Aneurysmal bone cyst of the frontal bone - A radiologic-pathologic correlation

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ABSTRACT

We present a case of 27-year-old female who presented for a progressive frontal swelling with ipsilateral headache. Subsequent CT scan revealed an extradural and expansile multiloculated mass with thin and strongly enhanced septations and MRI evaluation showed internal hyperintensity on T2 with no restriction of diffusion and confirmed the multiple cystic spaces with enhancing septations and rare hemorrhagic fluid-fluid levels. Surgery was performed and diagnosis of aneurysmal bone cyst was made on frozen section. Identification of USP6 fusion gene by in situ hybridization technique permitted to confirm the diagnosis of primary ABC. Although aneurysmal bone cyst (ABC) of the skull is a very rare entity and accounts for 2-6% of all ABCs, we should think about it in front of osteolytic and cystic skull changes even with very few fluid-fluid levels. Following description of our case and differential diagnoses, we conduct a literature review of skull ABCs imaging characteristics and discuss the interest of USP6 rearrangement identification.

CASE REPORT

Clinical history

A 27-year-old female presented to the emergency room with a two-month history of progressive localized swelling of the right forehead painless and renitent at palpation with ipsilateral and worsening headache. An episode of dengue hemorrhagic fever with bilateral retinal damage was the only finding in her past medical history with partial vision recovery. Neurological examination was normal. On fundus exam, she had no papilledema but signs of chronic retinopathy.

Imaging

Computed tomography (CT scan) with and without contrast agent (venous and late phase) was performed. It showed an expansile extra-axial lytic lesion of the right frontal bone of 6.5cm in diameter causing destruction and thinning of the outer and inner cortex with a thin residual rim of bone shell of the inner cortex. The mass had a slight extra-cranial extension but was dramatically protruding intracranially causing a compression on the right frontal lobe with cerebral midline shift of 7 mm to the left. It was in direct contact with the superior sagittal sinus but no tumor involvement or thrombosis of the sinus was observed. There was no clear infiltration of the dura. The lesion was multiloculated,
containing multiple cysts, of 2 to 5 mm of size, delimited by strongly enhancing septations, and large anomalous drainage veins. No solid nodule was detected (Figure 1). Magnetic resonance imaging (MRI) revealed the cystic mass of soap-bubble appearance displaying a low intensity signal on T1-weighted images, high signal intensity on FLAIR, with hemosiderin deposits on magnetic susceptibility images (gradient-echo T2 weighted), and intense septal enhancement on gadolinium T1-weighted images. The dura was also enhanced. Rare fluid-fluid levels were present, more visible on gradient-echo T2 weighted. No diffusion restriction was found (Figure 2).

The lesion had no enhanced metabolism on positron emission tomography-computed tomography (PET-CT) with 18F-FDG (Figure 3).

Our two main radiological diagnoses were a primary ABC or aneurysmatic changes associated with another bone tumor (so-called secondary ABC) because the localization was atypical for a primary ABC. A telangiectatic osteosarcoma was also considered as a differential diagnosis because of destructive behavior of the lesion with high vascularization and hemorrhagic fluid-fluid levels within the cystic cavities that are difficult to distinguish from ABCs. The diagnosis of meningioma was mentioned but was rapidly dismissed because of no dural thickening. Moreover, the multicystic appearance with hemorrhagic deposits would be very atypical for a meningioma.

Surgical treatment
The intervention, carried out under general anesthesia, consisted of gross total resection through frontal craniectomy. Fronto-temporal arc-shaped skin incision of the forehead was followed by dissection of the temporal muscle and preparation of the frontal bone. At this point, an osseous tumor mass of the outer cortical layer of the frontal bone was discovered. Tumor expansion was evaluated with neuro-navigation. Trepanation holes and circular incision around the tumor lesion were set. Then, the excised skull part was carefully mobilized to dissect dura from tumor. Then, the tumor attached to the excised skull could be removed as an entity. Immediate pathologic analysis was carried out. As the dura seemed locally invaded, all invaded areas were excised and replaced by plastic surgical material. Because of the bone defect a cranioplasty was made using bone cement (Palacos). No neurological deficit was encountered after the intervention. Post-surgery imaging control showed a complete resection of the lesion (Figure 4).

Macroscopy
On the inner side of the skull, a round multiloculated tumor mass of 5 x 2 cm with multicystic appearance was noted. Cyst content was in part hemorrhagic, with a mother-of-pearl wall. Macroscopic aspects are shown in Figure 5 with the radiologic correlation in Figure 6.

Histology
The mass consisted of multiple spaces of different size, round or multangular, at times multiloculated containing blood and macrophages and rare multinucleated cells. Cystic spaces had no endothelium; they were lined by connective tissue of dense and hypocellular aspect or by a proliferation of fusiform elements with oval nuclei and multinucleated giant cells without atypia or mitosis. Some macrophages with foamy cytoplasm were also present. In some places, metaplastic bone trabeculae were found parallel to the cyst walls. The tumor penetrated the bone tissue without expanding beyond the periosteum of the outer layer of the skull. The native bone of the skull was thinned out in the central part of the lesion and thicker in the peripheral part. The trabeculae of the spongiosa were thickened by new bone of irregular architecture, but the hematopoietic bone marrow showed no abnormality. The dura was covered by tissue of ABC but remained not invaded. Rearrangement of the USP6 gene locus by fluorescence in situ hybridization (FISH) was found. Microscopic views with hematoxylin eosin coloration are shown on Figure 7.

DISCUSSION

Etiology & Demographics:
Aneurysmal bone cysts (ABCs) were first described in 1942 [1] by Jaffe and Lichtenstein. They are benign, expansile osteolytic lesions containing thin-walled, blood-filled cystic cavities. These lesions commonly involve the metaphysis of long tubular bones, vertebrae or flat bones of patients younger than 20 years. ABC of the skull is a very rare entity and accounts for 2-6% of all ABCs [2, 3]. We describe a case of ABC of the skull with an interesting correlation of radiologic findings and pathology.

Final pathological and molecular diagnosis was a primary aneurysmal bone cyst of the frontal bone. It was a difficult clinical and radiological diagnosis due to the unusual location and highly destructive behavior.

ABCs are rapidly growing benign bone tumors that account for 1-2% of all primary bone tumors. Eighty per cent of ABCs are seen within the first two decades of life. These lesions typically arise from the metaphysis of a long tubular bone. They are also commonly found in the vertebrae. Skull bones are a very rare location with an incidence of 2-6% of all ABC [2, 3] with calvaria more frequently involved than skull base. Less than fifty cases of frontal ABC have been reported in the literature [4]. Other than the frontal bone, ABCs have been reported in the ethmoidal, sphenoidal, temporal, occipital and parietal bones as well as the facial bones such as mandible, maxilla or zygoma [5]. Most ABCs are primary, but thirty percent of all ABCs are associated with another skeletal lesion and have been called secondary ABCs. In reality these are not ABCs but rather aneurysmatic changes. In some cases, aneurysmatic changes can completely obscure the underlying lesion. Lesions displaying aneurysmatic changes include fibrous dysplasia, giant cell tumors, non-ossifying fibromas, hemangiomas, osteoblastomas, simple bone cysts, chondroblastoma, chondromyxoid fibromas; aneurysmal changes also occur in osteosarcomas [6].

Clinical & Imaging findings:
Clinically, presentation depends on location. In skull vault, pain and local swelling are the major symptoms of ABCs with usually no cranial nerve compromise, contrary to
skull base involvement [7]. In cranial ABCs, the most common radiographic appearance is that of an eccentric and expansile lesion with a narrow zone of transition and cortical thinning. CT usually shows an expansile lytic lesion with widening of diploic spaces, septations and a well-defined thin margin that strongly enhanced after contrast. On MRI, usually a well-defined expansile mass lined by a T1 and T2 hypointense rim, with internal septations that divides into small cavities is seen. The internal cysts present low to medium signal intensity on T1-weighted images and high intensity on T2-weighted images. The hypointense rim surrounding the lesion is an important finding and suggests a benign process with integrity of periosteal membrane. After gadolinium injection, the peripheral capsule and internal septations strongly enhance. The hallmark of an ABC, slightly present in our case, is the fluid-fluid levels that represent the sedimentation of red blood cells in hemorrhagic cavities [8, 9]. Fluid levels are present on CT in 35% of cases [10]. Sensitivity of MRI to detect fluid-fluid levels is higher than that of CT, especially on gradient-echo T2-weighted because of deoxyhemoglobin deposits. However, this is not constant and not specific. Fluid-fluid levels may be also observed in telangiectatic osteosarcoma, chondroblastoma, fibrous dysplasia, recurrent malignant fibrous histiocytoma and classical osteosarcoma [7]. Secondary ABCs usually present a solid nodular component, although it is not constant, depending on the companion lesion associated. FDG PET could be useful for atypical or rare presentation as in our case. Typically, cystic components of primary ABCs have no increased metabolism on FDG PET whereas peripheral margin could have increased activity. It could help for differential diagnosis of malignant tumor such as telangiectatic osteosarcoma or when there is a suspicion of accompanied secondary lesion, either malignant or even benign such as giant cell tumor [11,12,13].

Differential Diagnoses: Secondary aneurysmal bone cyst or telangiectatic osteosarcoma were the main differential radiological diagnoses in our case. Secondary aneurysmal bone cyst is an expansile lesion associated with characteristics of companion lesion. Telangiectatic osteosarcoma accounts for <5% of all osteosarcomas. Radiologically it is distinguished by more invasive behavior as cortical interruption, periosteal reaction and soft-tissue involvement, and histologically by spaces, often blood-filled, separated by septa containing highly malignant cells.

Histological & Immunohistochemistry findings: Histological characteristics of ABCs are well defined and histologic evaluation is imperative for definitive diagnosis. Macroscopically, ABC is a relatively well-circumscribed, multicystic and hemorrhagic lesion. Microscopically, ABC shows multiple cystic spaces limited by connective tissue septa, composed of spindle cells or osteoclast-type giant cells. Atypical mitoses should not be seen. The stroma of the lesion is fibromyxoid (or “loose”), and inflammatory cells are common. Immature bone formation can be also identified, often along the fibrous septa [14].

The identification of the recurrent involvement of USP6 fusion genes in ABCs led to a better understanding of the pathogenesis. First, it was thought that ABC was a consequence of vascular disturbance, possibly associated with an underlying lesion, causing increased local vascular pressure and vascular disruption, with the formation of expansive hemorrhagic areas [13]. In 2004, the clonal neoplastic nature of ABC was proved with identification of the genes involved in the cytogenetic rearrangement in primary ABC [15]. This rearrangement is a translocation t(16;17) (q22;p23) that results in the fusion of the promoter region of the osteoblast cadherin 11 gene (CDH11) on chromosome 16q22 to the entire coding sequence of the ubiquitin protease USP6 gene on chromosome 17p13. CDH11 belongs to a large family of cell surface glycoproteins involved in calcium-dependent cell adhesion and then CDH11 gene is involved in the process of osteoblastic differentiation [16]. In ABC, as there are no CDH11 coding sequences in the fusion transcript, the gene has only a role of promoter that up-regulates the transcription of USP6 and overexpression of USP6 protein. USP6 is a ubiquitin-specific protease involved in many cellular processes as protein turnover, inflammatory signaling, intracellular trafficking and cell transformation [17]. One hypothesis is that USP6 induces matrix metalloproteinase (MMP) production that would lead to osteolysis, inflammation, and expansive vascularization [18]. In ABC, only fibroblast-like spindle cells have the USP6 rearrangement. The detection of USP6 rearrangements by fluorescent in situ hybridization (FISH) has a sensitivity of approximately 70% and a specificity of 100%. In secondary ABCs, no rearrangements of USP6 locus are found, suggesting a different pathogenesis. Similarly, there is no USP6 fusion gene in the most important differential diagnoses of ABCs, including telangiectatic osteosarcoma, giant cell tumor, chondroblastoma, or simple bone cyst [19], that makes its identification very helpful for the diagnosis.

Treatment & Prognosis: The optimal treatment of ABCs is total excision. Because the lesion is benign, extensive or radical surgery is generally not indicated. However, complete surgical resection may be more difficult to achieve when the lesion is large or when it involves the skull base. In such complex areas, partial excision or intralésional curettage with adjunctive therapy such as pre-operative arterial embolization should be considered. Radiotherapy has been abandoned because of the risk of sarcomatous degeneration. Percutaneous treatment such as sclerotherapy or cryotherapy have been also reported [20]. In secondary ABCs, treatment depends of the primary lesion identified. Recent studies have indicated a local recurrence rate from 10 % to 20% in primary ABCs treated by total excision in referral centers, depending of the patient’s age, the lesion’s size, the presence of mitosis and the completeness of the resection [21].

TEACHING POINT

ABCs should be in the differential diagnosis of rapidly growing calvarial masses in young patients although it is a rare entity in this location. Presence of fluid-fluid levels with cyst and fibrous septa enhancement and identification of USP6 fusion gene strongly suggest the diagnosis, but the absence or very few fluid-fluid levels don’t exclude the diagnosis.
REFERENCES


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Hermann et al.

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FIGURES

Figure 1: 27-year-old female with right frontal aneurysmal bone cyst.
Findings and technique: Axial images of non-contrast (figures 1a and 1b) and early contrast CT scan at 45 seconds (venous phase, figure 1c) and late contrast CT scan at 5 minutes (figure 1d) in bone (figure 1a) and soft tissue windows (figures 1b, 1c and 1d). There is a local cortical destruction of outer layer of the frontal bone (white arrow) with thin rim of bone shell on medial side of the lesion (gray arrow). On early contrast images large drainage veins are inside the tumor (red arrow) and the margin of the lesion with probably the dura are slightly enhanced (green arrow). Late contrast images show a progressive and heterogeneous enhancement of the peripheral and septations delimitating multiple cysts (blue arrow). Mass effect leads to midline shift (double white arrow).

Figure 2: 27-year-old female with right frontal aneurysmal bone cyst
Findings and technique: Axial FLAIR (figure 2a), coronal T2W (figure 2b), sagittal T1W (figure 2c), axial gradient-echo T2W (figure 2d), axial DWI (figure 2e) and contrast enhanced axial, coronal and sagittal T1W MR images (figures 2f, 2g and 2h). They show a well-defined frontal extradural mass with hypointense peripheral capsule on T2 corresponding to dural and cortical bone (white arrow), internal hyperintensity on FLAIR and T2 (black arrow), internal hypointensity in T1, and hypointense hemosiderin deposits (red arrow). There was a small fluid-fluid level on gradient-echo T2W images (arrowhead). There was no diffusion restriction and a strong septal enhancement with multiple small hypointense cysts (blue arrow).
Musculoskeletal Radiology: Aneurysmal bone cyst of the frontal bone - A radiologic-pathologic correlation

Hermann et al.

Figure 3 (left): 27-year-old female with right frontal aneurysmal bone cyst. Findings and technique: PET/CT performed with administration of 18F-FDG. No increased metabolism of the lesion is seen on 18F-FDG PET/CT imaging (black arrow) with mean SUV of 2 inside the lesion compared to SUV max of 9.7 in normal cortical parenchyma.

Figure 4: 27-year-old female with right frontal aneurysmal bone cyst. Findings and technique: Post-operative contrast enhanced sagittal T1W MR image (figure 4a) and non-contrast axial CT image (figure 4b). After surgery the lesion was completely removed and replaced by an extra-dural fluid collection toward the cranioplasty (white arrow).
Figure 5: 27-year-old female with right frontal aneurysmal bone cyst. Findings: Gross pathology of the resection specimen after surgery on external (5a) and internal (5b) views and after central cutting on coronal view at different magnification (5c and 5d). The mass is in continuity with the skull bone and presents a multiloculated architecture with multiple and variable size blood-filled and non-blood-filled spaces (star). The connecting angle between the lesion and the cortical bone is suggesting for an osseous tumor (arrowhead). Technique: Photography were obtained from surgical biopsy specimens.

Figure 6: 27-year-old female with right frontal aneurysmal bone cyst. Findings: Gross pathology of the resection specimen in correlation with MRI coronal view and superposed with CT scan coronal view. It shows an excellent radiologic-pathologic correlation.
Figure 7: 27-year-old female with right frontal aneurysmal bone cyst

Findings: Microscopic views from the resection specimen at different magnification (figure 7a x 2, figure 7b x 4, figure 7c x 16 and figure 7d x 40). On figure 7a, the lesion (L) is in direct contact with the dura (D) which presents two layers (white arrows). Thin foci of new bone are visible (gray arrow). Multiple cystic cavities containing variable numbers of red blood cells (blue circle) and lined by fibrous septa (black arrow) are visible on figures 7b, 7c and 7d. These fibrous septa are composed of loose fibrous tissue containing a uniform population of plump fibroblasts or spindle cells (black arrows on figures 7c and 7d). Some osteoclast-like multinucleated giant cells are also present in the connective tissue (green arrow on figure 7d).

Technique: Photomicrographs were obtained from surgical biopsy specimens and prepared using hematoxylin and eosin (H&E) staining.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Radiography</th>
<th>CT</th>
<th>MRI</th>
<th>Histology</th>
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<tr>
<td>Primary aneurysmal bone cyst</td>
<td>Expansile lesion developed eccentrically, no cortical interruption</td>
<td>Multiloculated lesion with cystic components and enhanced-septations.</td>
<td>Multiloculated lesion with hypointense rim and internal septations enhanced after contrast. “Honeycomb” appearance.</td>
<td>USP6 rearrangement</td>
</tr>
<tr>
<td>Secondary aneurysmal bone cyst</td>
<td>Expansile lesion associated with characteristics of companion lesion</td>
<td>Expansile lesion with cystic and sometimes a nodular solid component</td>
<td>Secondary ABC must be suggested if there is a solid nodular component, even it is not always present. Soft-tissue involvement depending on companion lesion</td>
<td>Allow to distinguish primary and secondary ABCs. No USP6 rearrangement</td>
</tr>
<tr>
<td>Telangiectatic osteosarcoma</td>
<td>Expansile lesion with predominately osteolytic or expansile component</td>
<td>Expansile lesion with more invasive behavior as cortical interruption. Fluid-fluid levels can be present.</td>
<td>More nodular solid component with soft tissue involvement and fluid-fluid hemorrhagic levels</td>
<td>No USP6 rearrangement</td>
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Table 1: Differential diagnosis table for primary aneurysmal bone cyst.
Aneurysmal bone cyst of the frontal bone - A radiologic-pathologic correlation

Etiology
Initially it was thought that ABC was the consequence of a vascular disturbance or may follow trauma; however, several recent studies have provided evidence of clonal neoplastic nature.

Incidence
Rare. Skull involvement accounts for 2-6% of all ABCs and less than 50 cases have been reported according to our searches.

Gender ratio
No gender predilection.

Age predilection
Most of the cases occur in the first two decades of life.

Risk factors
No established risk factors currently reported in the literature.

Treatment
Complete surgical removal is the treatment of choice and is curative. Other treatment modalities have provided evidence of efficacy including arterioembolization or sclerotherapy.

Prognosis
Excellent prognosis, depending particularly on the completeness of surgical resection.

Findings on imaging
- Radiography: fusiform and expansile lesion located eccentrically, often referred to as having a “soap bubble” or “blowout” appearance.
- CT: multiloculated lesion originating in the diploe and expanding both intracranially and extracranially. There are both solid and cystic components with fluid–fluid levels in 35% of cases. Solid septations usually show enhancement on post-contrast study.
- MRI: reveals an expansile and well-defined lesion surrounded by a hypointense T1W and T2W fibrous capsule. Hypointense internal septations separate the lesion into multicystic compartments of varying signal intensities, with fluid-fluid levels for some of the cysts, although it is not specific. The capsule and septations should enhance on post-contrast images, producing a “honeycomb” appearance. No soft-tissue involvement at the periphery of the lesion.
- CT and MRI are the imaging modalities for evaluation of ABC, suggesting the diagnosis and helpful in treatment planning.

Findings on histology
Blood-filled cystic spaces separated by fibrous septa, composed of fibroconnective tissue with occasional osteoclast-type giant cells and reactive new bone formation.

Table 2: Summary table for primary skull aneurysmal bone cyst.

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<th>ABBREVIATIONS</th>
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<td>ABC = aneurysmal bone cyst</td>
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<td>CT = computed tomography</td>
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<td>DWI = diffusion weight imaging</td>
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<tr>
<td>H&amp;E = hematoxylin and eosin</td>
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<tr>
<td>MRI = magnetic resonance imaging</td>
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<tr>
<td>TE = echo time</td>
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<tr>
<td>TI = inversion time</td>
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<td>TR = repetition time?</td>
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<td>USP = ubiquitin specific protease</td>
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<th>KEYWORDS</th>
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<td>Frontal aneurysmal bone cyst; ABC; CT and MRI findings; histopathologic correlation; USP6 rearrangement</td>
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