# Aneurysmal Bone Cysts of Soft Tissue Represent True Neoplasms

## A Report of Two Cases

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Aneurysmal bone cyst was first described by Jaffe and Lichtenstein in 1942[1]. It is considered a benign, locally aggressive lesion with a potential for local recurrence, and it typically appears in the metaphysis of the long bones and in the vertebral column[2-4]. Mostly, children and young adults are affected. No sex predilection has been observed. Radiographically, aneurysmal bone cyst is seen as a lytic lesion, usually eccentrically located and expansile but with well-defined margins. Histologically, there are blood-filled cysts separated by fibrous septa, with fibroblasts as well as osteoclast-type giant cells and reactive woven bone[5]. Historically, aneurysmal bone cyst was believed to occur exclusively in bone[6]. In 1972, Salm and Sissons noted soft-tissue lesions resembling aneurysmal bone cysts, and this was probably the first description of this entity[7]. For many years, aneurysmal bone cyst was thought to be a lesion, reactive in nature, caused by a circulatory abnormality leading to an increased venous pressure and resulting in dilation of the vascular network[2,8,9]. In recent years, strong evidence has supported the neoplastic nature of aneurysmal bone cyst[10-13]. In 1999, Panoutsakopoulos et al.[10] demonstrated chromosomal

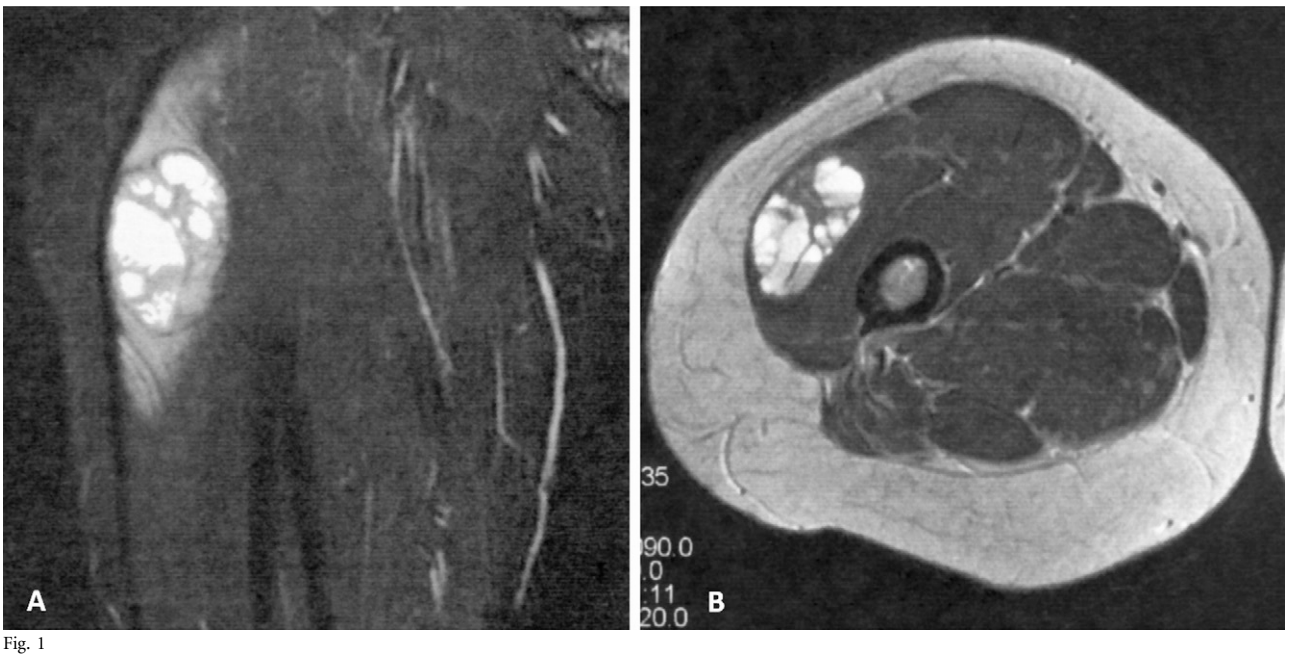


Fig. 1

Case 1. *A:* Coronal STIR (short tau inversion recovery) MRI sequence of the right thigh shows a well-circumscribed cystic lesion with multiple septae with surrounding edema in the vastus lateralis muscle. *B:* Axial T2-weighted TSE (turbo spin echo) MRI image through the center of the lesion shows the location of the lesion within the muscle. Typical fluid-fluid levels are seen.

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translocation t(16;17)(q22;p13) as a recurrent cytogenetic abnormality in primary aneurysmal bone cyst, which was confirmed by other groups[11-13]. We report two cases of soft-tissue aneurysmal bone cyst with USP6 locus rearrangement on chromosome 17p13. The patients were informed that data concerning their cases would be submitted for publication, and they consented.

## Methods

Tissue specimens from two cases of primary soft-tissue aneurysmal bone cyst were collected in 2007, fixed in 5% buffered formalin, and processed in standard fashion after decalcification, and micrometer sections were prepared with hematoxylin and eosin staining. The histological findings were reviewed by two bone and soft-tissue pathologists, and imaging studies were reviewed by an expert radiologist; the diagnosis of aneurysmal bone cyst was made with use of established diagnostic criteria[14]. Molecular cytogenetic analysis with fluorescence in situ hybridization (FISH) studies was performed on the paraffin-embedded tissue.

### *Fluorescence in Situ Hybridization (FISH)*[15]

Bacterial artificial chromosome (BAC) clones flanking the USP6 locus on chromosome 17p13 were obtained from the Children's Hospital Oakland Research Institute (Oakland, California). DNA isolation was performed according to Qiagen plasmid Maxi Kit specifications (Qiagen, Valencia, California). DNA was labeled with use of a Nick Translation Kit from Abbott Molecular (Vysis, Downers Grove, Illinois). Interphase molecular cytogenetic studies were performed on 4-μm paraffin-embedded thin sections that were deparaffinized in xylene (twice for fifteen minutes), dehydrated twice in 100% ethyl alcohol for five minutes, and treated with 10 mmol/L citric acid for ten minutes in a humid microwave. Tissue sections were then transferred to 37°C 2× standard saline citrate for five minutes, and protein was digested with Digest All-3 (Zymed, San Francisco, California). After brief washing in 1× phosphate-buffered saline solution, the slides were sequentially dehydrated in alcohol (70%, 85%, and 100%) and air-dried at room temperature. Tissue sections were denatured at 80°C for five minutes, and BAC probe hybridization was carried out overnight in a humidified chamber at 37°C. Tissue sections were then washed in 0.1% NP40/2× standard saline citrate at 76°C for four minutes and subsequently washed in 0.1% NP40/2× standard saline citrate at room temperature for one minute. Slides were then mounted in Vectashield mounting medium (Vector Laboratories, Burlingame, California) with 1.5 μg/mL of 4′,6-diamidino-2-phenylindole. Tumor samples were scored by two independent investigators and considered positive if >5% of 200 cells analyzed showed splitting apart of the flanking fluorescence in situ hybridization probes.

## Case Reports

CASE 1. A twenty-six-year-old woman had a two-month history of pain in the right thigh. Although she worked in a gym, no specific traumatic event was identified. On examination, a painful lump, 7 × 5 cm, was identified in the

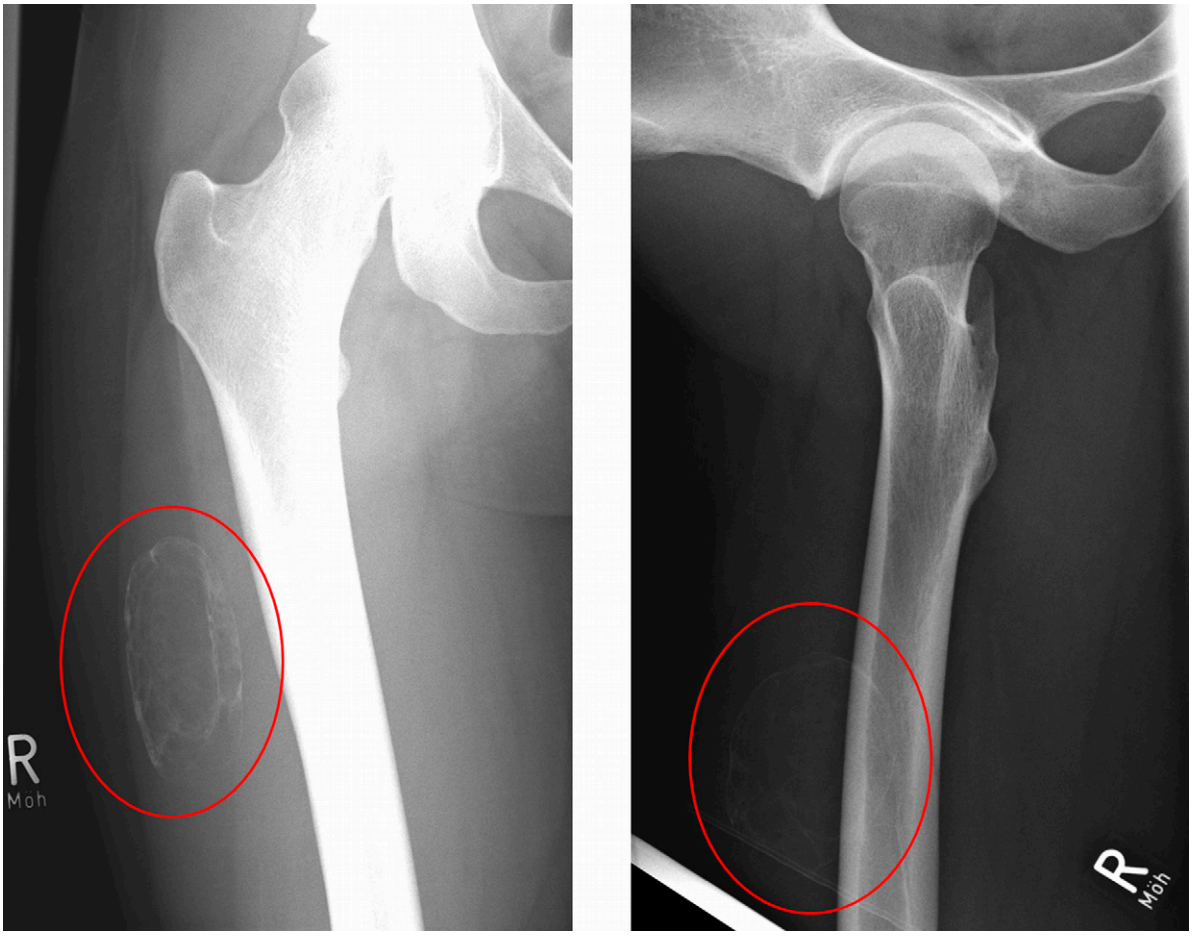


Fig. 2

Case 1. Anteroposterior and lateral radiographs of the right thigh show the oval-shaped ossification within the soft tissue.

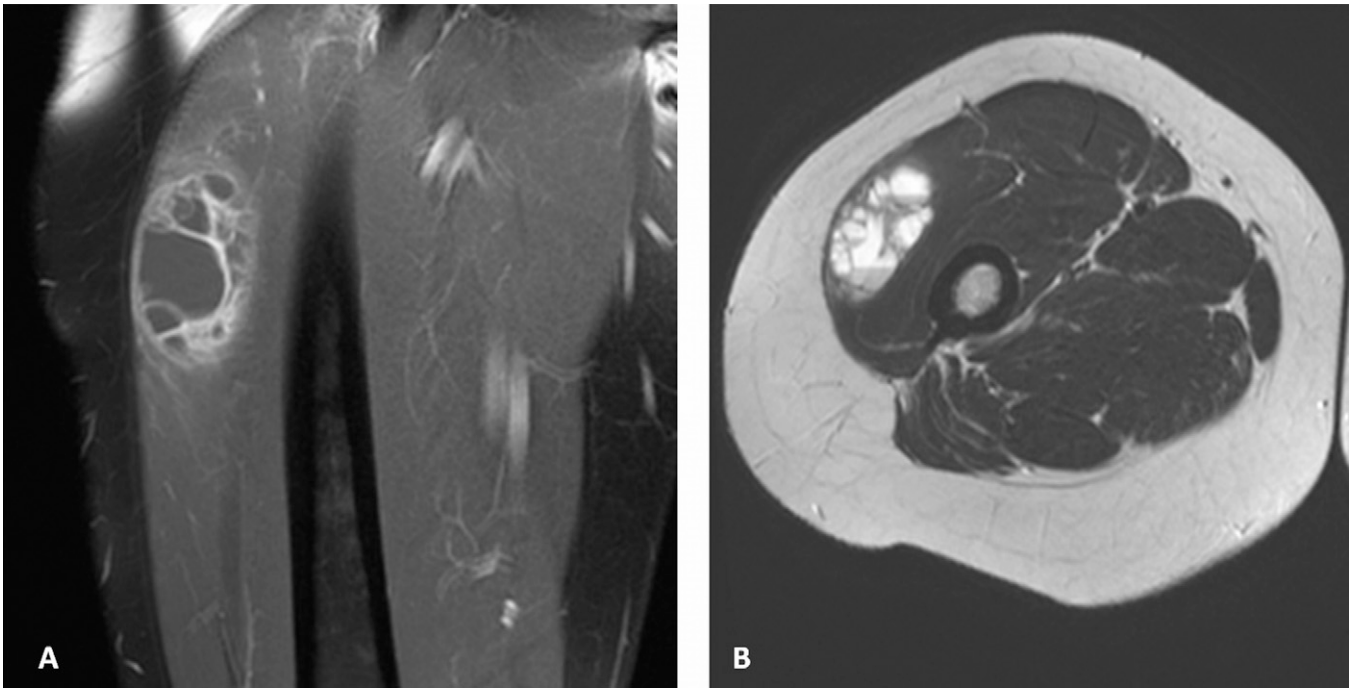


Fig. 3

Case 1. *A:* T1-weighted FS (fat-suppressed) TSE MRI sequence after administration of gadolinium contrast medium shows a well-demarcated lesion with peripheral and septal enhancement. *B:* T2-weighted TSE axial MRI sequence shows a well-demarcated lesion with multiple septae and typical fluid-fluid levels.

anterolateral aspect of the right thigh. There was no sign of inflammation, and the findings on examination were otherwise unremarkable. Radiographs showed a mass with a thin peripheral shell of ossification not connected to bone. Magnetic resonance imaging (MRI) showed a mass with multiloculated cystic spaces and fluid-fluid levels in the superficial aspect of the vastus

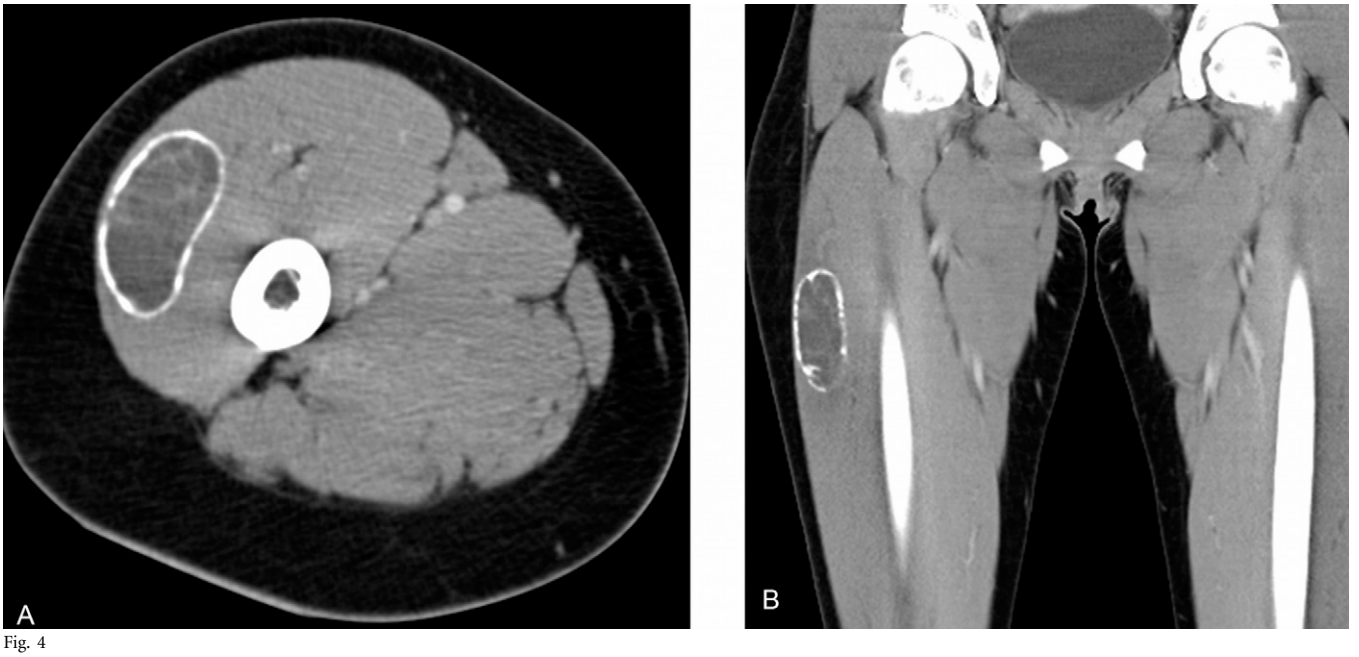


Fig. 4

Case 1. Axial CT scan (A) and coronal reconstruction of the lesion (B) show a well-circumscribed soft-tissue mass with low density and peripheral ossification (''eggshell'').

lateralis muscle (Fig. 1). As there was no sign of malignant disease, it was decided to follow the patient.

Four months later, the patient reported a change in the pain and consistency of the lesion. Radiographs and computed tomography (CT) revealed increased ossification (Figs. 2, 3, and 4), and follow-up MRI showed an increase in the size of the lesion with more prominent septae and fluid levels and diminished edema. Marginal excision of the lesion was performed.

After recovery from the surgery, the patient remained free of pain and recurrence, with unrestricted physical activity, as noted at the time of the latest follow-up, at thirty-six months.

*Histological findings:* Gross examination of the resection specimen showed a well-circumscribed 8 × 6 × 3-cm mass covered by muscle fibers. Sectioning revealed multiple cystic spaces bordered by an eggshell of bone at the perimeter of the lesion. Foci of multinucleated osteoclast giant cells were identified histologically. Atypical cells were not evident, and an infiltrative pattern was not seen (Fig. 5).

CASE 2. A thirty-eight-year-old man presented with a lump in the soft tissue of the distal part of the left upper arm, which he had had for one month. There was no history of trauma, and on examination there was a walnut-sized painful tense mass proximal to the lateral humeral condyle, which was firmly attached to the surrounding soft tissues. No other abnormalities were identified.

Radiographs showed a soft-tissue lesion with discrete ossifications proximal to the lateral humeral condyle. MRI showed a soft-tissue mass located in the brachioradialis muscle that was highly suspicious for sarcoma (Fig. 6). MRI with contrast medium showed uptake mainly in the periphery of the

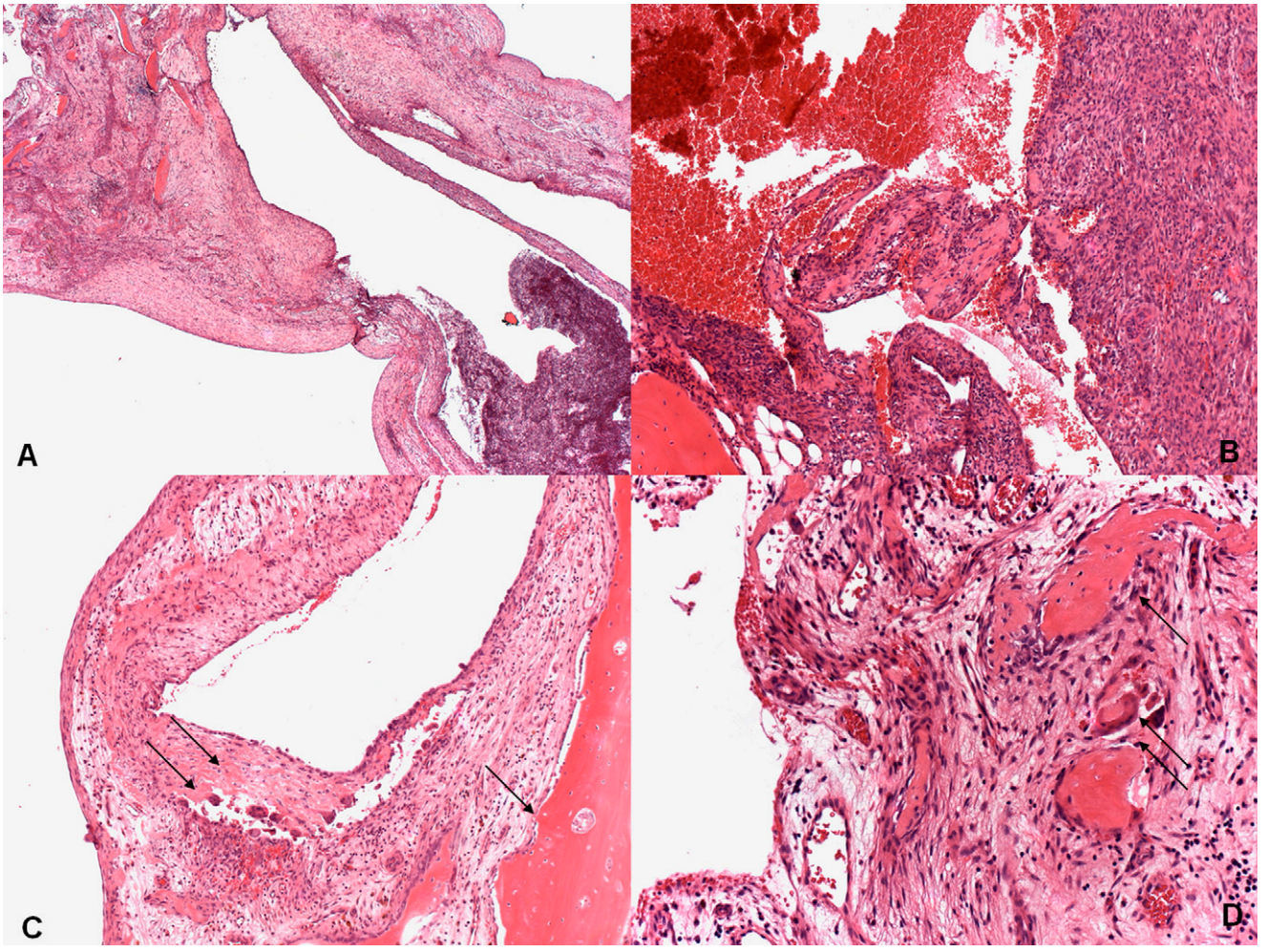


Fig. 5

Case 1. Histological features of the aneurysmal bone cyst of soft tissue (hematoxylin and eosin). *A:* Anastomosing branching of fibrous septa with bone formation of broad cystic and blood-filled spaces (×25). *B:* Collapsed cystic spaces with cellular fibrous septa without atypia and osteoid formation (×100). *C:* Eggshell layer of mature bone (single arrow) at the peripheral border of the lesion and osteoclastic giant cells in fibrous, less cellular septa associated with osteoid and woven bone trabeculae (double arrows) (×100). *D:* Higher magnification of fibrous septa with fibroblastic stroma component, scattered lymphocytes, and immature bone formation with osteoblastic rimming (single arrow) and osteoclastic resorption of bone (double arrows) (×200).

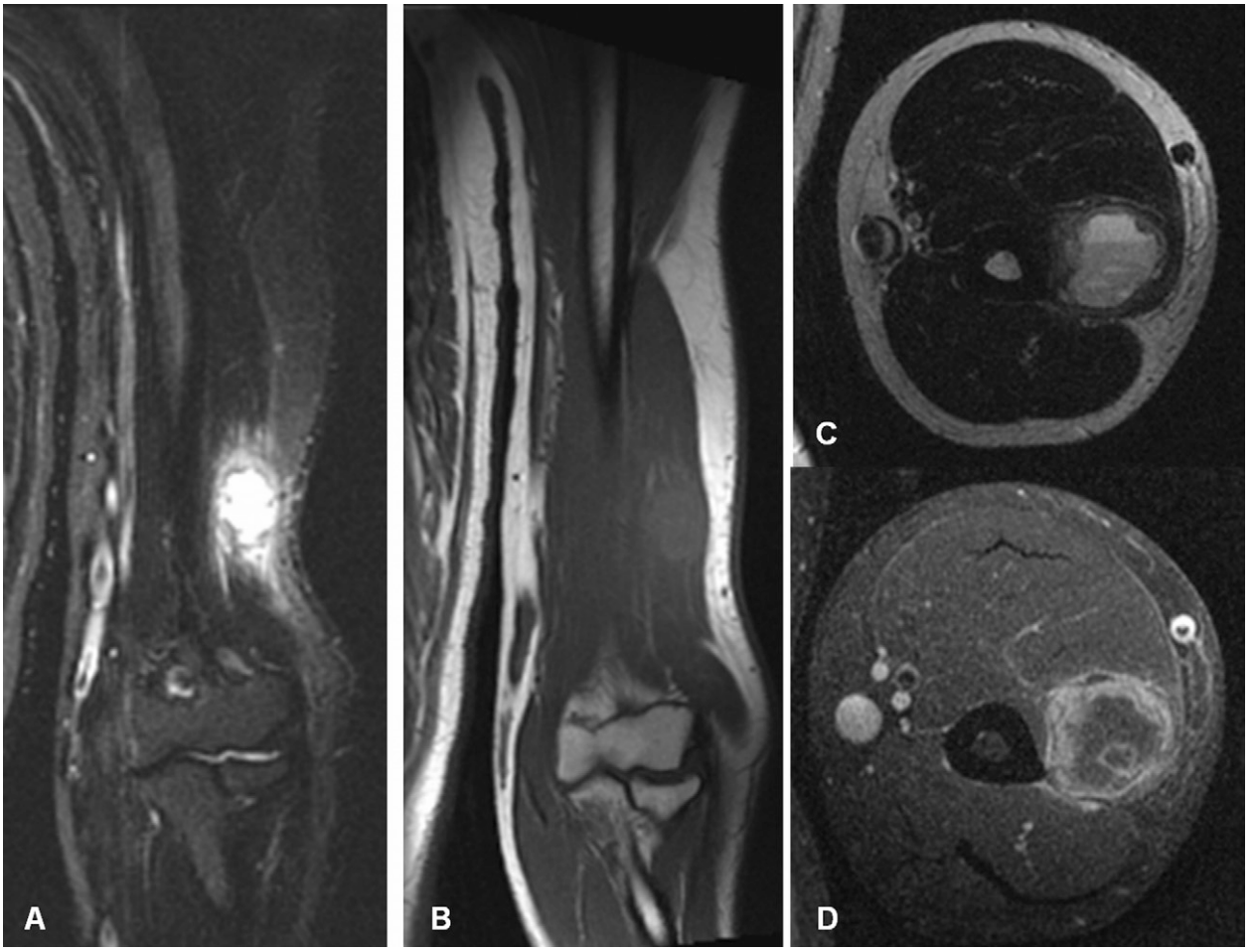


Fig. 6

Case 2. *A:* Coronal STIR MRI sequence shows a round hyperintense lesion with surrounding edema in the brachioradialis muscle. *B:* On the coronal T1-weighted TSE MRI sequence, the lesion is isointense. *C:* On the axial T2-weighted TSE MRI sequence, fluid-fluid levels are present. *D:* On the axial T1-weighted TSE MRI sequence after administration of contrast medium, marked peripheral and septal enhancement is seen.

lesion and within some septae, an MRI pattern sometimes seen with necrotic sarcomas and that has been reported with malignant fibrous histiocytoma[16].

A needle biopsy revealed a giant-cell-rich lesion that did not meet the criteria for malignancy. Staging CT of the chest and abdomen showed negative findings. Wide local tumor excision was performed. There was no recurrence at the time of follow-up twenty-nine months later.

*Histological findings:* Macroscopically, there was a firm, well-circumscribed mass, 4 × 3 × 2 cm, that, on cross section, demonstrated blood-filled multilocular cystic spaces with a well-demarcated eggshell of bone at the perimeter of the lesion (Fig. 7).

### *Fluorescence in Situ Hybridization (FISH)*

Both tumors had a balanced USP6 locus rearrangement demonstrated by fluorescence in situ hybridization.

## Discussion

The first two cases of soft-tissue aneurysmal bone cyst were probably reported by Salm and Sissons in 1972[7]. The number of published cases does not exceed twenty (see Appendix), with only a few epidemiological and histological reports. The appearance of soft-tissue aneurysmal bone cyst on radiographs and CT scans may be similar to that of myositis ossificans, but on MRI scans the presence of septae within the lesion and fluid-fluid levels help to differentiate it from myositis ossificans[5,6]. Nevertheless, it can be difficult to distinguish myositis ossificans from soft-tissue aneurysmal bone cyst on the basis of radiographic features in some cases[5,15]. Ossifying fibromyxoid tumor sometimes presents radiographically with bone formation at its periphery and can mimic soft-tissue aneurysmal bone cyst[17]. Also, extraskeletal telangiectatic osteosarcoma may have fluid-fluid levels within the lesion similar to those of soft-tissue aneurysmal bone cyst[18]. Histological features of soft-tissue aneurysmal bone cysts are indistinguishable from those of aneurysmal bone cysts within bone[1,4,5].

The histological differential diagnosis of soft-tissue aneurysmal bone cyst includes giant-cell-rich and cystic lesions of soft tissue, which can be problematic. These lesions include benign conditions such as nodular fasciitis, ossifying fibromyxoid

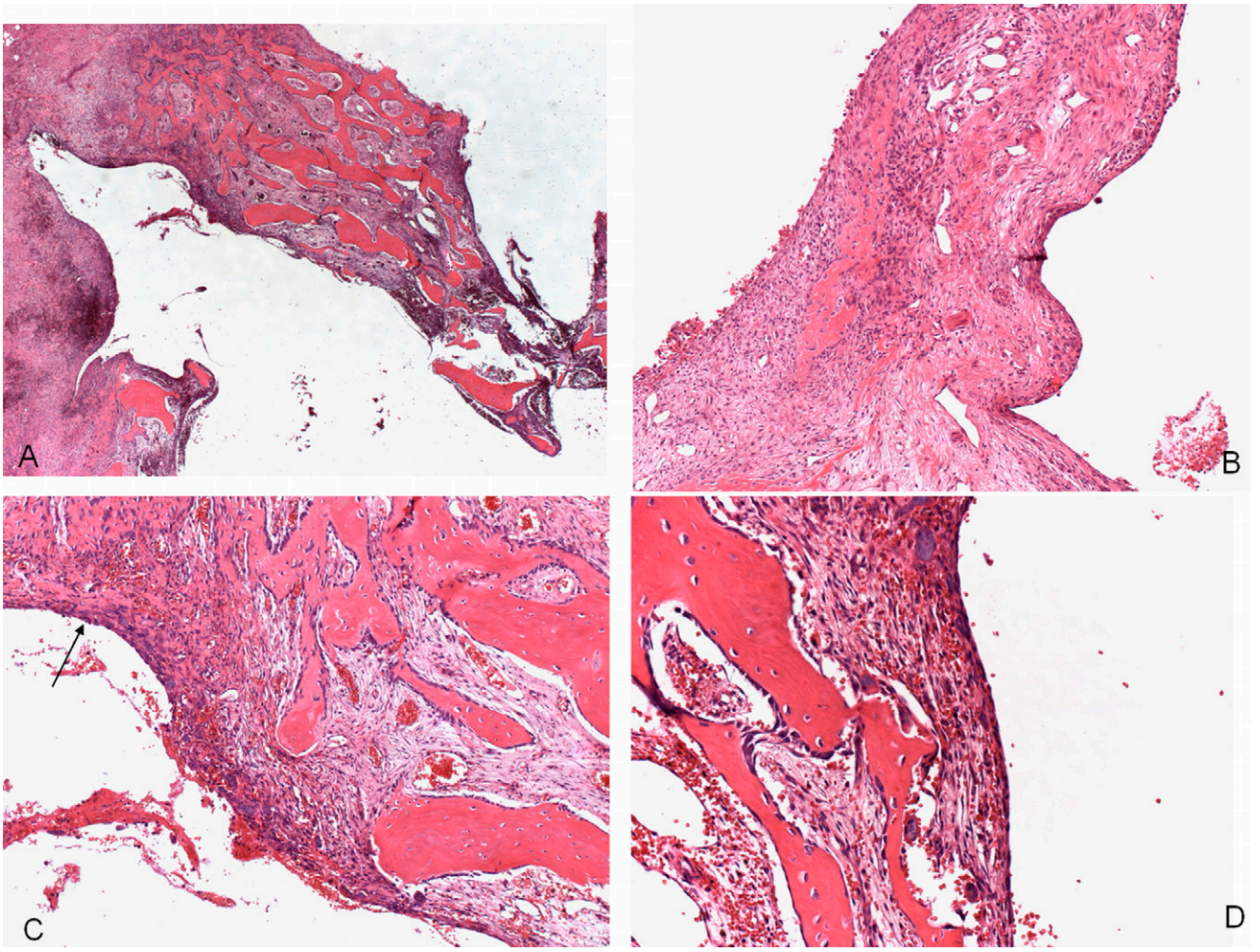


Fig. 7

Case 2. Histological features of the aneurysmal bone cyst of soft tissue (hematoxylin and eosin). *A:* In contrast to Case 1, in this lesion fibrous septa are much more compact and more bone formation of lamellar woven bone is seen (×25). *B:* Focal lace-like deposits of osteoid formation in fibrous septa with edematous stroma and capillaries (×100). *C* and *D:* Fibrous septa with lamellar woven bone and osteoid deposits (arrow in C) and osteoclastic, multinucleated giant cells in the fibrous stroma with hemorrhagic foci and osteoblastic rimming of mature woven bone (×100 [C] and ×200 [D]).

tumor, and giant-cell tumor of the tendon sheath as well as potentially malignant or malignant lesions such as giant-cell tumor of soft tissue and the telangiectatic subtype of extraskeletal osteosarcoma[19-21].

Aneurysmal bone cysts have been shown to have recurrent rearrangements of the USP6 gene on chromosome 17p13[11,22,23]. USP6—also known as TRE2 or TRE17—was first identified as a potential oncogene on the basis of its transforming properties when NIH-3T3 cells were transfected with Ewing sarcoma DNA[24,25]. It encodes a ubiquitin-specific protease (USP) and a TBC domain that mediates binding to the Arf6 GTPase[26]. USP6 has effects on cell adhesion and actin remodeling[27]. Oliveira et al. reported, in 2004, that the product of this chromosomal translocation creates a fusion gene in which the osteoblast cadherin 11 gene (CDH11) promoter region on 16q22 is juxtaposed to the entire ubiquitin-specific protease USP6 (Tre2) coding sequence on 17p13[28]. The fusion gene CDH11-USP6 and that USP6 rearrangement are specific for primary aneurysmal bone cyst and not found in the so-called secondary aneurysmal bone cyst, which is commonly associated with giant cell tumor, chondroblastoma, osteoblastoma, and fibrous dysplasia[28].

Rearrangements of USP6 have been found in approximately 70% of aneurysmal bone cysts (70% sensitivity) but have not been found in other tumors (100% specificity)[15,28].

Petrik et al. described an aneurysmal bone cyst-like reaction in the left carotid artery bifurcation in an otherwise healthy seven-year-old[29]. Since that time, there have been fewer than twenty case reports of soft-tissue aneurysmal bone cysts in the literature[5-7,15,19,28-33]. The histological features of soft-tissue aneurysmal bone cyst are identical to those of intraosseous aneurysmal bone cyst except for its extraosseous location[19].

Histological features of aneurysmal bone cyst overlap with those of other osseous lesions such as myositis ossificans, cherubism, and brown tumor[14,15]. In a 2008 study, Sukov et al. looked for USP6 rearrangements in soft-tissue aneurysmal bone cyst, myositis ossificans, cherubism, and brown tumor and found no such rearrangements in cherubism or brown tumor[15]. However, molecular cytogenetic studies revealed USP6 rearrangement in two of twelve specimens previously classified as myositis ossificans on the basis of their radiographic appearance[15]. One of the two patients presented initially with classic radiographic features of myositis ossificans, but the radiographic appearance changed to that of an aneurysmal bone cyst over time. It is also of interest that no inciting trauma could be identified for this patient. These data reported by Sukov et al. were verified by the analysis of our patients, both of whom were found to have USP6 rearrangements and no history of trauma. Nielsen et al. reported five cases of soft-tissue aneurysmal bone cyst, with no patient having a known history of trauma[5].

Nielsen et al. reported only one recurrence in their five patients with soft-tissue aneurysmal bone cyst, in whom an intralesional resection had been performed[5]. The other four patients had been free of recurrence for sixteen months to ten years, findings in concordance with those in other reports of a long disease-free survival after resection of soft-tissue aneurysmal bone cyst[6,7].

Given that soft-tissue aneurysmal bone cyst may be confused with other, similarly appearing lesions on radiographs, we believe that soft-tissue aneurysmal bone cyst might be more frequent than one would assume on the basis of the published literature. Therefore, fluorescence in situ hybridization analysis of USP6 rearrangement could be a very helpful tool for differentiating soft-tissue aneurysmal bone cyst from other soft-tissue tumors, especially myositis ossificans.

## Appendix

eA A table reviewing cases of soft-tissue aneurysmal bone cysts in the literature is available with the online version of this article on our web site at jbjs.org. ■

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