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Facts Sheets of Cartilage Tumors. Classifications and Differential Diagnosis – Review Article

Mulazim Hussain Bukhari, Samina Qamar, Farwa Batool, Kalyani Bambal, Mandeep Bedi, Manu Noaty

Authors

1. Prof. Dr. Mulazim Hussain Bukhari
Professor of Pathology
Punjab Medical College, Faisalabad

2. Dr. Samina Qamar
Assistant Professor, Pathology
King Edward Medical University, Lahore

3. Dr. Farwa Batool
Assistant Professor, Pathology
Punjab Medical College, Faisalabad

4. Dr. Kalyani Bambal
District Pathologist
Govt. Medical College, Nagpur, India

5. Dr. Mandeep Bedi
District Pathologist
Kasturba Medical College, Manipal, India

6. Dr. Manu Noaty
District Pathologist
Indra-Gandi Medical College, Simla, India

Corresponding Author
Prof. Dr. Mulazim Hussain Bukhari
Professor of Pathology
Punjab Medical College, Faisalabad
Contact: +92 300-8414743
Email: mulazim.hussain@gmail.com

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Summary: Tumors, which differentiate to cartilage, share characteristic features for the production of chondroid matrix by these tumor cells. The cartilage tumors are ranged from completely benign lesions to highly malignant. These are subdivided by location into peripheral, surface, central and intramedullary lesions. Benign bone tumors are a group of neoplasms that are most frequent in children and young adults, although they may also present in later stages of life. The malignant cartilage tumors affect bones and joints but rarely as compared to osteogentic tumors. The Malignant tumors cannot be differentiated from benign simply by biopsy without radiographic evidence. However, CT and MRI imaging may be of some use in defining the extent of tumour spread locally.

Keywords: Cartilage forming tumors, Chondromyxoidfibroma, Osteochondroma, Enchondroma, Osteosarcoma.

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INTRODUCTION

This group of tumors arise from bones and joints, produces cartilage matrix, not preexisting cartilage tissues. These are now classified into benign, intermediate (locally aggressive), intermediate (rarely metastasizing) and malignant grades by WHO (Table 1). [1]

Table 1: WHO, classification of cartilage tumors of the bone

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			

Chondrosarcoma (grades I-III), including primary and secondary variants and periosteal chondrosarcoma. Chondrosarcoma grade I (now officially termed atypical cartilaginous tumor) is reclassified as an intermediate (locally aggressive) tumor, better reflecting its clinical behavior. Chondrosarcoma is sub-classified into primary central chondrosarcoma, secondary central chondrosarcoma, secondary peripheral chondrosarcoma, periosteal chondrosarcoma. Secondary chondrosarcoma is currently subdivided into central (arising in a pre-existing enchondroma) and peripheral (juxtaposed to the cartilaginous cap of an osteochondroma) types.[2,3]

Genetics Association of Cartilage forming Bone Tumors.

It has been observed that IDH1 and IDH2 mutations are found in primary, secondary, central and periosteal chondrosarcomas as well as 50% of dedifferentiated chondrosarcomas. Mesenchymal chondrosarcoma carries a recurrent translocation resulting in a HEY1-NCOA2 gene fusion.[4]

In a study recurrent deletions were observed of 5q13.2, 5q14.2, 6q12, 6q16, 9p24.2, and 9p21.3. There was a significant association between high-grade tumor and the recurrent genetic deletions at 5q14.2 approximately q21.3, 6q16, 9p24.2, and 9p21.3. There was consistency between increased levels of aneuploidy and the progression of chondrosarcoma from lower to higher grades chondrosarcomas.[5]

Benign Cartilage forming Bone Tumors

Benign tumors of the bone consist of a wide variety of different neoplasms. These tumors vary in terms of incidence, clinical presentation and require a broad pattern of therapeutic moadlities.[6, 7]

These are a group are lesions such as osteochondroma, enchondroma and chondromyxoid fibromas. The common feature of these tumors is the presence of chondrocytic cells and the formation of cartilaginous tumor matrix. Some of these cartilage benign tumors are true neoplasms while others are hamartomas or developmental abnormalities.[8]

Subungual exostosis.

It is a type of myositis and also called Dupuytren's exostosis. It is a benign tumor of osteocartilaginous nature arising from the distal phalanx of the finger and toes in particular. It affects both sexes, most frequently occurring in the second and third decades of life and rarely in children younger than eight years. Radiologically it looks like calcifying lesion projecting from distal phalanx. [9, 10]

Differential Diagnosis. It should be differentiated from chondrobalstoma which does not arise from subungual region with different location, no spindle cell proliferation like subungual (Dupuytren) exostosis.

It should also be differentiated from sarcomas which have marked pleomorphic and infiltrative nature as compared to subungual exostosis. Radiology is helpful to differentiate these two lesions.

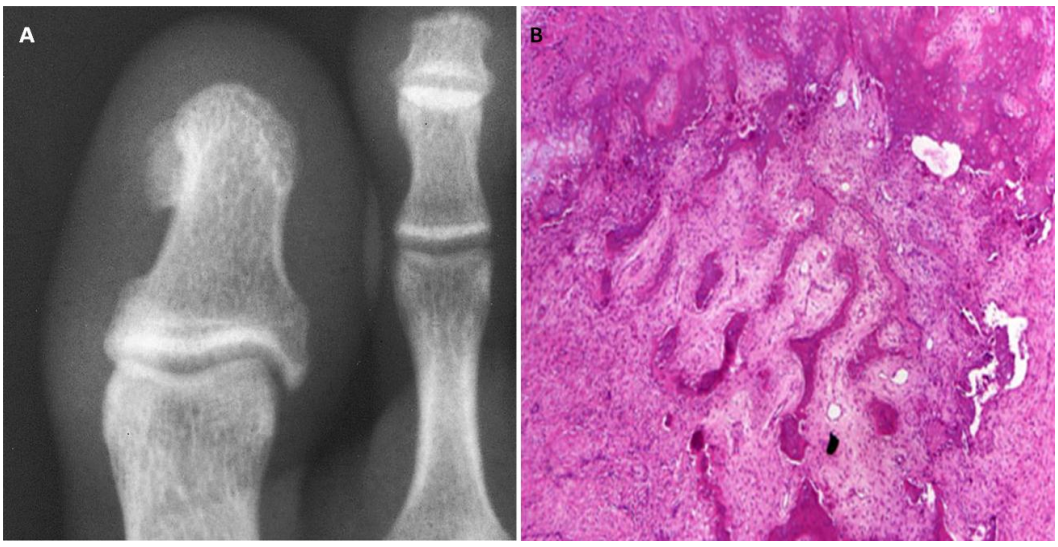

Figure 1: Radiological examination reveals (right), calcifying lesion projecting from the medial side of distal phalanx. On left side there is spindle cells proliferation on surface of cartilage, resembling a cap, with underlying trabecular bone formation

Bizarre parosteal osteochondromatous proliferation. BPOP is a reactive process and also known as Nora's Lesion. In this processes, there is heterotopic bone formation in the hands. On x-rays, these lesions are present on the surface and are well demarcated. There is an admixture of cartilage, loose fibrous tissue and bone formation in a haphazard arrangement. Although there is abundant cartilage and osteoid production, there is no cellular pleomorphism.[11]

Differential Diagnosis. Osteochondroma. These tumors do not arise in the hand. These are developmental lesions which affect the metaphases of long bones. The radiographic pattern in this patient does not show a stalk typical of an osteochondroma anywhere.

Osteosarcomas are extremely uncommon in the hand. Although there is abundant osteoid and cartilage in the lesion, there is no cellular pleomorphism.[12] (Figure 2)

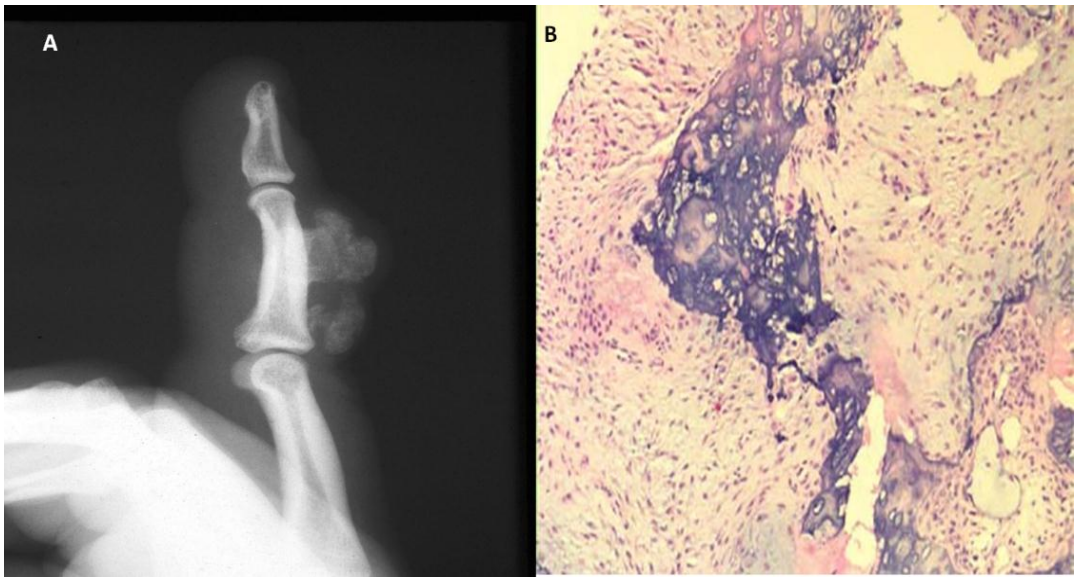

Figure 2: On right side, a radiograph showing a bony nodule on the ulnar aspect of her distal fifth metacarpal while on left side an admixture of cartilage, loose fibrous tissue and bone formation.

Osteochondroma

It is also called exostosis and is most common benign skeletal tumor skeletal tumor, 20 -50% of all benign bone tumors. It is most frequent in 1st and 3rd decade of life with mean age 10 years. There is slight male predominance as male to female ration is 1.5: 1. [13]

Site: Most often in metaphyseal area of cortex of long bones (distal area of long bones (distal femur, proximal tibia) comprising 40% around the knee joint (also shoulder and hip joints).[13, 14]

Multiplicity: It is usually solitary but sometimes appears as multiple lesions. [15, 16]

Chances of Malignancy: It has been seen that growth ceases after maturity but if persists after maturity, is an indicative of malignant transformation. Only < 1% risk of malignant transformation for solitary lesions. Malignancy has been seen more in multiple cases as compared to solitary lesions [14, 17]

Clinical Presentation: It usually appears as painless swelling but may be painful when associated with secondary pathology like fractures, bursa formations are causing mechanical irritations with nerves, vessels, tendons and muscles. [13]

Radiological findings: There is sessile or stalk like extension. Metaphyseal growth grows in opposite direction to joints (Fig 1). The cortex and medulla are continuous with underlined bones. On CT, it is determined if marrow and cortices of lesion are continuous with bone. On MRI, Proximity to other structures Proximity to other and covered with cartilage cap is determined.[13,18]

Gross Examination: It reveals an irregular bony mass and with bluish-grey cartilage cap.[13]

Histopathological examination: It shows thin fibrous layer of periosteum examination and a cartilage cap covering mature bones. Medullary canal is continuous with bone. The cap is represented by hyaline cartilage that contains evenly distributed chondrocytes. The junction between cartilage and bone looks like the epiphyseal plate containing multiple linear rows or columns of normal chondrocytes (Figure 3)

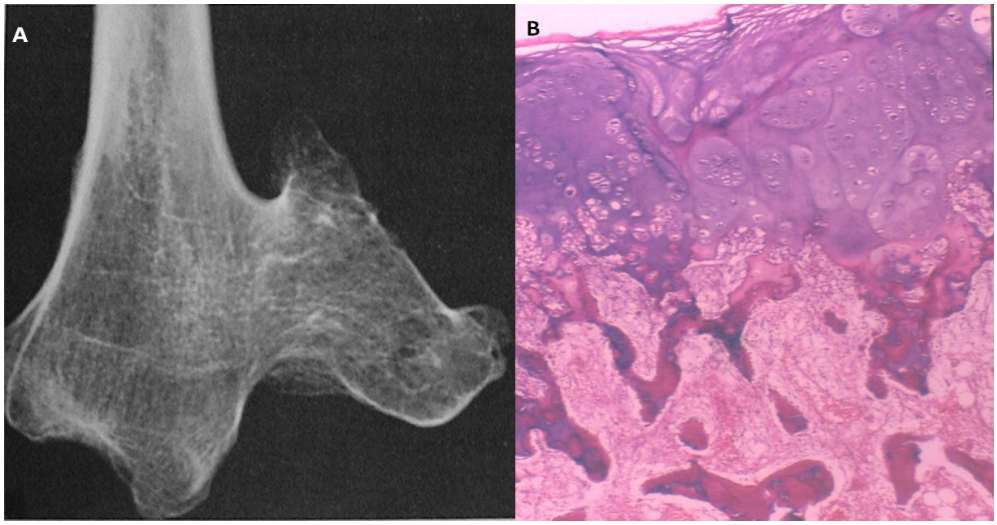

Figure 3: The radiological examination of Osteochondroma revales a stalk like extension and metaphyseal growth growing in opposite direction to joints. The cortex and medulla are continuous with underlined bones (Curtsey from URL. Orthopaedics One Images). Photomicrograph shows well-circumscribed lesions with mature bone trabeculae and fibro-fatty marrow, covered by mature cartilage

Differential Diagnosis of Osteochnroma (Table 2).[13, 14, 19]

A. Parosteal osteochondromatous proliferation these are also called Nora lesion. Nora's lesion, also known as "bizarre parosteal osteochondromatous prolifera tion" (BPOP), was first described in 1983 by the pathologist Nora. This lesion is defined as a proliferation of the bone. In most cases the lesion emanates from the intact cortical substance of short bones. [10, 11] (Table 2)
   1. These lesions usually involve small bones of hands and feet while osteochondromas occur in long bone. (Table 2)
   2. Age: These occur in third and fourth decades of life while the mean age of osteochondromas is 10 years. (Table 2)
   3. Radiology: Medullary component of lesion is not in continuity with the host bone while there is always continuity of medullary component in osteochondromas. (Table 2)
   4. Histologically, the cartilage is hypercellular with atypia and multinucleation in parosteal osteochondromatous proliferance, while in osteochondroma the hyaline cartilage cap (0.1-3 cm) is comprided of normally organized chondrocytes and with underlying cancellous bone having fatty or haemopoietic marrow.
   5. Chondroid nodules are separated by a spindle cell proliferation that exhibits mitotic activity (no atypical mitoses or nuclear atypia) while it is capped in osteochondromas. (Table 2)

B. Chondrosarcoma arising in an osteochondroma
   1. Clinical findings consist of pain and a rapidly enlarging mass while pain is rare in osteochondromas. (Table 2)
   2. Radiographic findings consist of thickened (more than 2 cm), irregular cartilaginous cap, radiolucent zones in cartilaginous cap, extension through periosteum into soft tissue, and evidence of bone destruction while narrow base, stalk, project from surface and pointing towards mid shaft. (Table 2)
   3. Histologic findings consist of increased cellularity, nuclear atypia represented by enlarged nuclei with open chromatin pattern, multinucleation, and mitotic activity while no such findings are seen in osteochondromas. (Table 2)
   4. Fibroblastic stroma is present in the medullary spaces instead of fat and hematopoietic tissue as seen in osteochondromas. (Table 2)
   5. The cartilaginous cap is present, it is composed of cytologically low-grade malignant chondrocytes without

endochondral ossification while benign cartilage is seen in osteochondromas. (Table 2)

C. Parosteal osteosarcoma.
   1. In Osteosarcoma on radiology, the continuity with the medullary component of the parent bone is not present but appears to be attached to the surface of the parent bone, while osteochondromas is always attached as a continuity with medullary compotent. (Table 2)
   2. The spindle cells between bony trabeculae instead of fat and hematopoietic tissue as seen in osteochondromas. (Table 2)

Enchondroma.

It is benign, intramedullary neoplasm of hyaline cartilage arises from the medulla of bony diaphysis. The majority of the lesions are solitary but these can occur multiple as a manifestation of a congenital syndrome (M. Ollier and Maffucci syndrome).[7]

Clinical Features. Painless swelling (pain due to stress fracture), patients from wide range of age (5-40 years). Sometime it is an incidental finding.[13]

Sites: Almost exclusively in appendicular skeleton, mostly in hands & feet.[8]

Radiology: Bone expanded by radioluscent lesion with thinning out cortex. Sometimes may have calcification like pop-corn appearance and tend to expand short tubular bones, e.g. metacarpals but cortex remains intact unless there is any other pathology like fracture. (Fig 4)

Histology: Lobules of mature, hyaline cartilage covered by bones well-demarcated and well-encapsulated there is proliferating nests of mature cartilage cells. The nuclei are small and uniform without atypia. Calcification may be seen. (Figure 4) Enchondromas with Ollier's and Maffucci's lesions of hands and feet are more cellular than long bones and should be carefully examined, sometimes atypical and binucleation may be seen in such conditions, therefore more sections are advised.[20]

Ollier''s Disease: It is rare, non-hereditary, multiple enchondromas of the extremities with shortened & deformed limbs. Usually about 30-50% of such cases develop sarcoma.[21]

Maffucci's syndrome: It is also rare non-hereditary, multiple, enchondromas. It is associated with haemangiomas, phleboliths, and deformities of bones. There is high incidence of malignancy like chondrosarcoma, vascular sarcoma or fibrosarcoma.[21]

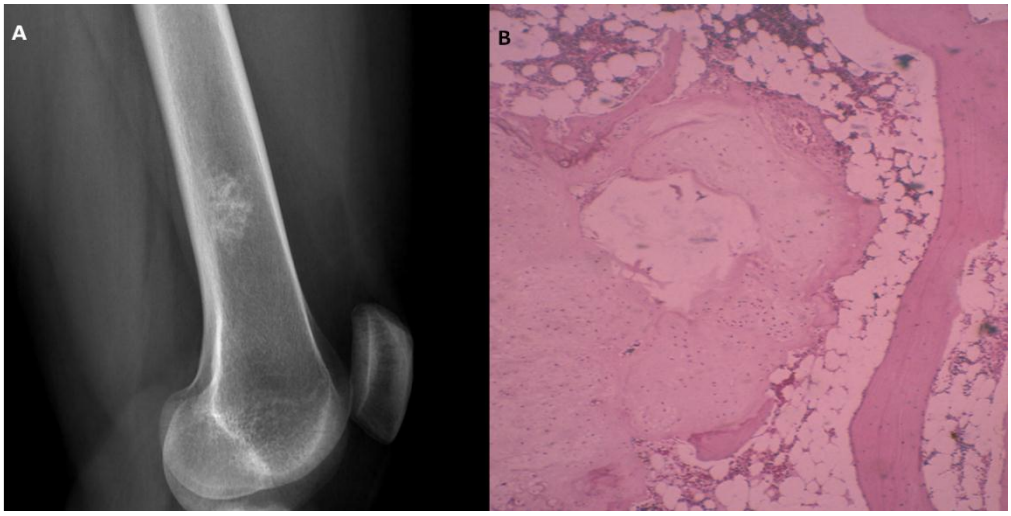

Figure 4: Radiological examination reveals a radiolucent lesion with thinning out of cortex and calcification like pop-corn appearance in metacarpals but cortex is intact (A). Photomicrograph shows (H&E 20X) lobules of mature cartilage encircled by bone trabeculla.

Differential Diagnosis.[13, 14, 19]

A. Prominent costochondral cartilage.

This condition sometimes may clinically mimic enchondroma. It is composed of histologically benign chondrocytes with an orderly and regular arrangement. While in Enchrdomas, there are lobulated, hyaline cartilage with on focal increased cellularity no nuclear atypia. (Table 3)

B. Fibrous dysplasia with chondroid differentiation.

It reveals a ground-glass diaphyseal lesion on radiological examination and histologically the

fibro-osseous elements are seen which is absent in enchondroma. (Table 3)

C. Low-grade chondrosarcoma (LGCS).

1. Pain is usually present in low-grade chondrosarcoma while pain is typically absent in enchondroma unless traumatized or pathologically fractured. (Table 3)
2. Radiographic features of LGCS includes cortical destruction, cortical thickening due to extension of tumor in haversian canals, and a soft tissue mass while these features are absent in enchondromas. (Table 3)
3. Histologically there is increased cellularity and binucleation in chondrocytes in LGCS but benign chondrocytes are seen in enchondromas. (Table 3)
4. The marrow permeation represented by cellular cartilage surrounding mature bone trabeculae and lobules of cartilage separated by fibrous tissue is seen in LGCS but lobulated, hyaline cartilage with no increased cellularity with no or mild nuclear atypia seen in enchondromas. There is no permeation seen in enchondromas. (Table 3)
5. In LGCS, it is extension of the tumor into haversian canals but not seen in enchondroma. In LGCS, there is prominent myxoid features which are not seen in enchondromas. (Table 3)
6. Proliferative index Ki-67 is high in LGCS while normal in ENC. In summary there is breaks through or erodes cortex, marked myxoid change, large tumors occupy marrow space and entrap bony trabeculae which are absent in ENC. (Table 3)

Chondrobalstoma

Rare benign neoplasm composed of immature chondroid cells and mature hyaline cartilage, accounting for 14% of bone tumors. Mostly between 5-25 years of age, males more common.[7,13,22]

Site: About 98% arises from epiphysis of distal femur, proximal tibia and proximal humerus, uncommonly from flat bones and those of hands and feet. The most common site of involvement is the proximal humerus, followed by the proximal femur, distal femur and proximal tibia. They can also occur in pelvis, calcaneus, patella, mid and hindfoot and in an older age group (40-50) and involvement of the skull has been reported. [22,23]

On radiological examination it is sharply demarcated lytic lesion with thin margin of increased bone density in epiphysis, may extend into metaphysis with spotty calcifications in patients with open epiphysis. Figure 4

Histopathology: On histological examination, there are sheets of oval, round or spindle chondroblasts with oval to round nucleus with clefts, grooves or indentations. (Figure 4) There are multinucleated giant cells, eosinophilic chondroid matrix and chickenwire calcification.[13]

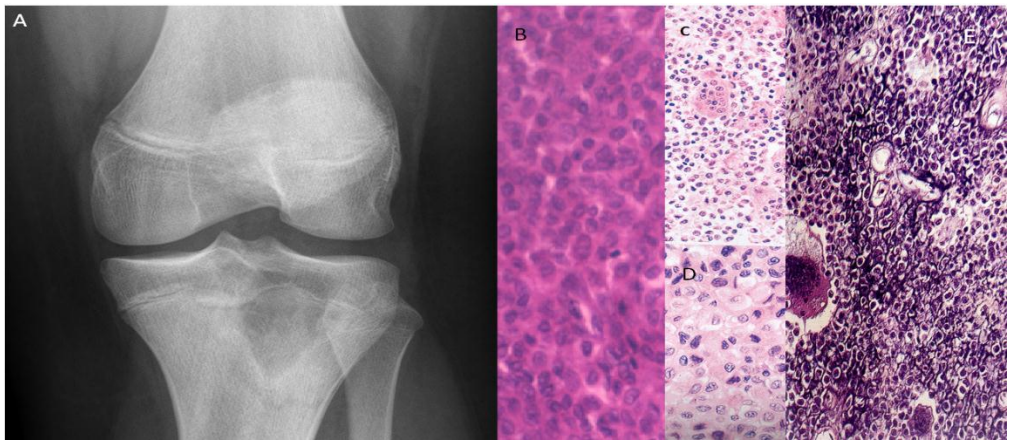

Figure 4: Radiological examination reveals a sharply demarcated lytic lesion with thin margin of increased bone density in epiphysis (A). There are sheests of monotonous polyhedral cells (B) with round to oval nuclei and cleaving (C&D). There is patchy distribution of giant cells (left) chickenwire calcification, and eosinophilicchondroid tissue (E).

Differential Diagnosis.[13, 14, 19]

A. Chondromyxoid fibroma. (Table 4)

1. It is metaphyseal in origin and with myxoid and pseudolobular pattern of pleomorphic

stellate cells while in chondrobalstoma is epiphyseal in origin and does not have myxoid or stellate cell in morphology.

2. It lacks calcifications and has more prominent and lobulated myxoid stroma while there is chicken wire calcification, and eosinophilic chondroid tissue in chondrobalstoma.

B. Giant cell tumor.[7] (Table 4)

1. It is metaphyseal in patients with closed epiphysis, while epiphysis in patients when it is still active. There are clustered giant cells that are larger and more numerous than chondroblastoma, no chondroid differentiation, no chicken wire matrix is present in GCT.
2. GCT usually occurs in skeletally mature patients while CB found in skeletal immature patients (10-25 years).
3. In GCT, stromal cells are without nuclear grooves are and negative for S-100 protein, which are characteristics of CB.

C. Eosinophilic granuloma. (Table 4)

May radiographically and cytologically (nuclear grooves) mimic chondroblastoma. Contains eosinophils and lacks chondroid matrix and calcifications which are seen in CB. The langerhan's cells are positive for CD1 in eosiniphilic granuloma.

D. Aneurysmal bone cyst.[7]

Chondroblastoma with prominent secondary aneurysmal bone cyst formation may mimic a primary aneurysmal bone cyst. S-100 protein may be useful in identifying stromal cells in chondroblastoma which are negative in ABC. (Table 4)

E. Clear cell chondrosarcoma. (Table 4)

1. CCCS is usually seen in older patients while the CB is seen in skeletal immature patients (10-25 years),
2. It is composed of cells with clear-staining cytoplasm while clearing is rare in CB.
3. It contains chondrocytic cells with cytologic malignant features which are absent in CB.
4. Tends to be more heavily calcified than chondroblastoma.

F. Chondroblastic osteosarcoma.

It may rarely involve the epiphyses and mimic chondroblastoma but contains tumor osteoid, which are absent in CB.

Chondromyxoid fibroma

Definition: Chondromyxoid fibroma (CMF) is a very rare benign cartilaginous tumour arises from metaphysis and contains lobules of chondromyxoid tissue, separated by fibrous septa. Mostly 10-30 years, male predominance, pain. [24]

Site: Mostly in metaphysis of the long bones (most common site proximal tibia), 25% cases in flat bones.[13]

Radiology: Eccentric, metaphyseal lesion, sharply demarcated, purely lytic defect with scalloped margins. Matrix calcification is uncommon. MR imaging will reveal a typical lobulated pattern suggestive of a cartilage tumor. (Figure 5)[25]

Histology: Lobules composed of spindle to stellate cells in abundant myxoid to chondroid stroma, fibrous septa contain large venules, muscular arteries & giant cells, reactive osteoid at edges.[13]

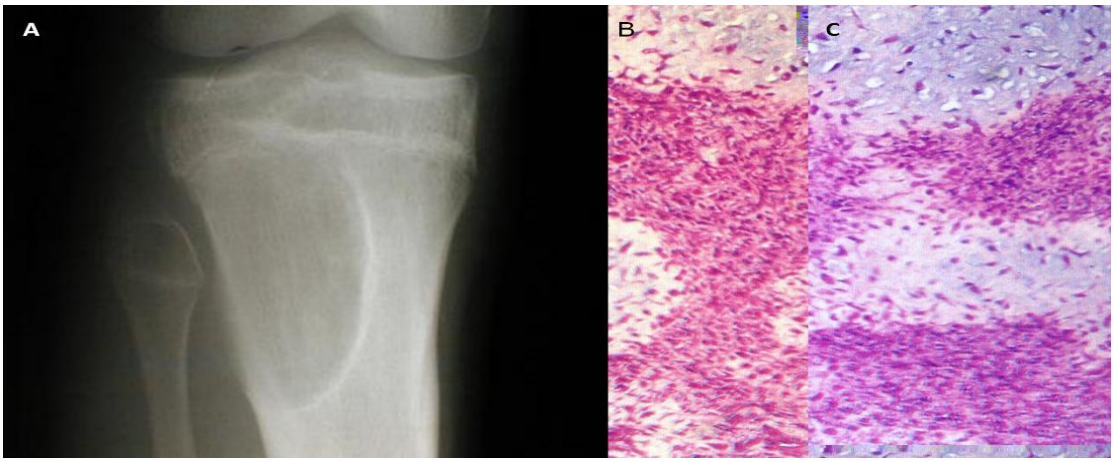

Figure 5: Radiograph of the proximal tibia reveals a large, lucent, slightly expansile, eccentric metaphyseal lesion with thin, sclerotic borders (A). Photomicrograph of chondromyxoid fibroma, lobulated tumor, separated with bands of fibroblast like spindle cells and osteoclasts (B&C).

Differential Diagnosis.[13, 14, 19]

Chondroblastoma: The cells are similar but not lobulated in CMF. It typically involves the epiphyses while CMF involves metaphysis. Calcifications seen both radiographically and histologically (chicken-wire appearance). (Table 4)

Fibromyxoma: It is similar to chondromyxoid fibroma but no cartilaginous areas, usually older adult.

Fibrous Dysplasia: The trabecular pattern is different as compared to CMF. There is lobulation in FD. (Table 4)

Chondrosarcoma: Similar histology but malignant radiologically, no hypocellular center, infiltrates surrounding tissue. (Table 4)

Chondrosarcoma

Location in Bone: The central tumor arises from the medulla of diaphysis while the peripheral arises from the cortex or periosteum of the medulla. The mesenchymal variant arises medulla or cortex of diaphysis.[13]

Gender: It is three times more common in males. While the mesenchymal variant does not show any difference.[26]

Age: Usually it appears in 30-60 years of age while mesenchylam variant appears a little bit early i.e. 20-60 year of age.[19]

Radiology: On conventional radiography, the distinction between enchondroma and central grade I chondrosarcoma cannot be reliably made. The localization in the axial skeleton and size greater than 5 cm are the only reliable predictors for malignancy. Low-grade central chondrosarcoma can be geographic in appearance and may show mild cortical expansion and/or endosteal scalloping. The presence of chondroid matrix is variable, ranging from pure lytic lesions, to few or dense calcifications. They have no associated soft tissue mass.[13]

Histology. Irregular lobules of immature cartilage, chondrocytes in clusters or groups; nuclei normal, enlarged or bizarre, cellularity greater at edges, matrix chondroid to myxoid, reactive osteoid at margins or centres. [13,19]

Grade based on: It is based on cellularity, nuclear pleomorphism and mitotic count.

Grade-I: Chrondrocytes with small, dense nuclei, some may be slightly enlarged, a few binucleated or multinucleated, matrix mostly chondroid, rare mitosis

Grade-II: More cellular, prominent at periphery, nuclei vesicular, enlarged & hyperchromatic, more than one nucleus in lacunae, myxoid stroma, scattered mitoses

Grade-III: Greater cellularity & pleomorphism, myxoid matrix, foci of necrosis, frequent mitoses

Important Points to remember.

1- Presence of endochondral ossification in a malignant chondroid neoplasm is not indicative of osteosarcoma

2-About 90% of chondrosarcomas are grade 1 or 2 . Cartilaginous tumors of the hands and feet generally behave as benign lesions, whereas cartilaginous tumors of the axial skeleton are usually aggressive. Pain is an important clinical feature that may be used to differentiate a benign chondroid process from malignant one.

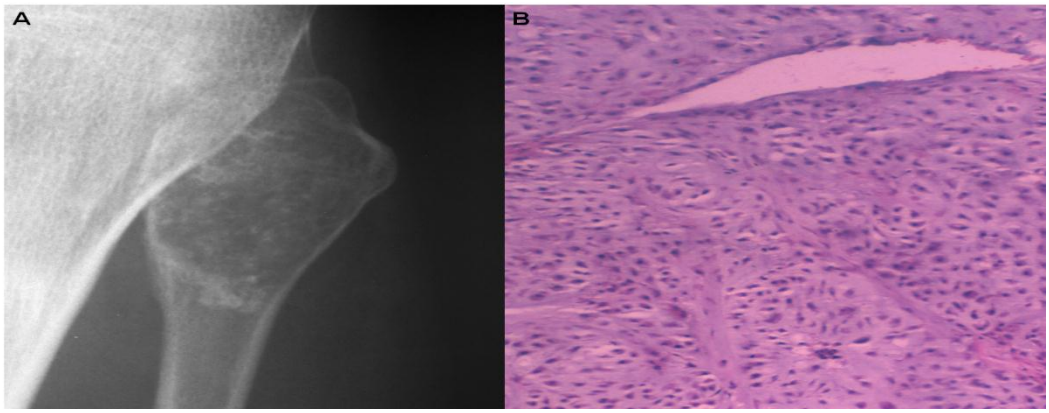

Figure: 6. Radiological findings of low grade chondrosarcoma of the left fibula head demonstrates a lucent lesion that contains the typical chondroid matrix calcification. Low-grade tumor (A).Low grade Chondrosarcoma (grade I) with binucleated chondrocytes. There are atypical nunclei and a permeative growth pattern around native trabeculae. This permeative growth pattern is diagnostic of malignancy in most primary bone tumors (B)

Differential Diagnosis of Chondrosarcoma.[13,14,19]

A. Enchondroma (Table 5)

Location in Bone: It arises from Medulla of diaphysis

1-Age: Younger than Chondrosarcoma

2-Clinical and radiographic features are needed to differentiate this tumor from grade 1 chondrosarcoma.

3-Pain: Typically not painful .

4-Radiographically: The tumor lacks evidence of an aggressive process (intramedullary lucent lesion without cortical destruction). Radiology: X-ray is determinative, for chondrosarcoma one must see permeation of tumor through cortex into soft tissue.

5-Histologically: The tumor may have features similar to those of a grade 1 chondrosarcoma . Loubular pattern is a defined histopathologic feature of well-differentiated chondrosarcoma; a fibrous tissue separates the lobules. Enchondroma lobules are regular and the fibrous tissue consists of mature connective tissue. On the other hand, well-differentiated chondrosarcoma consists of irregular lobules with cellular fibrous tissue around the tumor. Lobules of chondroid tissue are separated by normal hematopoietic tissue, whereas in chondrosarcoma, fibrous tissue separates lobules. It is believed that presence of binucleated chondrocytes is required for the diagnosis of well-differentiated chondrosarcoma.[14]

B. Fracture callus. (Table 5)

1-Age: Any age

2-Clinical and radiographic features do not support the diagnosis of chondrosarcoma. History can help in differential diagnosis

3- Composed of benign chondrocytes

C. Chondroblastic osteosarcoma (Table 5)

1-Age: Occurs in a younger age group than chondrosarcoma

2-Careful sampling of the tumor identifies tumor osteoid and tumor cells make bone. Chondroid matrix is predominant in chondroblastic osteosarcoma, intimately associated with non-chondroid elements. The neoplastic chondrocytes are mostly characterized by severe cytologic atypia and reside in lacunar spaces, hyaline matrix or float singly or in cords in myxoid matrix. Myxoid and other forms of cartilage are uncommon, except in the jaws and in the pelvis.

3-Radiographically, this tumor exhibits features of an osteoid-producing tumor; prominent periosteal reaction and cumulus cloud–like mineralization.

Clear Cell Chondrosarcoma

It is a rare variant with good prognosis. It occurs usually 3rd to 4th decade of life, more common in males with predilection for epiphyses of long tubular bones. Clear Cell Chondrosarcoma is a destructive low-grade malignant tumor, which presents in adults. Clear cell chondrosarcoma is uncommon and accounts for about 2% of all chondrosarcomas. [13,18]

Radiology: It involves long bones. There are well defined, lytic, with punctate radio densities corresponding to areas of mineralization.[18]

Histology: There are lobules of tumor cells with sharply defined borders, clear or ground-glass cytoplasm with vacuoles, central nuclei with occasional prominent nucleoli, numerous osteoclast-type giant cells, often mixed with small trabeculae of reactive bone. Three common epiphyseal tumors include giant cell tumor, clear cell chondrosarcoma, and chondroblastoma (Figure 7). There are sheets of round cells with clear cytoplasm admixed with multinucleated giant cells and, in areas, a chondroid-like stromal.[13]

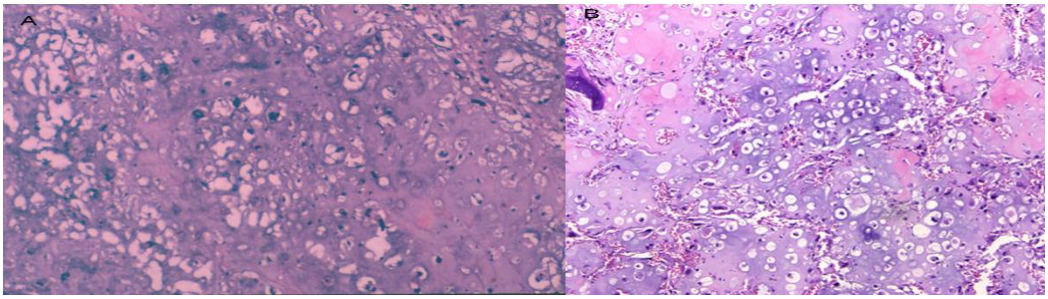

Figure 7: High grade Chondrosarcoma. Photomicrograph shows irregular lobiues of immature cartilage with myxoid cortex (A). Photomicrography of Clear cell Chondrosarcoma, there is increased celluarity on the margins, binucleation, trinucleation with pelomorphisim and frequent mitosis (Curtesy from Johns Hopkins) (B)

Differential Diagnosis of Clear Cell Chondrosarcoma.[13, 14, 19]

Chondroblastoma: It lacks prominent clear cells and bony trabeculae. (Table 6)

Osteoblastoma: It lacks chondroid differentiation. (Table 6)

Aneurysmal bone cyst. Clear cells and cartilaginous differentiation are absent .(Table 6)

Intramedullary chondrosarcoma. Multinucleated giant cells and reactive bony trabeculae are absent within the malignant cartilage. (Table 6)

Metastatic renal cell carcinoma. Clear cells in renal cell carcinoma are positive for PAX2+, vimentin and cytokeratin, typically negative for S-100 protein; however, staining may be variable. (Table 6) Metastatic renal cell carcinoma has a prominent delicate vascular background surrounding clear cells.[19]

Mesenchymal Chondrosarcoma.

There are dimorphic patterns of well-differentiated cartilage and abrupt boundary from undifferentiated stroma, composed of small round to oval cells resembling lymphoma, hemangiopericytoma or Ewing's sarcoma/PNET. Should be considered in patients with malignant biomorphic cartilaginous tumors arising in the mandible or maxilla.[27]

Dedifferentiated Mesenchymal chondrosarcoma.[13, 14, 19]

Age: It occurs in older age group and is more likely to affect the appendicular skeleton.

Morphology: It exhibits abrupt, sharp margins between the chondroid component and the dedifferentiated component; lacks hemangiopericytoma-like pattern. (Table 7)

Ewing sarcoma of bone: It lacks chondroid component. It is positive for CD99. (Table 7)

Embryonal rhabdomyosarcoma: It lacks chondroid component and expresses muscle markers (desmin, actin, and myoglobin). (Table 7)

Hemangiopericytoma/ Solitary Fibrous Nodule: Lacks chondroid component. It is positive for CD-34. (Table 7)

Conventional Condrosarcoma: The conventional chondrosarcoma consists entirely of hyaline cartilage. The population of small round blue cells in mesenchymal chondrosarcoma mitigates against a conventional chondrosarcoma. (Table 7)

Lymphoma: Older age group with diffuse distribution of monotonous cells replacing the bony trabeculaes sometime hyaline cartilage present indicate that this is a cartilaginous tumor. Immunohistochemistry can help, the lymphoma is LCA positive and S100 negative. (Table 7)

De-Differentiated Chondrosarcoma.

It is a high grade malignant neoplasm composed of a well differentiated cartilaginous tumor, usually low grade conventional chondrosarcoma, with either high grade pleomorphic, undifferentiated pleomorphic or sometime spindle cell sarcoma like areas. (Figue 8).[13]

Age: Bimodal age distribution; patients with exostosis may develop chondrosarcomas earlier in life.[18]

Radiology: The low grade component manifests as mineralized area with rings and arcs while the high grade component is lytic and aggressive, with permeation and destruction of underlying bone.[14]

Molecular Genetics. It is considered that IDH-1and IDH2 overexpression and SOX-9 is identifies chondrogenic differentiation, particularly useful in high-grade areas seen on biopsy without sampled cartilaginous areas. The mutation of tumor suppressor gene p53 is also seen in such malignancies although not useful in practice.[27, 28]

Differential Diagnosis De-Differentiated Chondrosarcoma.[13, 14, 19]

1. Chondroblastic Osteosarcoma. It is seen in young patients. There is gradual transition from high grade cartilaginous tumor to spindle cell sarcoma in COS while in DDCH, abrupt and sharply demarcated transition zone between the chondroid and dedifferentiated components is an important histologic feature in the diagnosis of dedifferentiated chondrosarcoma (Table 8)
2. High-grade spindle cell sarcoma / undifferentiated pleomorphic sarcoma of bone. These tumors lack cartilaginous areas. (Table 8)
3. High-grade intramedullary chondrosarcoma. May contain spindle cell areas suggestive of dedifferentiated chondrosarcoma; however, there is a gradual rather than an abrupt transition between the spindle cell and the chondroid components. (Table 8)
4. Mesenchymal chondrosarcoma . Typically occurs in a younger age group and exhibits a more gradual transition between the cartilaginous component and the undifferentiated component. (Table 8)

5. Metastatic sarcomatoid carcinoma. No cartilaginous Markers are usually helpful. The absence of keratin positive cells rules this diagnosis out. (Table 8)
6. Conventional Chondrosarcoma. The presence of high grade spindle cells admixed with giant cells in a pattern of malignant fibrous histiocytoma is not seen in conventional chondrosarcoma. (Table 8)

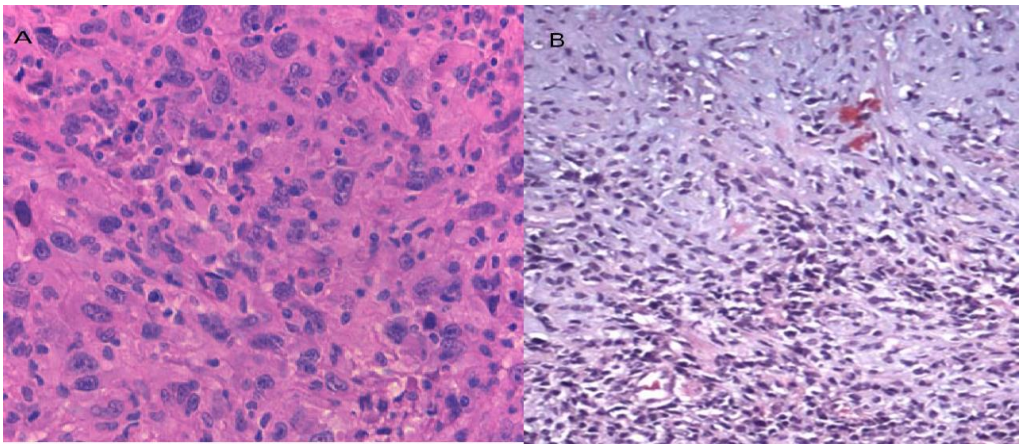

Figure 8: A Photomicrograph of De-differntiated, highgrade atypical cells and B. The malignant cartilage with abrupt transition of cellular components. The tumor is showing biomorphic picture. The cellular competent, like small cell and cartilaginous portion. The transition between two competent is gradual. (A curtesy from Johns Hopkin Unknown surgical conference. (B)

The Prognosis of Chondrosarcoma.

1-Grades: Grade I tumors have good prognosis but always do not have 100% survival, mainly due to problematic local recurrence or progression into high grade upon occurrence. The histological grading is subject to variability in interpretation, with grade II and III chondrosarcoma often grouped together even though there is a wide spectrum of outcome. [26]

Age: The most important predictors in chondrosarcoma for poor survival are histological grade and age above 50. [13]

Pathological Fracture: Poor prognosis and a wide excision with adequate reconstruction are preferable to reduce the risk for local recurrence. [26]

Histological Types. The prognosis in dedifferentiated chondrosarcoma is very poor, despite adequate wide surgical resection and adjuvant therapy. [13]

Staging: Inoperable, locally advanced and distance metastatic have poor prognosis as high-grade chondrosarcoma are insensitive to conventional adjuvant treatment such as radio- and chemotherapy, reducing life expectancy to minimal.[13, 26]

Table 2: Differential Diagnosis of Osteochondroma

Features	Osteochondroma	BPOP	Chondrosarcoma arising in an osteochondroma	Parosteal osteosarcoma
Site and Location	Long bone.	Small bones of hands and feet	Same bones but with multiple lesions	Same bone
Age in Years	30 years	Mean age 10	Older age	Older age
Clinical Symptoms	No pain	No pain	Pain Rapidly expanding mass	pain
Radiology	Always continuity of medullary component. No extension through periosteum in soft tissue.	Medullary component of lesion is not in continuity with host bone.	Extension through periosteum into soft tissue, and evidence of bone destruction while narrow base, stalk, project from surface and pointing towards mid shaft.	Continuity with the medullary component of the parent bone is not present. Appears to be attached to the surface of the parent none.

Histology	The hyaline cartilage cap is comprised of normally organized chondrocytes and with underlying cancellous bone having fatty or haemopoietic marrow. No mitosis, no atypia. Fibroblastic stroma is seen in hematopoietic tissue	The cartilage is hypercellular with atypia and multinucleation separated by a spindle cell proliferation	Increased cellularity, nuclear atypia multinucleation, and mitotic activity while. Fibroblastic stroma is present in the medullary spaces. The cartilaginous cap is present, it is composed of cytologically low-grade malignant chondrocytes without endochondral ossification	The spindle cells between bony trabeculae instead of fat and hematopoietic tissue as seen in osteochondromas.

Note: BPOP: Parosteal osteochondromatous proliferation

Table 3: Differential diagnosis of Enchondroma.

Features	Enchondroma	Prominent costochondral cartilage.	Fibrous dysplasia with chondroid differentiation or metaphysis	Low-grade chondrosarcoma
Site and Location	Medulla of diaphysis of small and long bones	Costal areas	Medulla of diaphysis	Medulla of diaphysis or periosteum of metaphysis
Age in Years	10-40 years	Any age	10-30	Old age
Clinical Symptoms	No pain	Same	No Pain	Pain
Radiology	Lytic lesions without aggressive features. Scalloped margins. When present in phalanges these are expansile lesions with characteristic calcifications "rings and arcs.	Same	Ground-glass matrix. may be completely lucent (cystic) or sclerotic. well circumscribed lesions. no periosteal reaction	cortical destruction, cortical thickening due to extension of tumor in haversian canals, and a soft tissue mass.
Histology	There is lobulated, hyaline cartilage with focal increased cellularity no nuclear atypia. Proliferative index Ki-67 is normal	It is composed of histologically benign chondrocytes with an orderly and regular arrangement. Proliferative index Ki-67 is normal	Large fibrous matrix with scattered curvilinear irregularly shaped trabeculae of immature, inadequately mineralized bone. There is no rimming by osteoblasts. Proliferative index Ki-67 is normal	Histologically there is increased cellularity and binucleation in chondrocytes. The marrow permeation represented by cellular cartilage surrounding mature bone trabeculae and lobules of cartilage separated by fibrous tissue. There is no permeation seen in enchondromas. There is prominent myxoid features which are not seen in enchondromas. Proliferative index Ki-67 is high

Table 4: Differentiation diagnosis of Chondrobalstoma

Features	Chondroblastoma	Clear Cell Chondrosarcoma	ABC	Giant Cell Tumors	Intramedullary Chondrosarcoma	Chondromyxoid Fibroma
Site	Epiphysis	Predilection for epiphyses of long tubular bones	Diaphysis	Metaphysis of epiphysis	Diaphysis	
Age in years	Younger age 10-30	3rd to 4th decades 30 – 40	Younger 10-20	>20 up to 40	Older 30-60	

Clinical Symptoms	Pain	Pain	No Pain	No Pain	Pain	
Radiology	Sharply and lytic lesions. Fine Calcification	Lesions are radiolytic with stippled radiodensities of cartilage	Lytic but demarcated	Soap bubble appearance	Sharply lytic	
Histology	It lacks chondroid differentiation. Nuclear grooves. Chiken wire stroma.	Round cells, with clear cytoplasm admixed with multinucleated Giant cells and chondroid stroma.	Clear cells and cartilaginous differentiation are absent	Clustered giant cells and more in number. No cartilage. No chicken wire matric. No nuclear groves. S100 ve	Multinucleated giant cells and reactive bony trabeculae are absent within the malignant cartilage.	

Table. 5. Showing differential diagnosis of Chondrosarcoma

Features	**Choncrosarcoma (CS)**	**Chondroblastic Osteosarcoma (COS)**	**Fracture Callus (FC)**	**Enchondroma (ECA)**	**Chondroyxoid Fibroma CMF)**
Site	Central: Medulla of diaphysis Peripheral: Cortex of metaphysis Periosteium of metaphysis	Medulla of Metaphysis	Any age	Cortex of metaphysis	Metaphysis
Age	Older age	Younger than CS	Any age	Younger than CS	Younger than CS
Clinical Symptoms	Always Pain	Always Pain	Always Pain	No Pain	No Pain
Radiology	Erosion of cortex with lytic lesion, with destructive and permeation	Irregular cortical destruction in an osteosarcoma (left)	No Erosion of cortex	No Erosion of cortex with lytic Lesion	No Erosion of cortex with lytic Lesion
Histology	Atypical nunclei and a permeative growth pattern around native trabeculae. Multinucleation	Osteoid is always seen with anaplastic chondrocytes	No atypical cells, no permeation	No or atypical cell, no permeation	No atypia and no permeation

Table 6: Differentiation of clear cell chondrosarcoma

Features	**Clear Cell Chondrosarcoma**	**Osteoblastoma**	**Chondroblastoma**	**ABC**	**Intramedullary Chondrosarcoma**	**Metastatic RCC**
Site	Predilection for epiphyses of long tubular bones	Medulla of metaphysis	Epiphysis	Diaphysis	Diaphysis	Kidney
Age in years	3rd to 4th decades	Younger age 10-23	Younger age 10-30	Younger 10-20	Older 30-60	> 45 years
Clinical Symptoms	Pain	Pain	Pain	No Pain	Pain	No pain
Radiology	The lesions are radiolytic with stippled radiodensities of cartilage	Well Circumscribed	Sharply and lytic lesions	Lytic but demarcated	Sharply lytic	Not lytic areas
Histology	Round cells, with clear cytoplasm admixed with multinucleated	Similar pattern but radiological evaluations arequored	It lacks chondroid differentiation	Clear cells and cartilaginous	Multinucleated giant cells and reactive bony trabeculae are	No giant cells and chondroid areas. positive for PAX2+, vimentin

	Giant cells and chondroid stroma	It lacks prominent clear cells and bony trabeculae		differentiation are absent .	absent within the malignant cartilage.	and cytokeratin, typically negative for S-100 protein.Prominent delicate vascular background surrounding clear cells

Table 7: Differentiation of Mesenchymal Chondrosarcoma

Features	Mesenchymal Chondrosarcoma	Dedifferntiated condrosarcoma	Conventional Condrosarcoma	Ewing's Sarcoma	Embryonal Rhabdomyosarcoma	Solitary Fibrous Nodule	Lymphoma
Location	Medulla or cortex of diaphysis	Medulla of diaphysis	Medulla of diaphysis	Medulla of Diaphysis or metaphysis	Not specific	Not site specific	Not specific
Age in years	20-60	Older age but may appear early in multiple exostosis patients	30-60	10-20	Younger than CS	Younger	Old age
Clinical Symptoms	Pain and fractures	Pain	Pain	Pain	No Pain	No Pain	No pain
Radiology	Same as Conventional lesions	Same as Conventional lesions	Same as Mesenchyma Condrosarcoma lesions	Cortical destruction with aggressive periosteal reaction Onion skin appearance	Soft tiss mass	Not helpful	Not helpful
Histology	The two components are uniformly mixed throughout the entire lesions	It shows two very distinct populations quite separate and discreate from each other	Small round blue cells are not seen	Monotonous cells no chondroid differentiationCD 99 +ve	No chondrocytes Desmin, Actin and myosin are positive	No cartilage CD 34 +ve	No cartilage. Markers helpful, LCA is positive in lymphomas and S 100 -

Table 8: Differentiation of De-differntiated Chondrosarcoma

Features	Dedifferntiated condrosarcoma	Chondroblastic Osteosarcoma (COS)	Mesenchymal Chondrosarcoma	Conventional Condrosarcoma	High Grade Sarcoma	Metastatic Sarcomatoid Carcinoma
Sites	Medulla of diaphysis	Medulla of Metaphysis	Medulla or cortex of diaphysis	Medulla of diaphysis	Not site specific	Not specific
Age in years	Older age but may appear early in multiple exostosis patients	Younger than CS	20-60	30-60	Old age	Old age
Clinical Symptoms	Pain	Always Pain	Pain and fractures	Pain	No Pain	No pain
Radiology	Same as Conventional lesions	Erosion and lifting of cortex with osteogenic element	Same as Conventional lesions	Same as Mesenchyma Condrosarcoma lesions	Not helpful	Not helpful
Histology	It shows two very distinct populations quite separate and discreate from each other	Osteoid is always seen with anaplastic chondrocytes	The two components are uniformly mixed throughout the entire lesions	Small round blue cells are not seen	No cartilage	No cartilage. Markers helpful, CK is helpful

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Name of Author	Contribution to the paper	Author's Signatures
Prof. Dr. Mulazim Hussain Bukhari	Main concept of manuscript	
Dr. Samina Qamar	Helped in preparations of manuscript	
Dr. Farwa Batool	Photography	
Dr. Kalyani Bambal	Read the article and made required changes	
Dr. Mandeep Bedi	Englsih language corrections	
Dr. Manu Noaty	Co-Author