

Cystic Lesions of Bone

Intraosseous Ganglion Cyst

Definition.

Intraosseous pseudocyst of unknown etiology that is filled with viscous mucinous material and is not associated with osteoarthritis in the adjacent joint.

General features.

Grossly and histologically intraosseous ganglion cyst is identical to soft tissue ganglion cyst.

Clinical features.

Intraosseous ganglion cyst is usually an asymptomatic lesion that is found incidentally on radiographic images taken for other reasons. Most patients are skeletally mature at the time of diagnosis. Rarely may it cause chronic pain that can be associated with physical activity¹.

Sites.

Usually develop in the subchondral area of bones, such as the hip, ankle, knee, ankle, and carpal bones¹. It is uncommon to get a ganglion cyst within the bones of the upper extremities.

Radiographic Features.

Usually eccentric, oval to round, well-defined, radiolucent with no internal matrix and is surrounded by a thin sclerotic rim. Most importantly there should be no degenerative changes in the adjacent articular cartilage in which case the cyst is considered a subchondral cyst. CT scan shows a well-demarcated lesion with sclerotic rims. On MRI, the cyst content has low-signal intensity on T1 weighted images and high-signal intensity on T2-weighted images (due to high water content).

Gross Findings.

Identical to soft tissue ganglion cyst. Within the bone the cyst is well-demarcated, 0.5-1.0 cm in diameter with surrounding sclerotic bone and filled with clear, gelatinous fluid.

Microscopic Findings.

Acellular mucoid material surrounded by spindle shaped fibroblasts embedded in an extracellular myxoid matrix – identical to what is seen in soft tissue ganglion cyst. The surrounding bone can show reactive changes with fibrosis and myxoid change. There is no lining to the cyst wall.

Immunohistochemical Findings.

No specific immunohistochemical findings.

Treatment.

Curettage if symptomatic; otherwise no treatment is necessary.

Prognosis.

Very low rate of recurrence.

Differential Diagnosis.

Intraosseous ganglion cyst has very characteristic histologic features. The only lesion that can mimic it microscopically is a subchondral cyst. *Subchondral cyst*, unlike intraosseous ganglion, develops secondarily to severe osteoarthritis, which, by definition, is absent in an intraosseous ganglion.

Unicameral Bone Cyst / Simple Bone Cyst / Solitary Bone Cyst

Definition.

Benign intraosseous pseudocyst filled with clear yellow (serous) fluid. It is usually unilocular but may be multilocular.

General features.

The etiology of UBC is unknown.

Clinical features.

Usually asymptomatic, unless it undergoes a pathologic fracture. Approximately 80% occur during the first two decades of life. Lesions in older individuals involving the pelvis, calcaneus and talus are usually incidental findings discovered on radiographic images done for other reasons. The male female ratio is 2:1.

Sites.

Most arise in long bones, the proximal humerus being the most common site (approximately 60%) followed by the proximal femur². In older individuals, they can involve the pelvis, talus and calcaneus. Very rarely arise in other bones.

Radiographic Features.

Well-delineated, lucent lesion that is usually located in the metaphyseal region of long bone. The lesion has a thin sclerotic rim and the cortex may be attenuated but it is never transgressed. Jaffe and Lichtenstein³ described two forms – an *active cyst* which is present in the metaphysis, abutting the epiphyseal plate; it hardly ever extends proximally to the plate. The cortex may be attenuated but there is minimal expansion of the bone and the diameter of the cyst does not exceed that of the epiphyseal plate. With time and growth of the individual the cyst “moves” into the diaphysis of the long bone and this is what Jaffe and Lichtenstein referred to as a *latent cyst*. In the presence of a fracture a small piece of cortex may get dislodged into the cystic cavity where it floats; this is the so called *fallen fragment sign*⁴. Occasionally the broken cortical fragment can still be attached to the periosteum, and unlike the fallen fragment, it will tilt, like a door on a hinge, again indicating the presence of a cystic lesion⁴. Computed tomography (CT) shows a well-demarcated lytic lesion. An MRI is useful in confirming the fluid content of the cyst and it is bright on T2-weighted images. In the presence of a fracture and intracystic bleeding the MRI scan can show fluid-fluid levels akin to what is seen in an aneurysmal bone cyst.

Gross Findings.

The gross specimen usually consists of curetting that is composed of thin fragments of fibrous tissue. Resection specimen consist of straw-colored fluid filled cyst surrounded by a translucent, attenuated fibrous wall. In the presence of a fracture the fluid is blood colored.

Microscopic Findings.

UBC is a pseudocyst that lacks an epithelial lining. The wall is composed of thin layer of fibrous tissue composed of spindle shaped fibroblasts embedded in an extracellular collagenous matrix. A characteristic feature, seen in the cyst wall in some cases, is the so-called ‘cementum-like substance’, that represents fibrin deposition which may act as a scaffold for the deposition of bone. UBC arising in the calcaneus may demonstrate unusual histologic features with abundant cholesterol clefts, giant cell reaction and hemorrhage. These unusual histologic features are thought to be secondary to intracystic hemorrhage which appears to be more common in this location⁵⁻⁷. In the setting of a pathologic fracture, there is hemorrhage, the fibrous wall is

thicker and more cellular with reactive bone formation and osteoclastic activity; these features may mimic an aneurysmal bone cyst.

Immunohistochemical Findings.

No specific immunohistochemical findings.

Treatment.

Resection when involving long bones such as the proximal fibula. Otherwise, curettage with bone grafting; steroid injection or percutaneous marrow grafting ⁸.

Prognosis.

In most patients, the cyst spontaneously regresses. Local recurrence after treatment ranges from 10-20%.

Differential Diagnosis.

Other cystic lesion can mimic unicameral bone cyst. *Intraosseous ganglion cyst* is usually in subchondral location in skeletally mature individuals; histologically intraosseous ganglion cyst is identical to soft tissue ganglion cyst with intracystic gelatinous material (instead of the straw-colored fluid seen in UBC). Fractured UBC can histologically have areas that are similar to what is seen in an *aneurysmal bone cyst*. ABC is more expansile than UBC, and on MRI contains the characteristic fluid-fluid levels.

Aneurysmal bone cyst

Definition.

Expansile benign neoplasm of bone characterized by multiple blood-filled spaces and t(16;17). In the WHO classification, aneurysmal bone cyst is classified as an intermediate, locally aggressive neoplasm ⁹.

General features.

First described by Jaffe and Lichtenstein in 1942 ³ aneurysmal bone cyst was until recently thought to be a non-neoplastic process possibly due to local circulatory abnormality. Currently, however, ABC is considered a neoplastic process characterized by t(16;17)(q22;p13) translocation that results in *CDH11-USP6* gene fusion in most tumors. In the so-called primary ABC, no underlying neoplasm is identified (de-novo ABC) and these account for approximately 70% of ABCs. In the so-called secondary ABC, a primary neoplasm is present which has undergone cystic and hemorrhagic changes (ABC-like changes), are almost always seen in benign tumors the most common tumors being giant cell tumor of bone, chondroblastoma, fibrous dysplasia, chondromyxoid fibroma and osteoblastoma, however, it can rarely be seen in malignant tumors such as osteosarcoma. ABC needs to be thoroughly sampled microscopically, especially the solid component of the tumor, to exclude an underlying lesion.

Clinical features.

Patients usually present with pain (which can be secondary to a pathologic fracture), swelling, limitation of motion or a palpable mass. Tumors involving the axial skeleton may cause neurologic symptoms. Most tumors arise in the first two decades of life and it is more common in females ¹⁰.

Sites.

When involving long bone, it usually involves the metaphysis, the most common location being the distal femur and proximal tibia but almost any bone can be affected ^{10,11}. When arising in the axial skeleton it usually involves predominantly the posterior elements.

Radiographic Features.

When involving long bones the tumor is typically expansile, eccentrically metaphyseal located, lytic with internal trabeculations that are caused by endosteal scalloping of the cortex by the tumor. The tumor may also involve the metaphysis and diaphysis or metaphysis and epiphysis¹⁰. It can also arise from the surface of the bone (subperiosteal) without involvement of the medullary cavity¹². When arising in the axial skeleton the tumor typically involves the posterior elements usually with extension into the vertebral body. The periphery of the tumor is usually surrounded by a thin shell or reactive bone formation. On CT scan the tumor is lytic, multiloculated and with well-defined margins. MRI scan demonstrated multiple, variable sized cysts exhibiting the characteristic fluid-fluid levels on T2 weighted images. The fluid-fluid levels are caused by the settling of red blood cells leaving the serum on the surface. ABC is hot on bone scan. In secondary ABC imaging studies may show an underlying lesion.

Gross Findings.

A completely resected specimen consists of a large blood filled multicystic mass (sponge-like), the cysts being separated by a fibrous and gritty septae. The peripheral soft tissue component is surrounded by a shell of reactive bone formation. The tumor may show more solid areas that represent a solid component of ABC or the presence of an underlying tumor that has undergone secondary ABC-like changes.

Microscopic Findings.

ABC is well-circumscribed and is composed of multiple blood filled cystic spaces, separated by fibrous septa. The fibrous septa are composed of cellular proliferation of neoplastic spindle shaped cells, scattered unevenly distributed osteoclast-type giant cells and reactive woven bone rimmed by osteoblasts. The woven bone typically follows the contour of the fibrous septa being parallel to the cystic spaces. In approximately one third of tumor the bone is basophilic or blue in appearance – so called blue bone. Mitotic figure may be numerous, atypical mitotic figures are not seen¹⁰. Necrosis may be seen in the presence of a pathologic fracture. In solid ABC, the tumor has the histologic features of an expanded fibrous septa without the cystic changes.

Immunohistochemical Findings.

No specific immunohistochemical findings. p63 can stain some tumor cells.

Molecular and Other Special Techniques.

The majority of ABCs show t(16;17)(q22;p13) translocation that results in the gene fusion of *CDH11* (osteoblast cadherin gene) to *USP6* (ubiquitin-specific protease gene)¹³. Alternatively, ABCs may show variant translocations (such as t(1;17), t(3;17), t(9;17), t(17;17))^{14,15}. The translocation seem to be restricted to the spindle shaped cells and is not seen in other cell types¹⁶. Recently, using next PAF1B1-USP6 and RUNX2-USP6 has been identified in rare tumors using next generation sequencing (NGS)^{15,17}. These translocations lead to upregulation and overexpression of USP6 oncogene. *USP6* rearrangement is found in approximately 70% of primary ABC and is not present in secondary ABC¹⁶ and this can therefore be used to distinguish between a primary and a secondary ABC in difficult cases using FISH for USP6 translocation. The same genetic abnormality is seen in solid ABC and can be used to distinguish ABC from giant cell reparative granuloma¹⁸.

Treatment.

Treatment usually consists of curettage or en bloc resection. A variety of other different therapeutic options are available in selected patients including percutaneous injections, arterial embolization, radiation therapy and drug therapy using osteoclast inhibiting drugs such as bisphosphonate or denosumab¹⁹⁻²¹.

Prognosis.

Up to 30% local recurrence rate, usually shortly after the primary treatment. The presence or absence of CDH11-USP6 fusion does not affect prognosis. Centrally located tumors have a higher risk of local recurrence¹⁶. Spontaneous regression after incomplete removal is unusual but may occur. Very rarely can ABC metastasize²².

Differential Diagnosis.

A variety of benign and malignant bone tumors can undergo *secondary ABC*-like changes, the behavior of these tumors is that of the underlying lesion. Most tumors that undergo secondary ABC-like changes are benign and include giant cell tumor of bone, chondroblastoma, fibrous dysplasia, chondromyxoid fibroma and osteoblastoma. This distinction can be especially problematic on a small biopsy sample. Thorough sampling and microscopic examination of the curetted or resected specimen may be necessary to identify the underlying lesion. FISH for USP6 translocation confirms the diagnosis of a primary ABC, however a negative FISH does not distinguish primary from secondary. The most important differential diagnosis is distinguishing *telangiectatic osteosarcoma* from ABC as both can have similar radiographic features and gross appearance. Microscopically, however, the fibrous septae in telangiectatic osteosarcoma contain obviously malignant neoplastic cells, demonstrating pleomorphism and atypical mitotic figures.

Epidermoid Inclusion Cyst / Dermoid Cyst

Definition.

Benign intraosseous cystic lesion that is histologically identical to soft tissue epidermoid inclusion cyst. When adnexal structures are seen within the cyst wall the lesion is termed a dermoid cyst.

General features.

The etiology of epidermoid inclusion cyst is unknown. It has been suggested that it is caused by traumatic implantation of the overlying skin into the underlying bone²³. It is more common in males²⁴.

Clinical features.

Can be asymptomatic and an incidental finding radiographically. When symptomatic the patients complain of pain; rarely does it undergo a pathologic fracture. Lesion arising in the skull cause a painless lump.

Sites.

EIC is found in small bones (more commonly fingers) and the skull. Skull lesions are seen in children.

Radiographic Features.

Lytic, well-defined lesion with sclerotic borders.

Gross Findings.

Just as EIC of soft tissue, EIC of bone is cystic and filled with cheesy (keratinous) material. EIC of the small bones are small but EIC of the skull may be large (several centimeters).

Microscopic Findings.

The cyst wall is lined by keratinizing squamous epithelium and the cystic cavity is filled with keratin debris. The squamous epithelium overlies a thin fibrous tissue that abuts the adjacent bone that may show osteoclastic activity and bone resorption. When the cysts rupture, they are surrounded by florid histiocytic and giant cell reaction. In dermoid cyst, adnexal structures are present within the wall of the cyst.

Immunohistochemical Findings.

No specific immunohistochemical findings.

Treatment.

Curettage.

Prognosis.

Prognosis is excellent.

Differential Diagnosis.

Histologically there is no differential diagnosis as the microscopic features are very characteristic. Radiographically, however, EIC can simulate other tumors such as enchondroma, giant cell reparative granuloma, eosinophilic granuloma, glomus tumor and infection when presenting with pain and swelling.

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