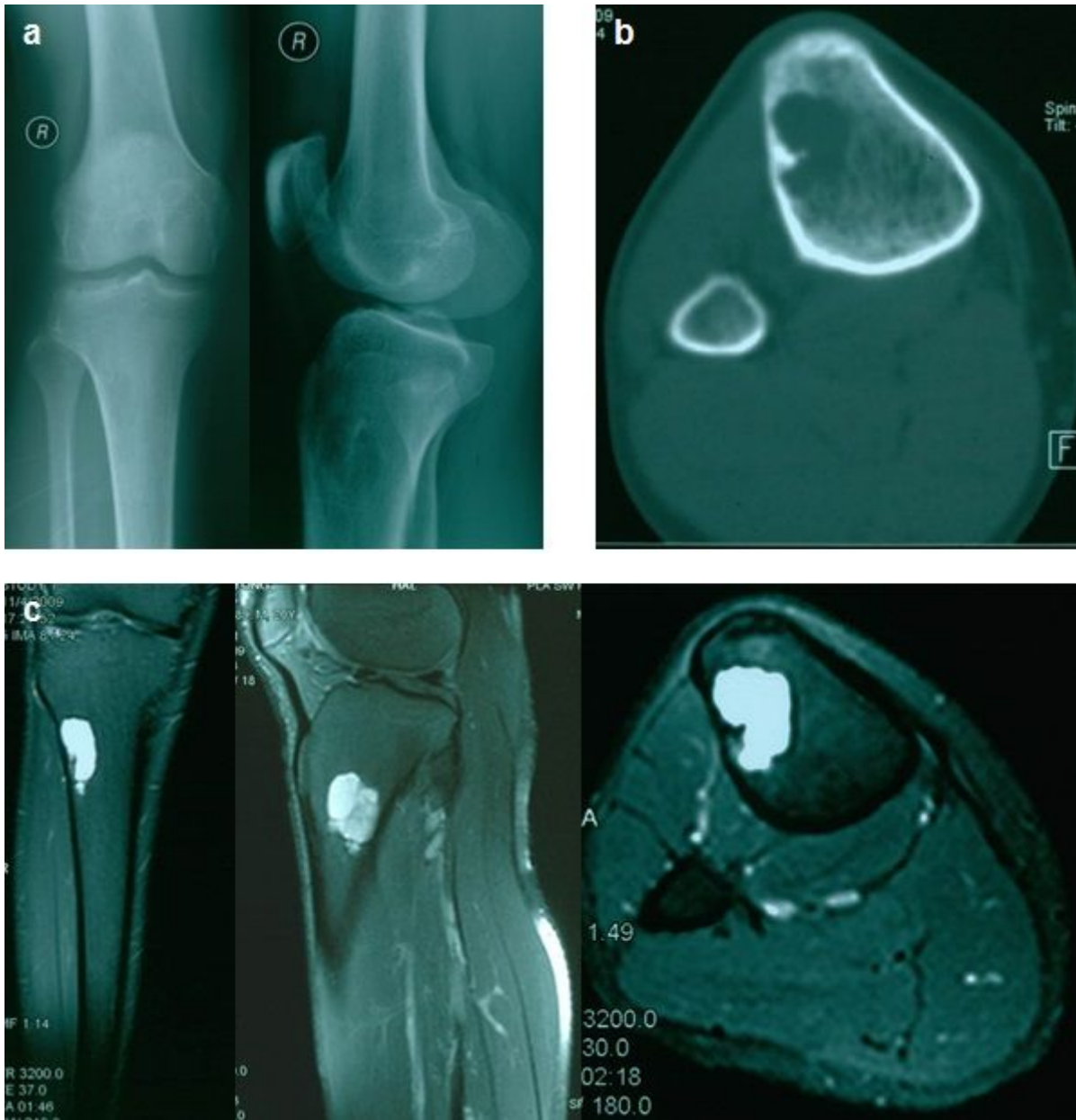


Figure 1

a The plain X-ray of the right knee revealed a circular area expansile ground-glass lesion, radiotransparent, wellcontoured. b The axis view of CT showed a ground-glass lesion involving the anterolateral, proximal tibia with radiotransparent and pseudo-septum, consistent with FD in combination with UBC. c Coronal, sagittal, and axial images of MRI by T2-weighted fat inhibition image formation showed no soft tissue mass, edema and periosteal reaction outside the lesion in T1-weighted and T2-weighted sagittal image.

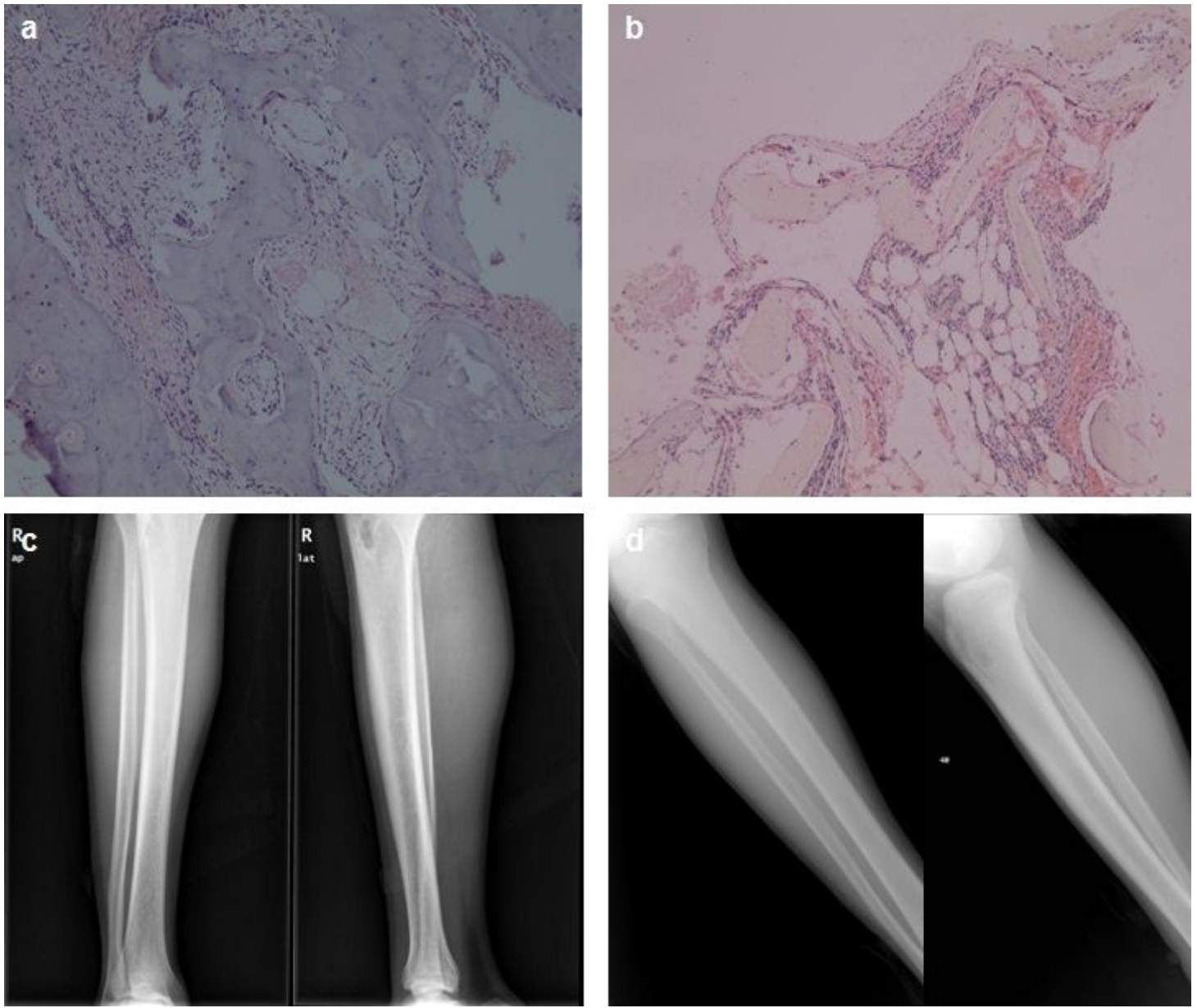


Figure 2

a The panoramic photomicrograph showing the character of fibrous dysplasia consisting of disconnected and contoured fibroblastic proliferation from the initial samples (hematoxylin and eosin, $\times 100$). b Transition area showing cementum-like pink amorphous material, thin layer of fibrovascular stroma, and loose fibroblasts in wall of cyst from the initial samples (hematoxylin and eosin, $\times 100$). c X-ray imaging of the right tibia showed 3 days after intracapsular curettage surgery. d Review of X ray film showed six months postoperative.

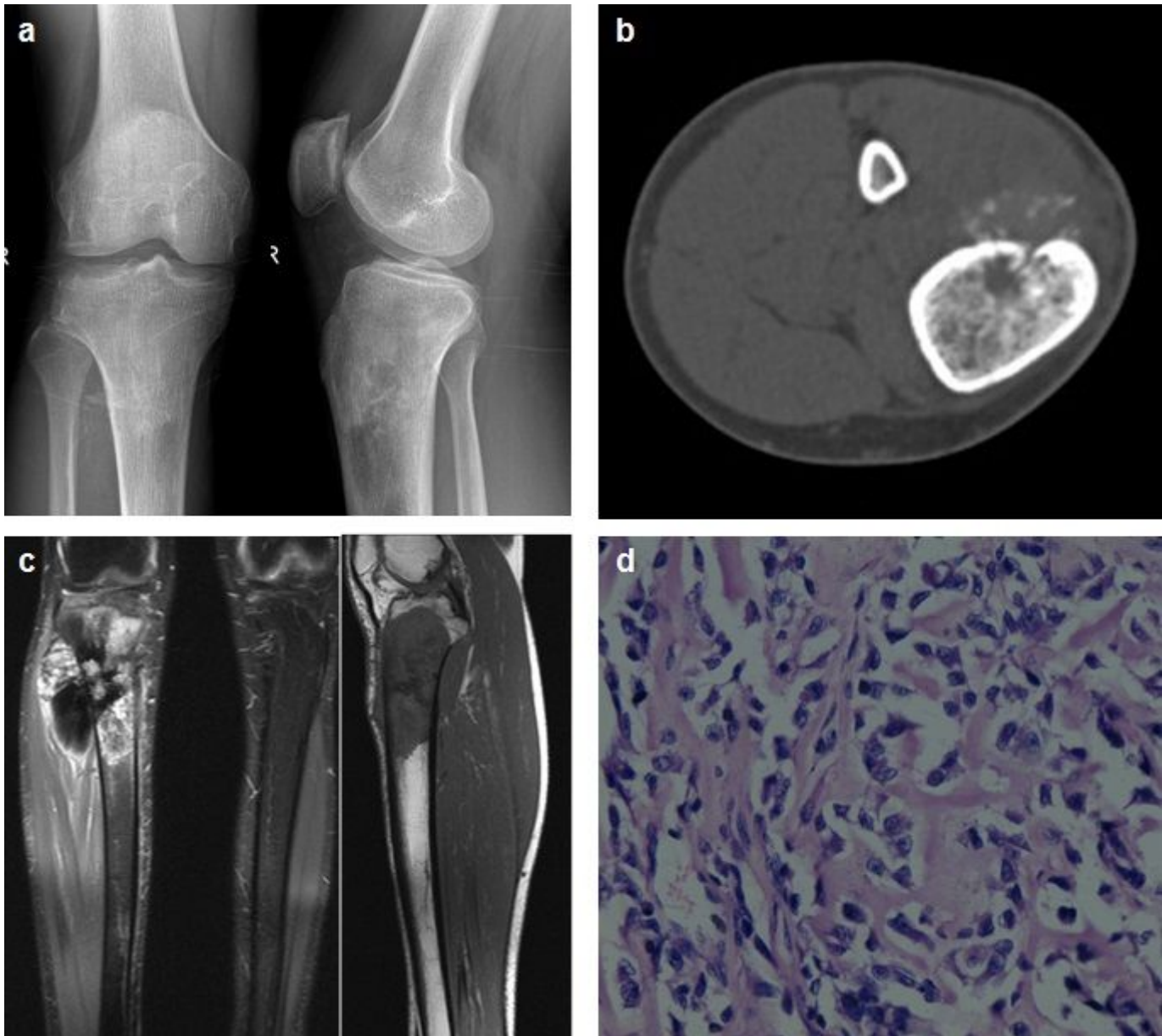


Figure 3

a The plain X-ray revealed osteogenic destruction of the right proximal tibia, periosteum reaction, and soft tissue mass were observed at 2 years after surgery. b The Axis image of CT showed obvious periosteal reaction and hyperplasia at the proximal right tibia. c The Coronal and sagittal MRI images of the right knee clearly demonstrated malignant changes, periosteum reaction, edema, soft tissue hyperplasia, and lobulated sarcomatoid changes of the proximal tibia at 2 years postoperative follow – up. d Higher power view of typical osteosarcoma showing tumor cells with cytological atypia and characteristics of epithelioid cells from the open biopsy amples (hematoxylin and eosin, ×400).

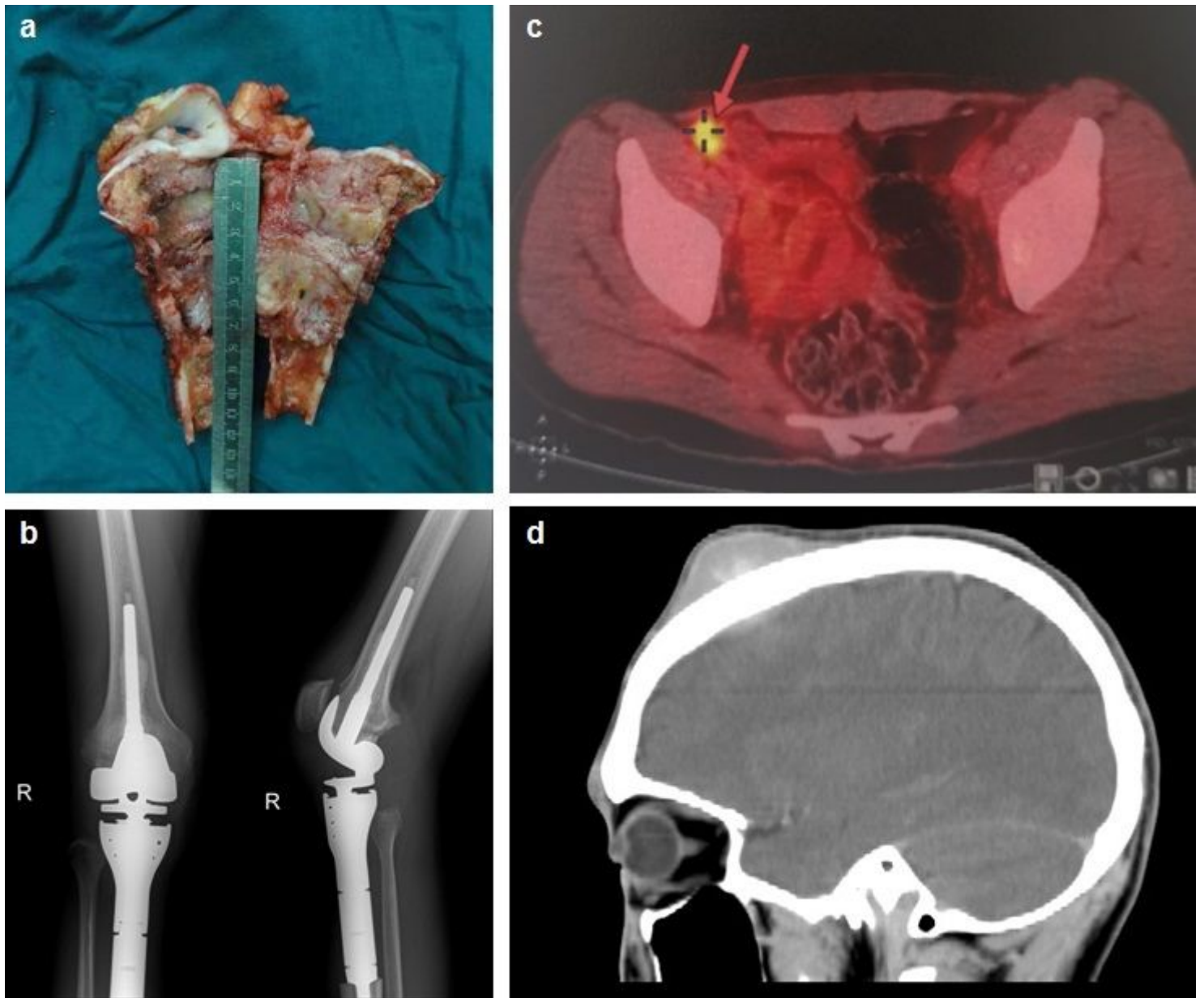


Figure 4

a Appearance of the removed right proximal tibia segment after limb salvage in the operation room, fish-like tumor tissue with osteosarcoma malignant transformation invasive. b At one month post limb salvage operative, the plain radiograph of the right knee showed normal condition endoprosthesis. c The image showed one of multiple lymph node metastases in the groin examined by PET - CT at two months follow - up. d The left frontal and intracranial metastasis were found by cranial CT examination at eight months follow.