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Short Communication

The Multinucleated Millpond-Aneurysmal Bone Cyst

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Preface

Aneurysmal bone cyst is designated as an uncommon, expansive, benign, osteolytic lesion delineating blood-filled spaces of variable magnitude demarcated by fibrous tissue septa and intermingled with osteoclast-like giant cells along with reactive bone. Aneurysmal bone cyst is a non-malignant neoplasm simulating vascular lesions denominated by blood- filled vascular channels. Previously, incidence of aneurysmal bone cyst was contemplated at 0.14 per ten individuals [1].

Disease characteristics

Essentially benign, aneurysmal bone cyst progresses rapidly and can exceptionally metamorphose into an osteosarcoma. The aggressive lesion can emerge as a locally destructive neoplasm and engender a pathological fracture within weakened, fragile bones [1,2].

Aneurysmal bone cyst is an exceptional osseous neoplasm comprising of an estimated 1% to 6% of primary osseous tumours. Majority (80%) of incriminated subjects are children and adolescents beneath < 20 years. A slight female predominance is discerned with an estimated female to male ratio of 1.3:1 [1,2].

As aneurysmal bone cyst primarily manifests in paediatric subjects, incrimination of the growth plate invokes permanent deformities of limb length. Aneurysmal bone cyst represents within metaphysis of long bones (67%), vertebral column (15%) or posterior pelvis (9%). Infrequently, the tumefaction arises within craniofacial bones and epiphyses [1,2].

On genetic analysis, around 69% of primary aneurysmal bone cysts demonstrate a clonal, gain- of- function genomic translocation t (16;17). Pertinent genomic fusion t(16;17) engenders an upregulation of TRE17/ubiquitin-specific protease 6 (USP6) oncogene with consequent activation of nuclear factor kappa-light-chain- enhancer of activated B cells (NF-κB) and matrix metalloproteinases (MMPs). Aforementioned MMPs denature extracellular matrix which permits a rapid tumour evolution. Also, upregulation of TRE17/ubiquitin-specific protease 6(USP6) oncogene arrests osteoblastic maturation. Secondary aneurysmal bone cysts are devoid of aforesaid chromosomal translocation. An estimated 63% tumours exhibit anomalies within 17p13.2 genetic locus [1,2].

Disease pathogenesis

Aneurysmal bone cyst is a neoplasm of unknown aetiology. Nevertheless, the tumefaction can arise due to vascular malformations within the bone. Cogent theories implied in the emergence of aneurysmal bone cyst are a) Aneurysmal bone cyst occurs on account of diverse, primary bone tumours. An estimated proportion of 34% of accompanying bone neoplasia are indicated, frequently denominated by chondromyxoid fibroma, chondrosarcoma, fibrous dysplasia, giant cell tumour of bone, osteoblastoma or osteosarcoma [3,4]. b) Aneurysmal bone cyst can configure as a primary bone tumour. c) Aneurysmal bone cyst can articulate at a site of a preceding tumour. As per current hypotheses, a segment of aneurysmal bone cyst is considered to be neoplastic. Although of obscure aetiology, aneurysmal bone cyst probably arises due to a vascular malformation. Vascular aberrations with enhanced pressure consequently expand the bone along with bone erosion and resorption of incriminated bone [3,4].

Tumour staging

Pertinent staging of aneurysmal bone cyst is contingent to "Enneking's" staging of benign musculoskeletal neoplasia

- Stage 1 is constituted by latent or inactive tumefaction. The neoplasm is asymptomatic and discerned incidentally.
- Stage 2 is comprised of active neoplasia detected on account of clinical symptoms arising within incriminated individuals. The tumour is consistent, progressive and can be palpable.
- Stage 3 demonstrates aggressive neoplasia as the tumour is typically accompanied by significant clinical manifestations, a probably overt anomaly with accompanying inflammation. Essentially benign, stage 3 neoplasia behave as a low grade malignancy [1,3].

Clinical elucidation

Aneurysmal bone cyst is commonly discerned within flat bones, metaphysis of multiple posterior vertebrae, shaft of long bones and exceptionally within soft tissues or walls of major arteries. Aneurysmal bone cyst is common within the femur, tibia or vertebral column, although no bony site of neoplastic incrimination is exempt. Aneurysmal bone cyst can arise secondary to traumatic injury or within a pre-existing bony neoplasm represented by giant cell tumour, chondroblastoma or fibrous dysplasia. Expansible aneurysmal bone cyst can manifest pain and inflammation besides disruption of joints or epiphyseal growth plate [4,5].

Typically, an insidious onset of pain within weeks or months with a soft tissue swelling or palpable mass is observed. Few subjects represent with sudden onset of pain on account of pathological fracture. Neurological symptoms are exemplified in occasional instances where aneurysmal bone cyst impinges upon a nerve or incriminates the spinal cord. Pathologic fracture may manifest with consequent osseous and soft tissue oedema [3,5].

Histological elucidation

On gross examination, a spongy, haemorrhagic tumefaction enveloped with attenuated, shell-like reactive bone is discerned. Tissue specimen obtained is minimal as compared to enlarged tumefaction discerned upon conventional radiography. Macroscopically, aneurysmal bone cyst is comprised of cystic cavities imbued with blood and haemosiderin pigment, encompassed within subperiosteal fragments of reactive bone [5].

On microscopic examination, enlarged, cystic, blood filled expanse separated by fibrous tissue septa are observed with alternating foci of solid tumour. Cysts and septa are layered by fibroblasts, myofibroblasts, and histiocytes although an endothelial lining is absent. Clusters of osteoclast - like, multinucleated giant cells admixed with loosely configured, spindle-shaped cell stroma, reactive woven bone and degenerated foci of calcifying fibromyxoid tissue are delineated. Haemosiderin deposits are visible [4,5].

Tumefaction is devoid of cellular or nuclear atypia and malignant osteoid. Cystic cavities are subdivided by septa of trabecular bone or osteoid and lack an endothelial layer. Intervening stroma is constituted by fibroblasts, spindle- shaped cells, osteoid and multinucleated giant cells. Giant cells are typically exemplified within the periphery of cystic cavities, thus engendering a classic appearance of "pigs at the trough". Mitotic figures are variable although common and atypical mitotic figures are absent [4,5].

Differential diagnosis

Aneurysmal bone cyst requires segregation from giant cell tumour, giant cell reparative granuloma of the jaw, haemangioma, hypo-cellular variant of low grade osteosarcoma, solitary bone cyst or telangiectatic osteosarcoma [1,2].

Aneurysmal bone cyst necessitates a demarcation from chondroblastoma which is a cartilaginous neoplasm. Typically, chondroblastoma is predominantly situated within the epiphyses (95%) and apophyses of long bones. Chondroblastoma is non malignant and usually manifests as perpetual pain and swelling within an extremity, independent of physical activity. On conventional radiography, chondroblastoma delineates a sclerotic, well circumscribed lesion situated within the epiphyses, traversing the growth plate and accompanying peri-tumoural oedema [1,2].

Fibrous dysplasia is a neoplasm predominantly of children or young adults. Fibrous dysplasia is a benign tumefaction wherein healthy bone is replaced by fibrous connective tissue and immature trabecular bone. Fibrous dysplasia appears on account of erroneous osteoblastic differentiation and maturation. Usually incidental, fibrous dysplasia is typically asymptomatic and mandates no surgical or therapeutic intervention. However, fibrous dysplasia can engender morbidity with expansible lesions compressing adjacent anatomic structures. Fibrous dysplasia can be monostotic with incrimination of singular bone or polyostotic with multiple implicated bones. Fibrous dysplasia morphologically delineates a ground glass matrix [1,2].

On radiography, lytic lesions of fibrous dysplasia demonstrate cortical thinning with endosteal scalloping and a well circumscribed bony perimeter. Occasionally, a "rind sign" is exhibited, pro-

duced by dense layer of reactive, sclerotic bone encompassing the lesion [1].

Giant cell tumour typically emerges in adults with skeletal maturity. Giant cell tumour is an aggressive, non malignant, osteolytic neoplasm exemplifying distant metastasis such as benign pulmonary deposits. Although non malignant, an estimated 8% of giant cell tumours delineate malignant metamorphosis. Chronic pain and localized swelling with restricted mobility of adjacent joint is encountered. Pathologic fracture of weight bearing joints may ensue besides incrimination of subchondral plate. Plain radiographs typically depict a lesion within the epiphysis with an eccentric lytic focus. Giant cell tumour frequently occurs in concordance with secondary aneurysmal bone cyst [1,2].

Telangiectatic osteosarcoma (TOS) simulates an aneurysmal bone cyst in appearance or clinical representation. Gadolinium based magnetic resonance imaging (MRI) can differentiate betwixt the neoplasia by exhibiting nodular configuration of soft tissue circumscribing the cavities of telangiectatic osteosarcoma, in concurrence with sarcoma-like architecture. Telangiectatic osteosarcoma is accompanied by cortical destruction of the bone with concordant soft tissue tumefaction. Necrosis can occur. A cogent tissue specimen enunciates malignant tumour cells in telangiectatic osteosarcoma [1,2].

Unicameral bone cyst (UBC) is a fluid- filled lesion with circumscribing fibrous layer of mesothelial cells and commonly emerges within first two decades. Pain due to pathological fracture within metaphysis of long bones can ensue. Plain radiography depicts an expansible lesion spanning the entire diameter of incriminated bone. The lesion displays a well defined perimeter in the absence of reactive sclerosis. In contrast to aneurysmal bone cyst, unicameral bone cyst is confined within the diameter of implicated bone. Pathognomonic radiographic feature of unicameral bone cyst is "fallen fragment" sign which indicates the presence of fractured, intramedullary bone fragments impacted within the cystic cavity [1,2].

Investigative assay

Aneurysmal bone cyst can be suitably and critically evaluated with imaging studies. Conventional radiography demonstrates eccentric expansion of the bone, cortical erosion, bone destruction and miniature, peripheral foci of periosteal new bone formation [6].

Conventional radiographs illustrate a cystic or osteolytic lesion with thin, eggshell-like sclerotic margins. Enclosed cystic cavity is traversed by several fibrous tissue septa. Circumscribing bone can be outwardly displaced from normal anatomical position on account of the aggressive, expansible tumefaction [6,7].

Computed tomography (CT) recapitulates lesion characteristics discerned by plain radiographs although fibrous tissue septa traversing the cystic cavity are well delineated and highlight "eggshell" bony perimeter of the neoplasm. Fluid- filled levels can appear within cystic cavities due to segregation of cellular debris from vascular plasma.

Computerized tomography (CT) can demonstrate specific fluid levels. Magnetic resonance imaging (MRI) depicts a distinctive "honeycomb appearance" with fluid levels. Magnetic resonance imaging (MRI) simulates features discerned on computerized tomography (CT). T1 contrast- enhanced and T2 weighted images enunciate fibrous tissue septa traversing the lesion with tumour perimeter delineating minimal T1 and T2 signal intensities. Fresh and old aggregates of haemorrhage imbued within cystic cavities are discernible on magnetic resonance as foci of hyper-intense signals on T1 and T2 weighted imaging sequences. Also, double density fluid levels can be observed [6,7].

Assessment of haematological parameters is minimally beneficial although an aneurysmal bone cyst can enunciate elevated alkaline phosphatase values due to amplified activity of osteoblasts [6,7].

Therapeutic options

Aneurysmal bone cyst can be treated with simple curettage. An estimated 25% of aneurysmal bone cysts reoccur following appropriate curettage, thus an aggressive curettage procedure with subsequent bone grafting is preferred. Alternatively, an en bloc tumour resection can be adopted [7].

Preferably, aneurysmal bone cyst requires appropriate management from an orthopaedic oncologist. Surgical intervention of the cyst is a preferential therapy to circumvent pathological fractures. Contingent to magnitude of lesion and region of incriminated bone, an intra-lesional curettage or intra-lesional resection of the neoplasm or en bloc, comprehensive surgical eradication is an optimal treatment option.

Intra-lesional curettage is denominated by complete evacuation of contents of the cystic cavity and packing of expansible lesion

with bone grafts or bone strengthening cement [7,8].

Intra-lesional surgical resection is preferred therapeutic modality, identical to intra-lesional curettage, where osseous partition is incised in order to extract contents of the cavity. Thus, enhanced proportion of bone remains intact, a manoeuver which decimates morbidity, in contrast to en bloc surgical eradication. Following evacuation of cystic cavity, bone graft or bone strengthening material is instilled which promotes bone healing [7,8].

Intra-lesional surgical resection differs from intra-lesional curettage wherein a resection permits employment of varied categories of adjuvant therapy which decimates proportionate tumour reoccurrence. Also, an expansive aperture for accessing the cystic cavity is adopted . Applicable adjuvant therapies are constituted by high- speed burr, argon beam coagulation, phenol and cryotherapy. Intra-lesional excision is beneficially adopted for treating aneurysmal bone cyst abutting a joint or associated anatomic structures and where maintenance of normal anatomical architecture is crucial for appropriate function [7,8].

En bloc surgical eradication is comprised of comprehensive removal of cystic cavity contents. On account of concomitant procedural mortality, en bloc surgical excision is relevant for treating relapsing aneurysmal bone cysts unamenable to minimally invasive surgical procedures.

Selective artery embolization (SAE) is a treatment option which can be considered prior to commencing surgical manoeuvers. SAE can be employed as an adjuvant therapy or a primary treatment modality in instances associated with severe decimation of function or joint destabilization resulting from localized or broad surgical extermination of the tumefaction. In an estimated 40% instances subjected primarily to SAE, repetitive embolization procedures are mandated [7,8].

Radiotherapy can be utilized as an adjuvant therapy for treating reoccurring aneurysmal bone cysts. However, adoption of radiotherapy is associated with significant side effects. Radiation- induced sarcoma can be discerned in subjects receiving an external beam irradiation for vertebral aneurysmal bone cysts [7,8].

Additionally, diverse medical therapies with monoclonal antibodies can be considered for treating candidates unamenable to surgical therapy [8].

Therapeutic outcomes

Surgical extermination of aneurysmal bone cyst is contemplated as curative. Aneurysmal bone cyst demonstrates spontaneous tumour reoccurrence in around 19% individuals. Tumour relapse is discerned within first year following surgical eradication [6].

Nevertheless, regular evaluation of tumour recrudescence for up to 5 years following surgery is mandated. For skeletally immature individuals, tumour reoccurrence can impact prospective bone evolution with engenderment of bone deformities [6,8].

Surgical complications are contingent to location of tumefaction within the skeleton. Additionally, possible primary or secondary haemorrhage, secondary bacterial infection, superficial wound infection and osteomyelitis can ensue. Bone epiphysis or growth plate can be devastated in instances where tumefaction is adjacent to a growth plate. Pulmonary embolism can ensue due to venous thromboembolism or fat embolism [6,8].

Alleviation of tumefaction with appropriate recovery is contingent to location of tumefaction, magnitude of surgical excision and degree of bone reconstruction as applied with pertinent bone grafts or bone cement. Physical and occupational therapy can be beneficially adopted to decimate morbidity associated with aneurysmal bone cyst [8].

Figure 1: Aneurysmal bone cyst exhibiting several multinucleated giant distributed within a spindle cell stroma, enlarged foci of haemorrhage and segments of reactive, woven bone [9].

Figure 2: Aneurysmal bone cyst demonstrating a cavity lined by fibroblasts, myofibroblasts, a lack of endothelium, osteoclast-like giant cells, calcified fibromyxoid tissue and an abundant spindle cell stroma [10].

Figure 3: Aneurysmal bone cyst exemplifying multitudinous, osteoclast-like giant cells admixed within spindle-shaped cellular stroma, segments of woven bone and a cystic cavity devoid of endothelium [11].

Figure 4: Aneurysmal bone cyst enunciating a multinucleated giant cell disseminated within a spindle cell stroma, calcification of fibromyxoid tissue and fragments of bone [12].

Figure 5: Aneurysmal bone cyst exhibiting innumerable multinucleated giant cells with intermixed cellular stroma of spindle cells, calcified fibromyxoid tissue and woven bone [13].

Figure 6: Aneurysmal bone cyst depicting a cavity lined by fibroblasts and myofibroblasts imbued with numerous multinucleated giant cells, a cellular stroma with predominant spindle-shaped cells and foci of reactive bone [14].

Figure 7: Aneurysmal bone cyst delineating several multinucleated giant cells commingled within a spindle-shaped stroma, fragments of reactive bone, calcified fibromyxoid tissue and aggregates of myofibroblastic cells [15].

Figure 8: Aneurysmal bone cyst depicting multiple osteoclast-like giant cells intermingled within a spindle cell stroma, fibromyxoid tissue and reactive bone [16].

Figure 9: Aneurysmal bone cyst demonstrating osteoclast-like multinucleated giant cells dispersed within a cellular stroma, calcified fibromyxoid tissue, reactive bone and discrete fibrous tissue septa [17].

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9. Image 1 Courtesy: Cureus.com.
10. Image 2 Courtesy: Science direct.
11. Image 3 Courtesy: Annals of thoracic surgery.
12. Image 4 Courtesy: Bone tumour.org.
13. Image 5 Courtesy: ePathologies.com.
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