VOLUME - 9, ISSUE - 7, JULY - 2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Orthopaedics

DIAGNOSTIC CHALLENGES IN CARTILAGINOUS BONE TUMOURS - INCISIONAL / EXCISIONAL BIOPSY

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ABSTRACT Cartilaginous tumours are among the most common tumours of the appendiceal skeleton, which share a common characteristic feature of production of chondroid matrix by the tumour cells and range from benign to intermediate to malignant behaviour. Distinguishing cartilaginous lesions, especially benign versus malignant lesion is a diagnostic challenge for the pathologists and require correlation with clinical, radiological (including CT, MRI), special stains and IHC for a definite diagnosis as there is no gold standard to resolve this challenge. This challenge jumps multifold, when small incisional biopsy material is evaluated, which may not represent the entire lesion. Accurate diagnosis a critical step which can affect the treatment protocols, which may range from simple curettage and bone grafting to amputation, irradiation or palliative management. Here we present 4 rare cartilaginous tumours, where HPE of incisional biopsy and excisional biopsy yielded different diagnosis. One of the case is suggestive of metachondromatosis, which is a very rare lesion.

KEYWORDS : Enchondroma, chondroblastoma, chondrosarcoma, Immunohistochemistry (IHC), Aneurysmal bone cyst (ABC).

INTRODUCTION:

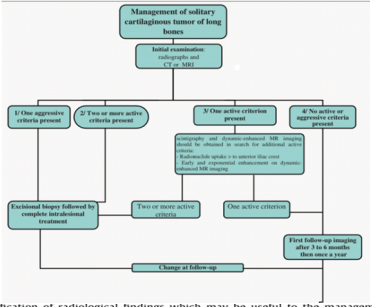
Cartilaginous tumours are the most common tumours of the bone and are classified as benign, intermediate and malignant tumours by WHO and are the ones which pose the most common diagnostic challenge for the pathologist and clinician and collaboration with radiologist with a multidisciplinary approach is essential for accurate diagnosis.

"BIOPSY SHOULD BE REGARDED AS THE FINAL DIAGNOSTIC PROCEDURE AND NOT AS A SHORT CUT TO DIAGNOSIS". This statement by Jaffe (1) sums up the solution to the diagnostic challenges faced. Biopsy should be done only after complete clinical, radiological and laboratory investigations with a provisional clinical diagnosis and the clinician should not rush into a hasty biopsy for instantaneous diagnosis (2) as the pathologist has the most difficult task of giving a diagnosis purely on microscopic appearance, which will be extremely dangerous as the tumours can be extremely heterogenous and variegated. Correct approach is to always narrow down to differential diagnosis in correlation with clinico radiological correlation.

Clinical findings like age (For eg - Ewing's Sarcoma in 0 - 10 years, Osteosarcoma in 10 - 22 years and Chondrosarcoma in 30 - 84 years), anatomic location (For eg - Chondromas in feet, hands, Ewing's in diaphysis of long bones, osteoclastoma in epiphysis of long bones), matrix composition (calcification favouring cartilaginous tumours and ossification favouring bone tumours), interface (sclerotic rim favouring slow growing lesion and non sclerotic margin favouring rapidly forming lesion) & radiological findings (3) (geographic pattern of bone destruction favouring benign and locally aggressive lesions like chondroblastoma and moth eaten appearance indicating aggressive growth like malignant tumours and permeative pattern of bone destruction with broad transition zone favouring malignant tumours like Ewing's and osteosarcoma, multiple lesions favouring Langerhans cell histiocytosis and metastasis) and PET scan (very useful for staging, For eg - AJCC System recommends that tumour with skip metastasis are classified as Stage III and distance metastasis as Stage IV - IVa being metastasis to lung and IVb being metastasis to other sites including bone).

MR criteria, (4) useful for certain lesions especially in differentiating chondroma and Low Grade Chondrosarcoma is based on Dynamic Gadolinium enhanced MR Sequences and Geinaerdlt et al found that early and exponential enhancement with Gadolinium is common in chondrosarcomas. Bone Scintigraphy Criteria (5) in a study by Murphy et al found that tumour uptake was superior to that of uptake of anterior iliac crest in chondrosarcomas. Based on X-Ray and CT changes, the lesions are classified as active and aggressive and based on these with MR criteria and bone scintigraphy, an algorithm was made for solitary central cartilaginous tumour of long bone (Table 1.1 &1.2).

Management of a solitary central cartilaginous tumour of long bones - European Journal of Radiology



Classification of radiological findings which may be useful to the management decision. (European Journal of Radiology)

Active	Aggressive
Pain related to the lesion	Pathologic fracture arising with minimal trauma
Endosteal scalloping > 2/3 of the cortical thickness	Pluri-lamellar or spiculated periosteal reaction
Extent of endosteal scalloping along > 2/3 of the lesion length	Moth-eaten or permeative osteolysis
Cortical thickening or hyperostosis	Cortical destruction
Cortical remodelling with enlargement of the diameter of the medullary cavity	Presence of a soft tissue mass
Delayed bone scintigram showing an intense uptake greater than that of the AIC in the absence of fracture	
Early and exponential enhancement on dynamic gadolinium-enhanced MR sequences	

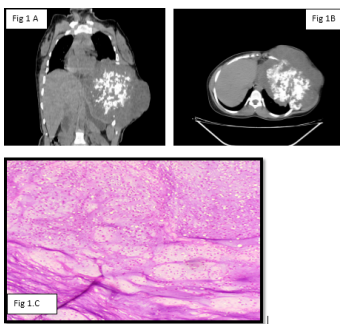
Analyzing small biopsy material and without radiological features will lead to erroneous diagnosis like cases presented below.

Methods:

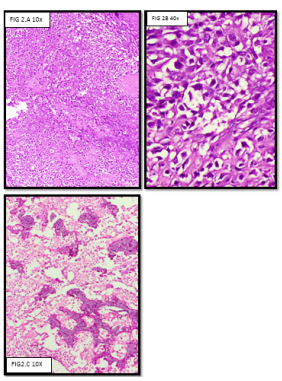
This study is a retrospective study of rare and malignant cartilaginous tumours over a period of 4 years between May 2016 to May 2020. As this is a case series, we chose to describe cases received during this period at Karuna Medical College, Palakkad and Histolab, Coimbatore.

Case Reports:

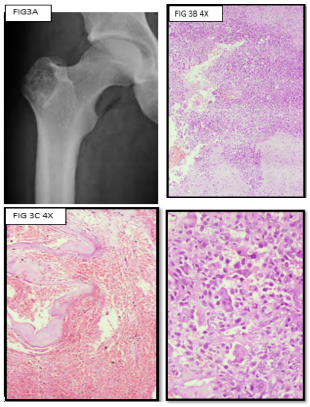
(1) 20 years female, presented with a mass in the back and gave history of mass being present right from birth and has been gradually increasing in size and has reached the present size, which was very gross and uncomfortable. She also gave additional information, that her sibling has multiple swellings in hands and feet, which was radiologically diagnosed as osteochondromas elsewhere. MRI of the lesion showed a large irregular hypodense lesion measuring 17x15.7x14.7cm arising from the antero lateral aspect of 6th rib on the left side with destruction of the rib with diffuse coarse calcifications (FIG 1.A &B). The lesion was infiltrating into the soft tissue of antero lateral chest wall with mass effects on lung, left hemi diaphragm, stomach & spleen. Patient also had lesions in left 2nd rib and right scapula. Incision biopsy was done and reported as Grade I Chondrosarcoma. The patient was referred to another centre in Chennai, where the tumour was removed with excision of anterior and lateral part of left 4th to 8th ribs with portion of left lower lung and the defect was closed with flap cover from the leg. The histopathology examination showed Enchondroma and patient is doing well during 2 years follow up (FIG1.C).



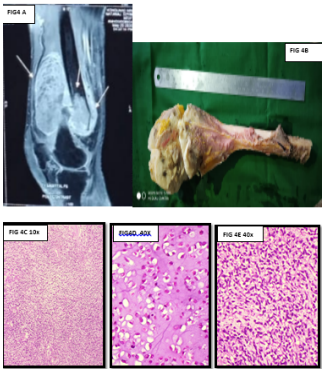
(2) 28 years male, presented with pain and mass in the lower leg with radiological findings showing a lytic lesion in epiphysis of tibia with cortical breaching and infiltration with soft tissue with spots of calcification . Initial biopsy showed ovoid to polyhedral cells with vesicular to lobated nuclei in a chondroid matrix with few osteoclastic giant cells. A diagnosis of chondroblastoma was made and as radiology indicated a malignant lesion, more tissue was requested and the repeat biopsy material showed many clear cells, chondroid matrix and woven bone and a diagnosis of clear cell chondrosarcoma was made (FIG2.A ,B &C).



(3) 20 years male, presented with pain in right hip and thigh and difficulty in walking. X-Ray showed a lytic lesion in proximal femur with sclerotic margin and biopsy showed dilated vascular channels and cystic spaces filled with blood with fibroblasts, osteoclasts and woven bone and a diagnosis of aneurysmal bone cyst was made(FIG3A). Curettage was done and sent for HPE, which showed typical features of chondroblastoma associated with aneurysmal bone cyst like areas (FIG3 B,C&D).



(4) 54 years male, presented with swelling around the knee with severe pain and MRI showed an intramedullary lesion in the distal femur measuring 10.5x3.5x3cm infiltrating the extra osseous tissue into the anterior and posterior compartment. Incision biopsy done elsewhere was diagnosed as malignant fibrous histiocytoma and we received the specimen of above knee amputation which showed medullary mass, infiltrating the cortex and surrounding soft tissue with pathological fracture. Histology showed a neoplasm with biphasic pattern of primitive mesenchymal and chondrocytic components with small, round to spindle cells which was consistent with Mesenchymal Chondrosarcoma.



DISCUSSION:

Table 2WHO classification of cartilaginous tumour of bone (2013) (6) (Table 2)

Benign	Intermediate Behavior Cartilage Tumors		Malignant
	Never metastasize (Locally aggressive)	Rarely metastasize	
Osteochondroma	Chondromyxoid fibroma	Chondroblastoma	Conventional Chondrosarcoma (Intramedullary, central, peripheral, juxtacortical/periosteal) (Grade II, grade III)
Chondroma 1-Enchondroma 2-Periosteal chondroma	Atypical cartilaginous tumor / chondrosarcoma grade I	Aggressive Chondroblastoma	Mesenchymal chondrosarcoma
Osteochondromyxoma			Dedifferentiated chondrosarcoma
Subungual exostosis			Clear cell chondrosarcoma
Bizarre parosteal osteochondromatous proliferation			
Synovial chondromatosis			
Osteochondromyxoma			

(Case1) Enchondroma (Metachondromatosis is a possibility):

Enchondroma, the most common benign chondrogenic tumour of hyaline cartilage is located in the medullary cavity of diaphysis and metaphysis and usually seen in the hands, feet and rarely in femur and humerus. It is extremely rare in

pelvis, scapula and ribs and our patient had multiple lesions in left ribs and right scapula, which is very rare. Though the radiological pictures were suggestive of an aggressive lesion, the final biopsy was confirmed as a benign cartilaginous lesion.

Multiple cartilaginous tumours are seen in multiple enchondromas, Maffuci's syndrome, Olliers disease and metachondromatosis. Multiple enchondromatosis may produce severe deformities and undergo malignant transformation, Maffuci's syndrome is a non hereditary condition with increase risk of ovarian and brain malignancy and have a 30% risk of chondrosarcoma, Ollier's – non hereditary lesion is associated with ovarian sex cord stromal tumours with a risk of less than 30% risk of chondrosarcoma. Metachondromatosis is an inherited autosomal dominant disease caused by loss of functional mutatic PTPNII gene, (7) where multiple benign cartilaginous tumours are seen with no malignant transformation. As the patient gives history of similar lesion in her sister, metachondromatosis is a possibility.

Treatment is usually intra lesional curettage and bone grafting, but this patient as the tumour was large had excision with bone graft and flap cover and is doing well in 2 years follow up.

Case 2: Clear Cell Chondrosarcoma:

It is a low grade malignant tumour and a subtype or separate entity from traditional chondrosarcoma with an incidence of 2% of all chondrosarcomas with a male predeliction. It is characterised by its special histological features, site of predeliction, slow growth and better prognosis. Rarely it can behave aggressive. Dominant cell is a chondrocyte and since the tumour is believed to arise from the second ossification centre, its predeliction to the epiphysis or apophysis of long bones is the general rule. However rarely it can occur in metaphysis, diaphysis or flat bones. It was first described in 1976 by Unni et al (8) as a rare mesenchymal neoplasm, which commonly affects proximal humerus and femur (our case involved the tibial bone). Radiologically it is an expansile osteolytic lesion with sharp interface between tumour and surrounding bone with high signal intensity on T2 weighed images. The cortex is thin, but intact and cortical breach should raise a suspicion of aggressive changes. As the earlier biopsy showed cells with clear cytoplasm with vesicular nuclei and chondroid material with few osteoclasts, a diagnosis of chondroblastoma was suggested and excision biopsy showed predominantly clear chondrocytes with condensation of powdery cytoplasm near the membrane or nucleus, with chondroid material and calcification with woven bone, osteoclasts and osteoblasts and diagnosis was consistent with clear cell chondrosarcoma. Some authors believe that clear cell chondrosarcoma may result from anaplastic changes of chondroblastoma cells into another subtype. Though they are considered Low Grade, few cases behave aggressive or high grade with early metastasis or synchronous location. Morphological features that help to predict aggressiveness are IHC positivity for metalloproteinase 1 & 2 (diffusely expressed in aggressive tumours) and electron microscopy appearance of absence of superficial microvilli. (9)

Simple excision, curettage, En block resection with wide margin of normal bone and soft tissue and rarely amputation is treatment of choice. It is very important to have a long follow up of these patients even for decades or life long because they tend to metastasize or recur even after an extended period. Minnaharitinen et al (10) reported as unusual case of clear cell chondrosarcoma with very late recurrence and lung metastasis, 29 years after primary surgery.

Case 3 – Chondroblastoma with Aneurysmal bone cyst like areas:

Chondroblastoma, a very rare chondrogenic neoplasm, less than 1% usually seen in teenage males was initially described by Ewing in 1928 (11) as calcifying giant cell tumour and in 1931 by Codman (12) as epiphyseal chondromatous giant cell tumour of the proximal humerus and finally corrected to chondroblastoma of bone by Jaffe & Lichenstein (13) in 1942. Aigner.T et al, (14) in his study suggested that chondroblastomas should be classified as a specific bone forming rather than cartilage forming neoplasms as the extra cellular matrix composition and gene expression pattern analysis showed osteoid and fibrous matrix of bone and not type II collagen of cartilage.

WHO, in its 2013 classification has called this an Intermediate malignant, rarely metastasing tumour, but is known for local recurrence with occasional metastasis. It usually arises in the epiphysis with open growth plate in skeletally immature patients. Radiologically, eccentric geographic destruction with sclerotic images is seen in the epiphysis. Aneurysmal cyst (ABC) like areas can be seen rarely in chondroblastoma and therefore if biopsy shows predominantly ABC like areas, the primary lesion can be overlooked, which happened in our case. Careful attention must therefore be paid to clinicoradiological features to allow distinction between the 2 entities and specimen should be sampled thoroughly with radiological correlation (Epiphyseal location with calcification will lean towards chondroblastoma) for a definite diagnosis.

(15) Huvos AG et al in 1970 found ABC changes in 20% of 25 chondroblastomas, while DC Dahlin et al (16) in their study identified ABC changes in 20 of their 125 cases (16%) and Schajowicz F et al (17) observed ABC changes in 17% of their cases. Casaderie et al analysed the literature from 1900 to 2009 of patellar tumours and of total 536 cases, 16% were chondroblastoma and 10 – 15% of them were associated with ABC changes. Cytogenetic mutation of K36M in either H3F3A or H3F3b is very useful and IDH1 and IDH2 (18, 19) seen in chondrosarcomas absent in this tumour. Even though both the lesions are treated with local resection and curettage, it is essential to clinch at the right diagnosis as chondroblastomas can recur, they require regular follow up at 1, 2, 3, 6, 9, 12 and every 6 months thereafter and imaging studies with bone marrow edema and cortical destruction on MRI are signs of recurrence. Radio ablation is also considered as an alternate therapy. Some complications after surgery such as limb length discrepancy and articular deformity may occur and patients need functional therapy as well.

Case 4 – Mesenchymal Chondrosarcoma:

This is a rare, high grade, unique malignant cartilaginous neoplasm with biphasic pattern composed of mesenchymal cells and chondrocyte components composed of small to ovoid cells with atypia and lobules of hyaline cartilage. These undifferentiated cells are thought to originate from cartilage forming primitive mesenchyme.

This tumour was first described by Lichtenstein and Berastein (20) in 1959 and later Dahlin (21) and Henderson reported 9 cases from the files of mayo clinic. The common sites include femur, facial bone and pelvis. Our patient presented with femoral lesion with pathological fracture. Both FNCLCC and NCI Grading systems call it high grade, thought it would not fulfill the formal histopathological criteria for this classification like increased mitosis and necrosis.

Mesenchymal chondrosarcomas differs from conventional chondrosarcoma in age distribution, rarity, high grade malignant behaviour, poor prognosis, high proportion of extra

skeletal tumour and unusual metastasis to lymphnodes and other bones. Cytogenetically, they are positive for HEY1 - NCOA2 rearrangement fusion protein by FISH, which is useful for potential therapy. (22, 23)

This tumour is very rare, for eg, a case study on review of case by Michael W Bishop et al (24) over a 24 years period, only 12 patients were identified with common sites being head and neck and another case study at a children's oncology group study (25) for non rhabdomyosarcomatous soft tissue sarcomas, of 551 eligible patients only 5 mesenchymal chondrosarcomas (0.9%) were identified. Rarity of this histologic entity has made it difficult to analyse the natural history and the best therapeutic options for patients. Diagnostic pitfalls include inadequate biopsy samples, which leads to erroneous diagnosis of non chondromatous soft tissue sarcoma. Aggressive surgical resection with CT & RT yields local control and reduces the likelihood of late recurrence and metastasis.

CONCLUSION:

Cartilaginous tumours, the most common tumours of the bone, always pose a diagnostic challenge to the clinician and the pathologist. A multidisciplinary approach and cooperation between clinician, radiologist and pathologist is essential along with representative adequate biopsy material for definite accurate diagnosis, which can be confirmed with IHC and cytogenetics.

"BIOPSY SHOULD BE REGARDED AS THE FINAL DIAGNOSTIC PROCEDURE AND NOT AS A SHORT CUT TO DIAGNOSIS".

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