Malignant transformation of an aneurysmal bone cyst of the femoral neck: A case report

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Abstract. Aneurysmal bone cyst (ABC) is a benign, distending, osteolytic and locally aggressive bone tumor that is mostly associated with trauma. Approximately 1% of bone tumors are ABCs, which are most prevalent in adolescents and are usually detected in the spine and long tubular bones. The diagnosis of ABC mainly relies on histopathology, malignant transformation is rare, and the chance of malignancy increases if there are multiple recurrences. Due to the rarity of reports of malignant transformation of ABCs into osteosarcoma, there is still considerable debate on the appropriate treatment strategy. The current paper presents a case of aneurysmal bone cyst malignant to osteosarcoma and the therapeutic measures to provide expertise for the diagnosis and treatment of ABCs that are malignant to osteosarcoma.

Introduction

With an incidence of 0.14-0.32 per 100,000 individuals in 1999, aneurysmal bone cyst (ABC) is an uncommon bone tumor that composes 1-2% of all primary bone tumors. Of these, ~70% are primary bone tumors, and 30% are secondary (1). ABC typically affects teenagers up to the age of 20 and is present in the femur, tibia, fibula, humerus, skull and spine (2). The pathogenesis of ABC is still unclear, and currently, the leading theories are vascular, trauma and genetic factors (3). Vascular injury resulting in reactive vascular malformations may be linked to the development of ABC, and arteriovenous fistula or intramedullary artery embolism are also considered to be risk factors for the onset of ABC (4). According to a previous study, rearrangement of the ubiquitin-specific protease 6 gene is directly associated with ABC (5).

The clinical symptoms of ABC mainly include pain, swelling and masses at the disease site, and the primary therapeutic options are as follows: i) Surgery, including local curettage and internal fixation of the bone graft and whole segment resection and reconstruction of the bone; ii) cryotherapy; iii) sclerotherapy; iv) radionuclide ablation; v) arterial embolization; and vi) chemotherapy, which is the primary choice for surgical treatment of ABC (6). Subsequently, 20-30% of ABC cases relapse following treatment; thus, high-risk factors for malignant transformation include recurrent recurrence, radiation therapy history and several surgical and internal fixation procedures, and osteosarcoma is the most prevalent malignant transformation (7).

In 1991, a case of recurrent malignant transformation of the ABC of the distal tibia into osteosarcoma was documented, and the patient was eventually treated with amputation (8). By using electron microscopy, Aho *et al* (9) examined four patients with ABC and discovered that one of them went on to develop malignant osteosarcoma seven years after receiving radiation. In another case report, the patient did not receive radiation therapy but developed osteosarcoma after receiving repeated surgical treatments, highlighting the potential for malignancy due to repeated surgery and internal fixation stimulation (10). In summary, the treatment of ABC malignant transformation into osteosarcoma is mainly lumpectomy and reconstruction, and if the disease continues to deteriorate in the later stage, amputation is the final treatment with a low survival rate.

With a deeper knowledge of malignant bone tumors, therapy for ABC malignant transition into osteosarcoma is now more standard. Expanded resection of the tumor is the primary treatment option, and it is supplemented by preoperative neoadjuvant chemotherapy and a full course of postoperative chemotherapy. With this course of treatment, the likelihood of limb preservation and 5-year survival rates improved from ~10-20% to ~60-70% in patients without metastases and to ~20-30% in patients with metastatic cancer (11). The present

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study intends to improve the knowledge of whether ABC has the potential to transform to other malignancies and provide clinical experience in terms of clinical and imaging presentation, diagnosis, treatment and prognosis.

Case summary

A 44-year-old Chinese man was sent to a local hospital in February 2015 with intermittent pain in the left hip, and an X-ray examination revealed a lytic lesion in the left femoral neck. It was advised that the patient be transferred to a hospital with a higher level of treatment. In March 2015, the patient was admitted to the 940th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army (Lanzhou, China). X-rays (Fig. 1), CT scans and magnetic resonance imaging (MRI) revealed a proximal lesion of the left femur (Fig. 2), which is typically considered a benign bone disease with a high probability of aneurysmal bone cyst.

After excluding contraindications to surgery, the patient underwent curettage of the left femoral neck tumor, iliac bone harvesting, tipped fibula grafting and internal fixation of the plate in March 2015 at the 940th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army (Lanzhou, China). The postoperative histopathological examination revealed that it was consistent with an aneurysmal bone cyst and recovered well after surgery (Fig. 3). The internal fixation was removed at our department in April 2016, and no evidence of recurrence was discovered. In June 2018, the patient consulted the Department of Joint Surgery again for left hip pain, considering a recurrence of aneurysmal bone cyst, and the patient underwent repeat left femoral neck aneurysm bone cyst curettage, iliac bone harvesting and plate internal fixation. Postoperative pathology showed recurrence of the aneurysm bone cyst (Fig. 4). In May 2019, the internal fixation was removed and no signs of recurrence were evident.

The patient returned to our Department of Joint Surgery in August 2020, suffering from left hip pain. The X-ray revealed that the bone density of the femoral neck was uneven, and the CT examination showed worm-eaten bone destruction. The tumor capsule showed sclerotic bands and the femoral head was normal in shape. According to the MRI results, the left femoral head and neck had a heterogeneous signal with a mixed long T2 signal shadow, and the upper femur medullary cavity had an irregular long T1 and long T2 signal with a morphology of ~1.8-cm. DWI also revealed a high signal. Based on the CT and MRI results of the patient and a history of repeated recurrences and multiple surgeries, the possibility of malignancy in the ABC was strongly suspected (Fig. 5). A surgical puncture biopsy was performed, and the pathological results showed high grade osteosarcoma of the left proximal femur (Fig. 6). Multitherapy, including neoadjuvant chemotherapy, surgery and postoperative chemotherapy, was chosen as the treatment plan after the patient and family completed the necessary informed consent forms and were informed of the present condition and treatment options.

The most widely used staging system in clinical practice is the surgical staging system proposed by Enneking, which has a good correlation with tumor prognosis and is adopted by the Musculoskeletal Tumor Society (MSTS) and the International Society for Limb Preservation, also known as MSTS surgical staging (12). This system stages limited malignant bone tumors according to the histological grade of the tumor (low malignancy, stage I; high malignancy, stage II) and the extent of local involvement (A, intra-interstitial; B, extra-interstitial), with the interstitial status of the tumor depending on whether the tumor breaks through the bone cortex. Patients with distant metastases (M1) are considered stage III. Based on the imaging of the patient, the patient had a stage IIA Enneking Surgical Staging System, which is highly malignant osteosarcoma; therefore, preoperative neoadjuvant chemotherapy and postoperative chemotherapy was administered. A total of four neoadjuvant chemotherapy sessions were performed before surgery [patient height, 170 cm; weight, 81 kg; body surface area, 1.95 m^2; protocol, injectable isocyclophosphamide (IFO) 12 g/m^2 continuous pumping for D1-3 days + erlotinib hydrochloride capsule 12 mg 1/day orally for 3 weeks; cisplatin 110 mg/m^2 intravenously + liposome doxorubicin 34 mg/m^2 intravenously]. Prior to neoadjuvant chemotherapy, three days of hydrotherapy were started.

As recommended in the Chinese Society of Clinical Oncology clinical guidelines for the management of classic osteosarcoma, two alternating chemotherapy regimens of eight doses at three-week intervals. During neoadjuvant chemotherapy, the disease is evaluated as follows: i) Stable, with no local recurrence or distant metastasis; ii) progressive, local recurrence or proximal metastasis; iii) deterioration, local recurrence of the tumor with proximal and distal metastasis or systemic metastasis. A change in chemotherapy treatment or early surgery may be needed if the disease worsens. Mestinon sodium injection (4.8 g) was supplied before chemotherapy, with the addition of IFO, and after chemotherapy to reduce urinary tract toxicity during IFO chemotherapy. During chemotherapy, the blood count of the patient was 2.51-2.98x10^9 cells/l, lymphocyte count was 0.61-0.75x10^9 cells/l and neutrophil count was 1.59-1.73x10^9 cells/l, indicating a degree II myelosuppression. After receiving recombinant human granulocyte-stimulating factor, diethylstilbestrol and caffeic acid pills, the condition of the patient reverted to normal. The patient also experienced gastrointestinal reactions, such as nausea and vomiting, which subsided after receiving 8 mg of ondansetron hydrochloride intravenously.

The status of the patient was determined to be stable and progression-free following the neoadjuvant chemotherapy course, with no local recurrence or distant metastases. The scope of tumor resection was determined according to the preoperative MRI lesion range to ensure a safe tumor margin (>5 cm of the lesion range), and then left proximal femoral resection and artificial hip tumor prosthesis replacement were performed. During the operation, the proximal femur was removed and the removed proximal femur was incised and the post-operative changes of the femoral neck scraping and implantation were seen. A small amount of bleeding was seen in the cross-section and the tissue was fish-like with unclear borders, a fish-like tissue with indistinct borders measuring ~0.5x0.5 cm at ~11 cm from the femoral ridge, same as preoperative imaging for high-grade osteosarcoma. The bone marrow tissue of the distal femoral cavity was removed and sent for pathological examination. The results of frozen section examination revealed no sign of tumor tissue.

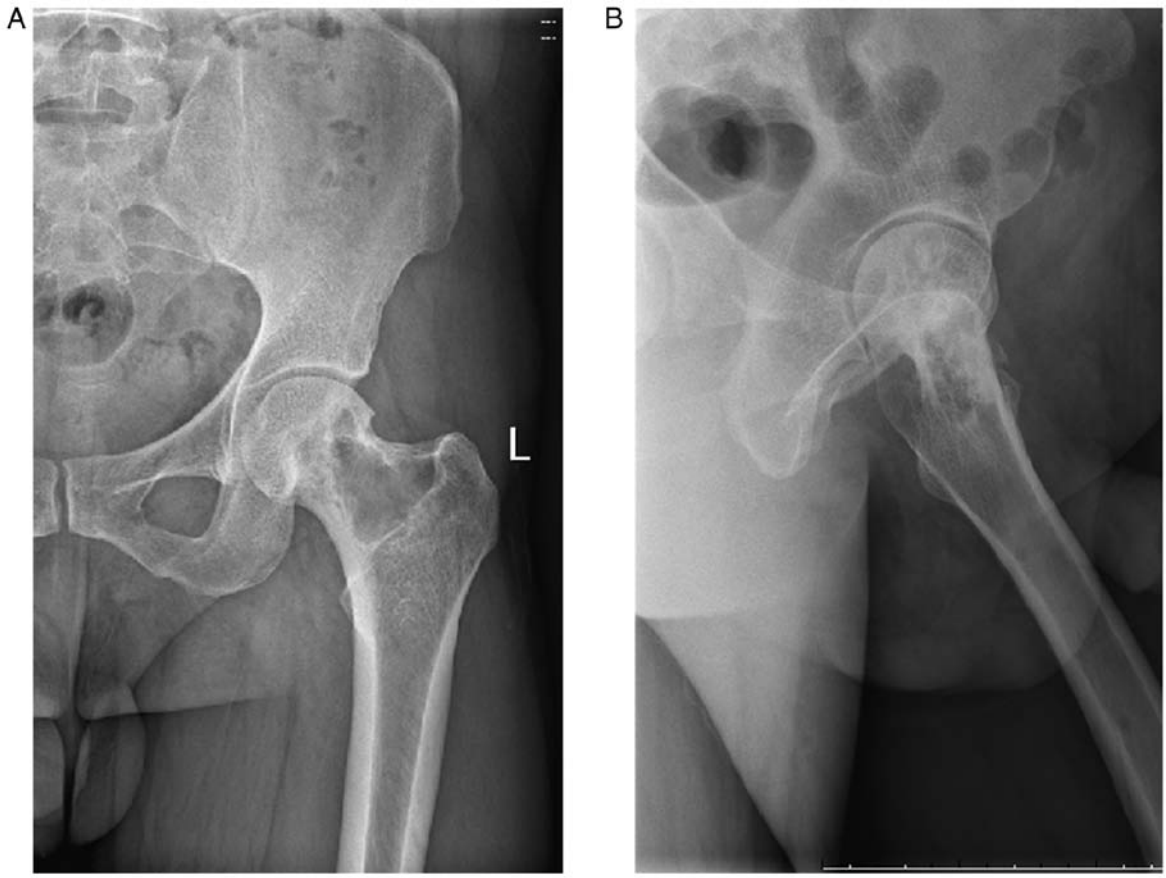

Figure 1. (A) Orthogonal and (B) lateral x-ray of the left hip joint. X-ray images indicate a benign bone disease with a high probability of aneurysmal bone cyst.

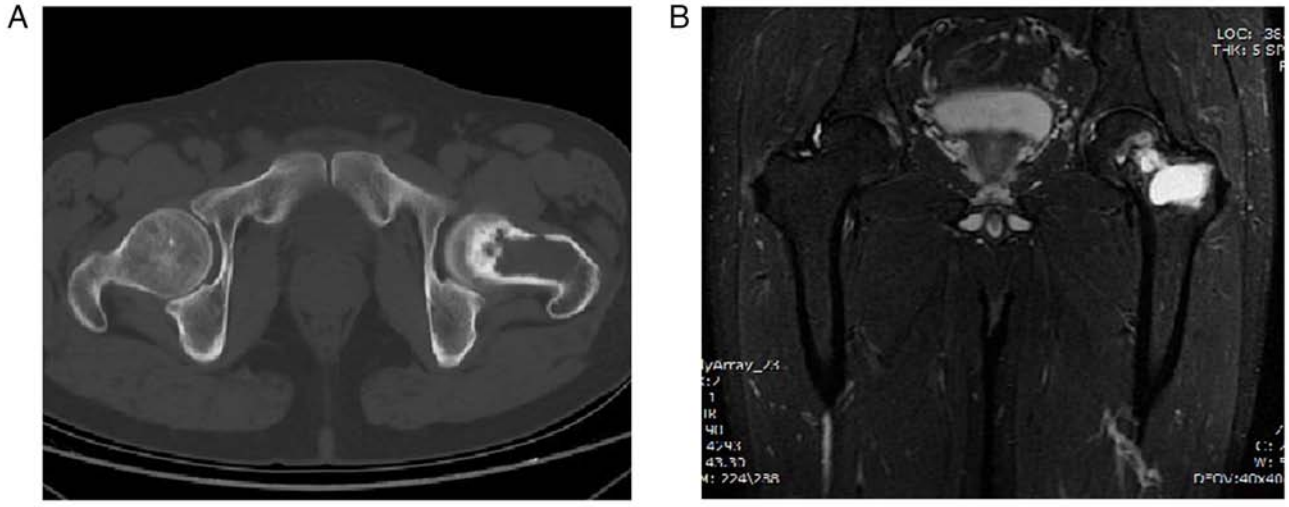

Figure 2. (A) Computed tomography image displaying a cystic shadow in the left femoral head and femoral neck with sclerotic margins, with a high probability of ABC. (B) Magnetic resonance imaging indicates an abnormal signal shadow in the left femoral head and femoral neck, further confirming the possibility of ABC. ABC, aneurysmal bone cyst.

Postoperative X-ray shows suitable external prosthesis and equal length of both lower limbs (Fig. 7). Postoperative treatment included the prevention of infection (cefuroxime sodium 1.5 g IV 2/day for 3 days), prevention of thrombosis (sodium heparin calcium 3075 iu subcutaneously), analgesia (parecoxib injection 40 mg intramuscularly) and functional hip exercises (for example, hip movement, muscle training, upright walking training). After the healing of the surgical incision, 8 rounds of chemotherapy were administered (protocol: injectable isocyclophosphamide 12 g/m^2 IV 24 h continuous pumping for 3 days + anrotinib hydrochloride capsule 12 mg orally 1/day for 3 weeks; cisplatin 110 mg/m^2 IV + liposomal doxorubicin 34 mg/m^2 IV, hydrotherapy for 3 days before chemotherapy). The two regimens were used alternately at 2-week intervals

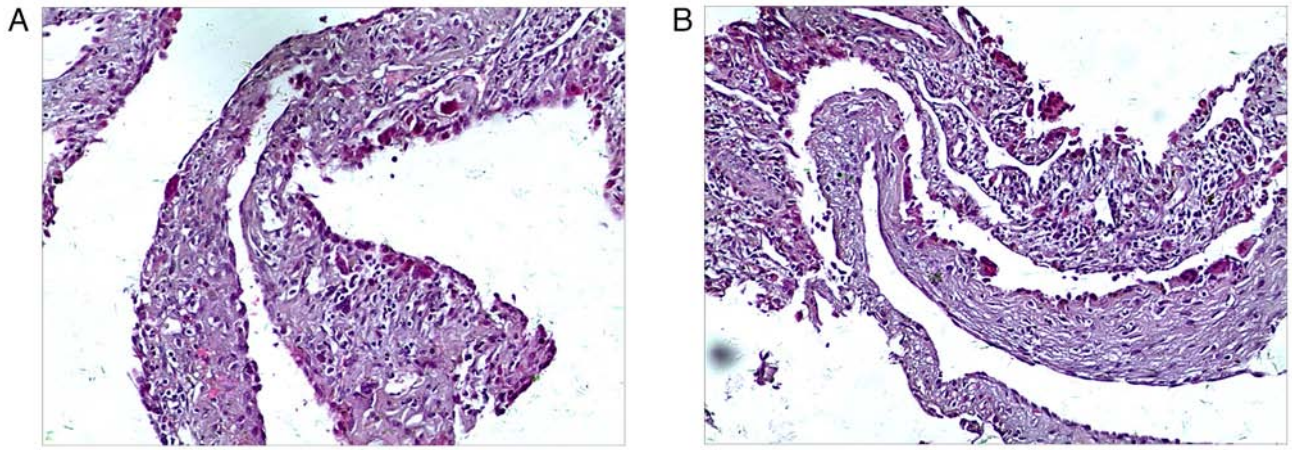

Figure 3. Pathology findings of the ABC: (A) and (B) are different fields of view under the same microscope (hematoxylin and eosin staining; magnification, x200). (A) A ribbon-like cyst wall structure was seen, with bleeding in the cyst lumen, spindle-shaped cells (the green arrow shows). (B) Multinucleated giant cells (the red arrow shows) in the cyst lining. This was consistent with an ABC. ABC, aneurysmal bone cyst.

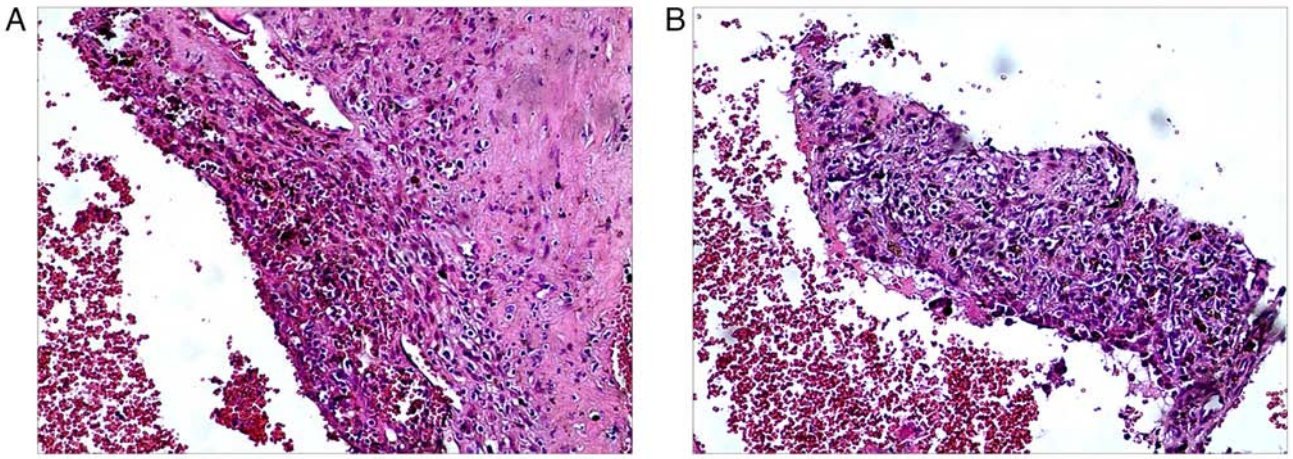

Figure 4. Pathology findings of the ABC recurrence: (A) and (B) are different fields of view under the same microscope (hematoxylin and eosin staining; magnification, x200). (A) The fibrous septum consisted of moderately dense, spindle-shaped fibroblasts with mild cell morphology and no heterogeneity. (B) Multinucleated osteoclastic giant cell reaction. This was consistent with the recurrence of ABC. ABC, aneurysmal bone cyst.

for a total of 8 sessions. The responses and side effects listed above occurred during postoperative chemotherapy and were treated symptomatically using the same strategy, and the chemotherapy process went well. The patient had good hip movement, no major pain, good walking ability, suitability for everyday life and employment and good alignment of the prosthesis without loosening or sinking on X-ray inspection at regular follow-up appointments two years following surgery (Fig. 8). The results of the review indicated that the tumor did not exhibit either local recurrence or distant metastasis

Discussion

A benign bone tumor that often occurs in adolescence and whose pathogenesis is yet unknown, ABC is an uncommon bone tumor with expansive, destructive and hemorrhagic characteristics (13). The histology of ABC is characterized by multiple blood-filled interstitial spaces, usually lined by a variety of cellular components, including multinucleated giant cells and fibroblast-like cells (14). Imaging can be used to diagnose ABC, but histopathology analysis is what determines the ultimate determination. The majority of ABCs are primary, and some are secondary, but both primary and secondary ABCs can develop into osteosarcoma, and certain benign or malignant tumors may be combined with ABCs (15). Despite the rarity of reports, the malignant transformation of ABC into osteosarcoma is more frequently linked to radiotherapy stimulation (16). Malignancy has also been reported in association with surgical treatment and stimulation by internal fixation (17), and a few reports have overlooked the possibility of coexistence with other tumors at the early stage of treatment (18).

In terms of the size of the lesion, the integrity of the bone shell and the internal calcification, CT has high diagnostic accuracy for ABC imaging diagnosis, and it can also display the cystic area and fluid plane of the aneurysmal bone cyst and the cystic septum (19). It can also show the cystic area, fluid level and interscapular space of aneurysmal bone cysts. Compared with CT, MRI has a higher resolution of soft tissues and can observe patients from multiple angles in coronal,

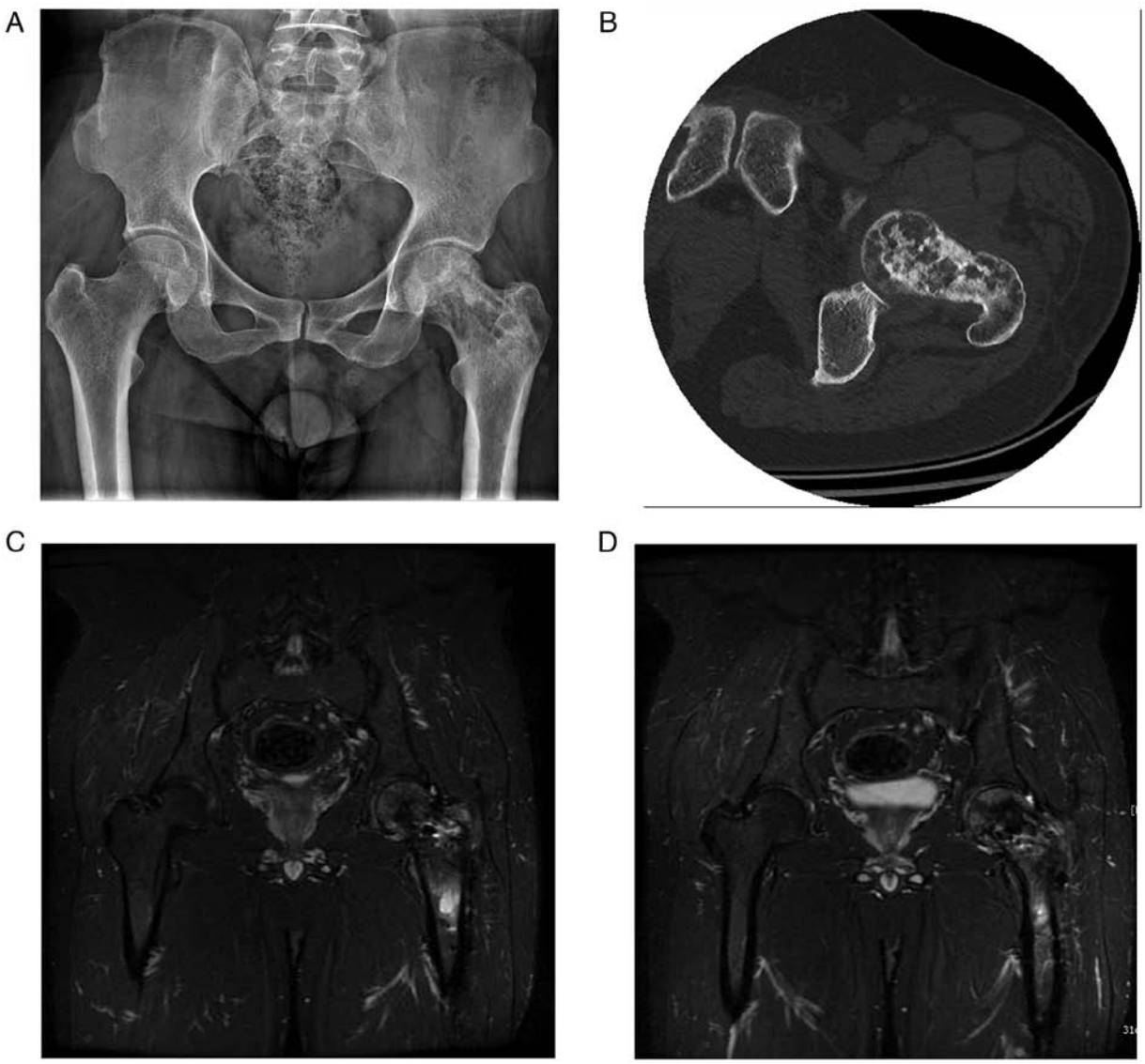

Figure 5. Imaging manifestations of aneurysmal bone cyst after malignant transformation: (A) X-ray examination shows heterogeneous bone density of the femoral neck. (B) CT examination reveals worm-like bone destruction of the left femoral head and neck with sclerotic bands in the tumor capsule and regular shape of the femoral head. (C) and (D) is the presence of tumour in the left femoral neck and proximal end observed on different levels of MRI. (C) MRI indicates heterogeneous bone signal in the left femoral head and neck with lengthy mixed T2 signal shadow. (D) A long T1 and long T2 signal with irregular morphology were seen in the medullary cavity of the upper femur; ~1.8 cm. Diffusion-weighted imaging exhibited a high signal.

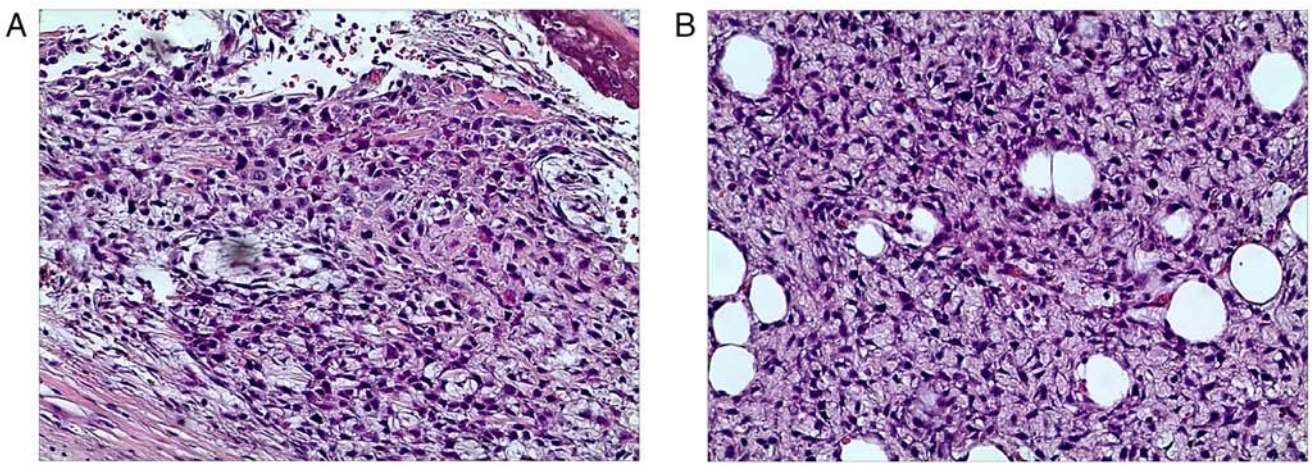

Figure 6. Pathology findings of aneurysmal bone cyst after malignant transformation: (A) and (B) hematoxylin and eosin staining (magnification, x200). The tumor area comprises heterogeneous cells with variable sizes, deeply stained nuclei, coarse granular chromatin and visible bone-like stroma formation, consistent with osteosarcoma of the left femoral head.

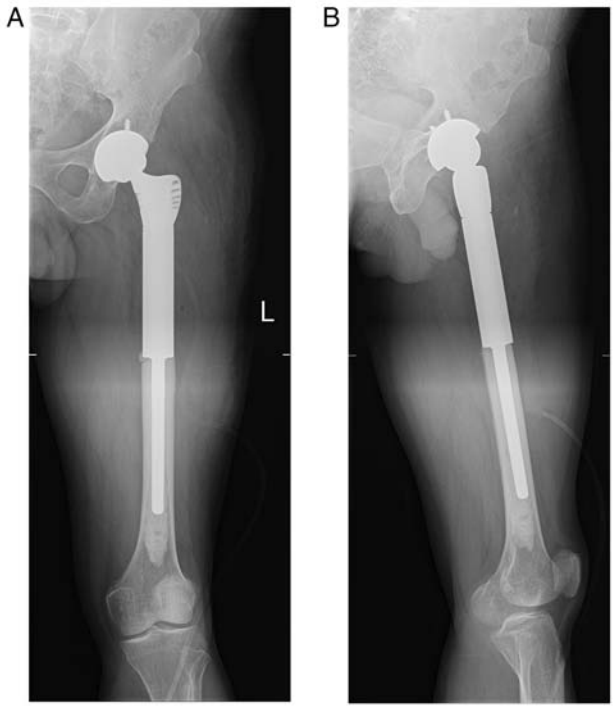

Figure 7. X-ray after tumor hip arthroplasty: (A) Orthogonal and (B) lateral x-ray of the left hip joint. Postoperative X-ray examination shows good position of the prosthesis.

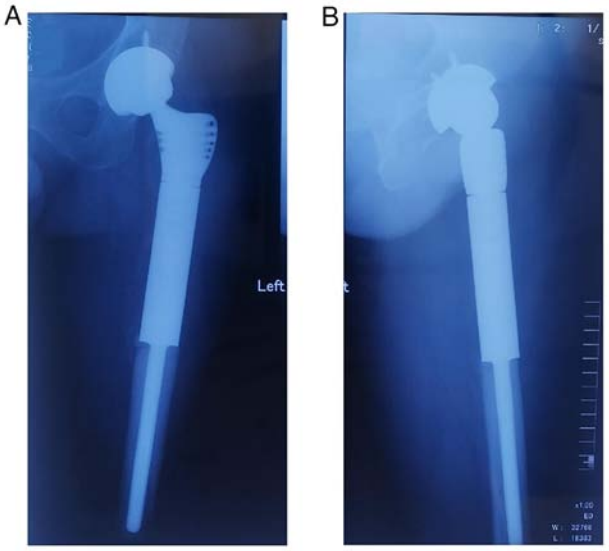

Figure 8. X-rays 2 years after surgery: (A) Orthogonal and (B) is a lateral x-ray of the left hip joint. X-ray examination reveals that the prosthesis is in a satisfactory location, with no loosening or sinking.

cross-sectional and sagittal planes and is more sensitive to hemorrhage, so that the internal structure and tissue hierarchy of bone cysts can be observed more clearly. In addition, the rate of fluid-fluid plane detection and cystic cavity detection is significantly higher in MRI compared with in CT, and the detection rate of pathological fractures is also higher in MRI compared with CT (20).

The ABC diagnosis was corroborated by prior imaging in the current case report, and all postoperative pathology samples sent out for analysis likewise revealed aneurysmal bone cysts. Imaging was abnormal after the second recurrence, with X-rays showing a heterogeneous density of the femoral neck, possibly related to the surgery. CT displayed worm-eaten destruction of the left femoral head and neck and wall of the aneurysm. Typical ABCs in MRI can show internal cystic cavities, low signal intervals of varying size and signal intensity, fluid planes within the lesion, cortical bone fractures and pushing at the border of the soft tissue, with equal or slightly low signal in T1WI sequences and mixed little high or high movement in T2WI. Reviewing the MRI revealed a heterogeneous signal in the femoral head and femoral neck bone, with a long mixed long T2 signal and a 1.8-cm irregular long T1 and long T2 signal in the medullary cavity of the upper femur. Therefore, after combining the CT and MRI results at the time of the evaluation of the patient, we hypothesized that the tumor could have undergone malignant transformation.

The malignant factors that emerged during the treatment of this case and a review of the relevant literature are considered as follows. First, there is the possibility of previously combined osteosarcoma, but the absence of osteosarcoma tissue in the first two pathological examinations was due to the osteosarcoma being in an early stage, the imaging presentation being unusual, the tumor being small and contained, or the inability to collect pathological sections (21). Second, it was considered that the first two pathological examinations were probably telangiectatic osteosarcoma, whose histological morphology was highly similar to ABC. Misdiagnosis or missing information might exist (22). The third factor was potential cancer caused by frequent irritation from surgery and internal fixation treatment (23). Therefore, the paraffin-embedded tissues from the two previous biopsies were once more subjected to histological examination to exclude the possibility of underdiagnosis or misdiagnosis. There was no osteosarcoma or telangiectatic osteosarcoma, and the patient had not received radiation therapy or other treatments. In conclusion, we hypothesized that the malignancy in the present case may be linked to several operations and ongoing irritation of the internal fixation.

There are various treatment options for ABC, including surgery, freezing, radiotherapy and medication, but the treatment modality changes immediately after malignant transformation into osteosarcoma. At this stage, the primary treatment modalities for osteosarcoma are extensive tumor resection, preoperative neoadjuvant chemotherapy and postoperative standardized chemotherapy. Preoperative neoadjuvant chemotherapy has been demonstrated to significantly increase patient survival, and, in a retrospective study, Hong *et al* (24) determined that patients who received preoperative neoadjuvant chemotherapy have a significantly improved 5-year survival rate. High-dose methotrexate, doxorubicin, cisplatin and isocyclophosphamide are still the major medications used in neoadjuvant chemotherapy; however, in the present case, anlotinib, a novel chemotherapeutic agent, and liposomal doxorubicin were also administered.

Doxorubicin, a classical chemotherapeutic agent for osteosarcoma, inhibits tumor cells by disrupting the structure and function of mitochondria (25). However, it has drawbacks, including difficulty in keeping blood levels of the drug stable, significant cardiotoxicity, high cardiotoxicity and resistance

of tumor cells (26). Therefore, in recent years, liposomal doxorubicin (L-DOX) has been used instead of doxorubicin. Haghiralsadat *et al* (27) demonstrated that L-DOX has a higher sensitivity and more stable blood levels of chemotherapy drugs compared with doxorubicin in the treatment of osteosarcoma. Another study showed less cardiotoxicity (L-DOX) (28). The main side effects of L-DOX are bone marrow suppression, gastrointestinal reactions, hypoproteinemia, stomatitis and transient sinus arrhythmias (29).

Anrotinib, a novel chemotherapeutic agent, is a multi-targeted tyrosine kinase inhibitor that suppresses the activation of downstream signaling pathways, phosphorylation of epithelial-mesenchymal transition and vascular endothelial growth factor receptor 2, tumor development and osteosarcoma chemosensitivity (30). In a retrospective study analyzed by Cai *et al* (31), the overall remission rate (ORR) and disease control rate (DCR) for osteosarcoma treated with the anlotinib regimen were 19 and 71%, respectively, with a median progression-free survival (PFS) of 5.4 months and overall survival (OS) of 17.9 months, which had higher ORR and DCR and possessed higher PFS and OS compared with the anlotinib chemotherapy regimen alone. This suggests that anlotinib in combination with other chemotherapies shows efficacy and tolerability in the treatment of refractory bone and soft tissue sarcoma. In the present case, the patient was assessed at the end of the neoadjuvant chemotherapy course, and the tumor was progression-free and metastasis-free for 2 years. With positive outcomes and no evidence of recurrence or distant metastases at follow-up, the chemotherapy regimen was continued postoperatively.

In summary, aneurysmal bone cysts should be treated with standardization, including in-depth intraoperative curettage of the lesion and routine postoperative examination. Patients with recurrent recurrence, radiation therapy and multiple surgeries should be cautioned of the potential for malignant transformation in clinical practice. Transformation of ABC in osteosarcoma is malignant process and it should also be treated in a standardized manner. Preoperative neoadjuvant chemotherapy and postoperative standardized chemotherapy are recommended, which can greatly improve patient survival and reduce recurrence and metastasis.

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Availability of data and materials

Not applicable.

Authors' contributions

XS, YQ and SZ conceived the study, participated in the design of the study, collected the data and images and drafted the manuscript. XS, YQ, HZ and LZ contributed to the revision of the article and the processing of the data and images. LS, JL, XY and HL participated in the study design and oversaw the manuscript drafting process. All authors have read and approved the final manuscript. XS and YQ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted with the consent of the patient, who signed an informed consent form.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying image.

Competing interests

The authors declare that they have no competing interests.

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