CHAPTER 10

Cartilage Tumours

Tumours which produce a chondroid matrix are logically grouped together although questions linger about their true histogenesis. It is also debatable as to whether some of these entities represent true neoplasms. They also range from completely benign lesions to highly lethal neoplasms. However, they have the common characteristic of producing chondroid matrix at least in foci.

Many benign cartilage tumours are asymptomatic, incidental findings on roentgenograms, whereas malignant tumours almost always produce symptoms. Roentgenographic findings are of critical importance in diagnosing cartilage tumours. It is reasonable to divide cartilage tumours into benign and malignant counterparts. However, benign tumours rarely undergo malignant transformation.

This chapter also contains a section on synovial chondromatosis, a lesion that does not originate from bone. It is included here because of its cartilaginous nature. It is a primary condition and the growth characteristics and locally destructive behaviour suggest a neoplasm. Malignancies affecting the synovial membranes are exceptionally rare.
Osteochondroma

Definition
Osteochondroma is a cartilage capped bony projection arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone.

ICD-O codes
Osteochondroma 9210/0
Osteochondromatosis NOS 9210/1

Synonyms
Osteochondroma: Osteochondromatous exostosis, solitary osteochondroma.

Multiple osteochondromas: Hereditary osteochondromatosis, hereditary deforming osteochondromatosis, hereditary chondrodysplasia, diaphyseal aclasis, metaphyseal aclasis, hereditary multiple exostoses.

Epidemiology
Solitary osteochondroma
Osteochondroma may be the most common bone tumour [988,1875,2155]. The reported incidence, 35% of benign and 8% of all bone tumours, probably is an underestimate as the majority are asymptomatic and not clinically apparent [2155]. Most reported cases have been in the first 3 decades with no known sex predilection.

Multiple osteochondromas
Approximately 15% of patients (of all osteochondromas) have multiple lesions [2155], with an incidence up to 1:50,000 in some series [1887]. The age of patients with multiple lesions is similar to those with solitary osteochondromas and there is also no sex predilection. Inheritance is autosomal dominant.

Sites of involvement
Osteochondromas generally arise in bones preformed by cartilage. The most common site of involvement is the metaphyseal region of distal femur, upper humerus, upper tibia and fibula [2155]. Involvement of flat bones is less common with the ilium and scapula accounting for most of the cases.

Clinical features
Signs and symptoms
Many, if not most lesions, are asymptomatic and found incidentally. In symptomatic cases, the symptoms are often related to the size and location of the lesion. The most common presentation is that of a hard mass of long-standing duration. Some cases present with symptoms related to secondary complications such as mechanical obstruction, nerve impingement, bursa forming over the osteochondroma, pseudoaneurysm of an overlying vessel, infarction of the osteochondroma or fracture of the stalk of the lesion [131,188,470,988,1072,1468,1681,1875,2119,2152,2155]. Increasing pain and/or growing mass may be a manifestation of malignant transformation of osteochondromas. It is estimated to be less than 1% in patients with solitary and approximately 1-3% in patients with multiple osteochondromas. Higher incidences, some up to 20% of malignant transformation in multiple osteochondromas have been reported because of case selection and variable criteria used [211,1131,1875,2155,2206].

Imaging
Solitary osteochondromas may be pedunculated or sessile lesions. The characteristic feature is a projection of the cortex in continuity with the underlying bone. Irregular calcification is often seen. Excessive cartilage type flocculent calcification should raise the suspicion of malignant transformation. CT scan or MRI images typically show continuity of the marrow space into the lesion. These modalities may also predict the thickness of the cartilage cap [464,775,2285]. A thick cap raises the suspicion of malignant transformation. Osteochondromas grow away from the site of active growth, most likely due to forces from adjacent tendons and muscles.

Multiple osteochondromas are similar to the solitary ones but are generally associated with remodeling defects of bone. Many are flat and cauliflower shaped.

Aetiology
The aetiology is not known. Based on the resemblance of the cartilage cap to the growth plate, several hypotheses have been offered. These include the possibility of breakage, rotation and aberrant growth of the physeal plate or herniation of the plate in the metaphysis [415,988,1457,1464,1718].
Osteochondroma

Macroscopy
An osteochondroma may be sessile or pedunculated. The cortex and medullary cavity extend into the lesion. The cartilage cap is usually thin (and decreases in thickness with age). A thick and irregular cap (greater than 2 cm) may be indicative of malignant transformation.

Histopathology
The lesion has three layers – perichondrium, cartilage and bone. The outer layer is a fibrous perichondrium that is continuous with the periosteum of the underlying bone. Below this is a cartilage cap that is usually less than 2 cm thick (and decreases with age). Within the cartilage cap the superficial chondrocytes are clustered, whereas the ones close to the transition to bone resemble a growth plate. They are organised into chords and undergo endochondral ossification similar to the zone of provisional mineralization. Loss of the architecture of cartilage, wide fibrous bands, myxoid change, increased chondrocyte cellularity, mitotic activity, significant chondrocyte atypia and necrosis are all features that may indicate secondary malignant transformation. Fractures within a stalk may elicit a focal fibroblastic response. Surface chondrosarcomas differ from osteochondromas by the absence of a stalk and the presence of lobular masses of cartilage that permeate and infiltrate the soft-tissues [1366]. Parosteal osteosarcoma may have a zone of typical cartilage simulating a “cap”. They are, however, radiographically and microscopically different from an osteochondroma. The characteristic fibroblastic proliferation and cytological atypia is not observed in an osteochondroma. Bunion and osteophytes are bony growths (often without a cartilage cap) that have no marrow cavity or sometimes a poorly developed one that is not continuous with the medullary canal of the underlying bone. Exostoses that arise in the cranio-facial and jaw bones are sometimes called tori (sing. torus). These are usually osseous proliferations that are reactive to an irritant. A similar traumatic aetiology is most likely responsible for the subungual exostosis and the so-called aural meatal exostosis. Bizarre parosteal osteochondromatous proliferation (Nora’s lesion) is a disorganized mass of bone, cartilage and fibrous tissue. Trevor disease (Dysplasia Epiphysealis Hemimelica) is a non-hereditary skeletal dysplasia that resembles an epiphyseal osteochondroma.

Genetics
It was long debated whether osteochondroma was a developmental disorder or a true neoplasm. Cytogenetic aberrations involving 8q22-24.1, where the EXT1 gene is located, have been found in ten out of 30 sporadic and in 1 out of 13 hereditary osteochondromas [264, 1430]. Moreover, DNA flow cytometry of the cartilaginous cap demonstrated aneuploidy (DNA index range 0.88-1.17) in four of 10 osteochondromas [238]. LOH detected by microsatellite analysis using DNA isolated from the cartilaginous cap was found almost exclusively at the EXT1 locus in 3 of 8 sporadic and 2 of six hereditary osteochondromas [238]. Fluorescence in situ hybridization revealed loss of the 8q24.1 locus in 27 of 34 (79%) osteochondromas [645].

Fig. 10.03 Outer aspect and cut section of osteochondroma of the upper fibula demonstrating the continuity of the cortex and marrow cavity of the osteochondroma with that of the underlying bone.

Fig. 10.04 Osteochondroma cut surface and outer surface showing the bony stalk and the overlying cartilage cap.

Fig. 10.05 A Osteochondroma, showing the outer perichondrium, cartilage cap and underlying stalk. Variable amount of endochondral ossification occurs at the bone/cartilage interface. B Endochondral ossification is often seen at the base of the osteochondroma. This is a normal feature and should not be interpreted as a malignancy invading into the stalk.

Osteochondroma 235
These findings suggest that both sporadic and hereditary osteochondromas are true neoplasms. The EXT genes, involved in hereditary multiple osteochondromas (HMO), are hypothesised to be tumour suppressor genes. Most of the mutations found in HMO patients are predicted to result in a truncated or non-functional protein. Germline EXT1 mutations combined with loss of the remaining wild type allele was demonstrated in three osteochondromas of two HMO patients (238). One sporadic osteochondroma was described to harbour a deletion of one EXT1 gene combined with an inactivating mutation in the other EXT1 gene (168). Although second mutations have been demonstrated in the minority of cases so far, these findings strongly suggest that inactivation of both copies of an EXT gene in a cartilaginous cell of the growth plate is required for osteochondroma formation in both hereditary and sporadic cases. Indeed, diminished levels of the EXT1 and EXT2 proteins (168) and of their putative downstream effectors (Ihh/PTHrP and FGF signalling pathway, see chapter 21) (241) were demonstrated in both sporadic and hereditary osteochondroma chondrocytes (168). Moreover, EXT mutations were described to induce cytoskeletal abnormalities (altered actin distribution) in osteochondroma chondrocytes (168, 169,1237).

**Prognostic factors**

Excision of the osteochondroma is usually curative. Recurrence is seen with incomplete removal, however, multiple recurrences or recurrence in a well excised lesion should raise the suspicion of malignancy.

**Fig. 10.06** Chromosomal band 8q24 rearrangement in sporadic osteochondroma (on the left). LOH at 8q24 in a patient with multiple exostoses is demonstrated by microsatellite analysis (D8S198). SSCP mutation analysis reveals aberrant bands (indicated by arrows) in both normal (N) and osteochondroma (T) DNA. Sequence analysis reveals a constitutional 15 bp deletion. The PCR fragment containing the mutation is run on a denaturing gel, illustrating loss of the wild-type allele (arrow).
Chondromas: enchondroma, periosteal chondroma, and enchondromatosis

This group of generally benign tumours of hyaline cartilage share many histological features. However, they differ with respect to location and clinical features. Enchondroma and periosteal chondroma are sporadic while enchondromatosis usually manifests as a congenital tumour syndrome (see Chapter 21, page 356).

**Enchondroma**

**Definition**

Enchondroma is a benign hyaline cartilage neoplasm of medullary bone. Most tumours are solitary, however, they occasionally involve more than one bone or site in a single bone.

**ICD-O codes**

Chondroma 9220/0  
Enchondroma 9220/0

**Synonyms**

Solitary enchondroma, central chondroma.

**Epidemiology**

Enchondromas are relatively common, accounting for 10-25% of all benign bone tumours (1674,2155). The true incidence is actually much higher since many tumours are detected incidentally and never biopsied. The age distribution is wide, ranging from 5-80 years. However, the majority of patients present within the second through fourth decades of life. The sexes are equally affected.

**Sites of involvement**

Half of all enchondromas in surgical pathology series occur in the hands and feet (1469,1874,2155). It is the most common bone tumour of the hand, where it most often affects the small tubular bones. The long tubular bones, especially proximal humerus and proximal and distal femur, are next in frequency.

Enchondromas are uncommon in the flat bones such as pelvis, ribs, scapula, sternum or vertebrae, and are exceedingly rare in the craniofacial bones.

**Clinical features / Imaging**

Enchondromas in the small bones of the hands and feet typically present as palpable swellings, with or without pain. Because they often expand these small bones and attenuate the cortex, they frequently present with pathological fractures. Long bone tumours are more often asymptomatic, and many are detected incidentally in radiographs or bone scans taken for other reasons. Tumours other than those located in small bones are usually painless unless aggravated by stress. Enchondromas are usually "hot" on bone scan.

Radiographically, enchondromas form well marginated tumours that vary from radiolucent to heavily mineralized. When present, the mineralization pattern is high-
ly characteristic, consisting of punctate, flocculent, or ring and arc patterns. Long bone tumours are usually centrally located within the metaphysis. Diaphyseal long bone tumours are less common, and epiphysyeal tumours are rare. Enchondromas in the small tubular bones can be centrally or eccentrically located, and larger tumours can completely replace the medullary cavity (2081). In small and medium-sized tubular bones and in thin flat bones, enchondromas are frequently expansile. By contrast, in the large long bones, such as the femur, tibia or humerus, only minimal degrees of bony expansion and endosteal erosion (or "scalloping") are acceptable. More extensive endosteal erosion is considered suspicious for low grade chondrosarcoma. Cortical destruction and soft tissue invasion should never be seen in enchondromas.

Macroscopy
Most enchondromas measure less than 3 cm and tumours larger that 5 cm are uncommon. Because most tumours are treated by curettage, the specimen is usually received in fragments. The tissue is white-grey and opalescent. Gritty yellow or red foci represent areas of calcification or ossification. In the intact state, enchondromas are well marginated. They frequently have a multinodular architecture, comprised by nodules of cartilage separated by bone marrow. This multinodular pattern appears to be more common in long bones compared to small tubular bones, where enchondromas usually have a confluent growth pattern.

Histopathology
In general, chondromas are hypocellular, avascular tumours with abundant hyaline cartilage matrix. They typically stain pale blue with haematoxylin and eosin due to high content of matrix proteoglycans. The chondrocytes are situated within sharply-edged lacunar spaces, and have finely granular eosinophilic cytoplasm that is often vacuolated. The nuclei are typically small and round with condensed chromatin. Slightly larger nuclei with open chromatin and small nucleoli are not uncommon. The cells can be evenly distributed or arranged in small clusters. More than one cell per lacuna, as well as occasional binucleated cells, can be present. Mitotic activity is very low, and usually not detectable. Focally, in some tumours, the matrix can be myxoid. Here, the chondrocytes, which are no longer confined to lacunae, assume bipolar or stellate shapes. Myxoid matrix rarely accounts for more than a minor component of a tumour. The architecture of enchondroma varies from confluent to multinodular. Delicate fibrous septa or thin mantles of lamellar bone surround the nodules. Normal marrow elements are often present between nodules. Although endosteal erosion is present in some cases, enchondromas do not invade into the Haversian system. The degree of mineralization is variable. Both basophilic stippled calcification and enchondral ossification account for it. Areas of ischaemic necrosis are common, especially in heavily calcified tumours. Here, the chondrocytes are reduced to eosinophilic bodies.

Enchondromas in the small bones of the hands and feet can be more cellular and cytologically atypical than long bone tumours. Without proper radiological correlation, such lesions can be mistaken for low grade chondrosarcomas.
Enchondromatosis

Definition
Ollier disease is a developmental disorder caused by failure of normal enchondral ossification. There is failure of normal enchondral ossification. Furthermore, there is production of cartilaginous masses (enchondromas) in the metaphysis and adjacent regions of the shafts and flat bone, with varying degrees of bone deformity. There is predominant unilateral involvement. The multiple enchondromas appear in childhood and there is a wide spread skeletal involvement.

Maffucci syndrome combines the features of Ollier disease associated with angiomatosis of the soft tissue (rarely viscera).

ICD-O code 9220/1

Synonyms
Multiple chondromatosis, multiple enchondromatosis, chondrodysplasia, Ollier disease, Maffucci syndrome.

Epidemiology
Enchondromatosis is rare. On average, patients are younger than those with solitary tumours, the majority presenting during the first two decades of life [2155]. It has been estimated that chondrosarcomas develop by age 40 in approximately 25% of patients with Ollier disease. In Maffucci syndrome the risk of secondary malignancy is even higher. Age at presentation is inversely proportional to severity of disease. Severe cases present in early childhood. The sexes are equally affected.

Sites of involvement
The localization and extent of skeletal involvement in enchondromatosis varies greatly among individuals, ranging from cases limited to multifocal involvement of a single bone to cases with widespread lesions and crippling deformation. The hand is the most common site. Other common sites are foot, femur, humerus, and forearm bones. In severe cases, the

Prognostic factors
Periosteal chondromas have been treated with intralesional, marginal, and en bloc excisions, and the recurrence rate is low regardless of type of surgery [144,1248].

Enchondromatosis

Definition
Periosteal chondroma is a benign hyaline cartilage neoplasm of bone surface that arises from the periosteum.

ICD-O code 9221/0

Synonyms
Juxtacortical chondroma, parosteal chondroma.

Epidemiology
Periosteal chondromas are much less common, accounting for less than 2% of chondromas [270,1874,2155]. They occur both in children and adults with equal sex distribution [144,1248,1256].

Sites of involvement
Periosteal chondromas occur most commonly in the long bones. Proximal humerus is a characteristic location. The small tubular bones are also common sites [144,270,1248,1256,2155].

Clinical features / Imaging
Periosteal chondromas present as palpable, often painful, masses [144,1248]. Radiographically, they appear as radiolucent or mineralized bone surface tumours that form sharply margined erosions (or "saucerization") of the cortex. Typically, the underlying cortex is thickened, and the tumour is bordered by solid periosteal buttressing.

Macroscopy
Periosteal chondromas form well-margined bone surface tumours. The cortex underlying the tumour is usually indented and thickened. Solid periosteal buttressing encloses the tumour on its sides. Tumours are usually less than 6 cm in greatest dimension [144,1248,2155].

Histopathology
Periosteal chondromas have a sharp margin with the underlying thickened cortex. They do not penetrate into cancellous bone. Although the degree of cellularity and the cytological features are similar to other chondromas, occasionally periosteal chondromas can be more cellular and show greater nuclear pleomorphism and more binucleation.

Genetics
One case of periosteal chondroma exhibited structural changes of the same band on both chromosome 12 homologues [1323].

Chondromas

Periosteal chondroma

Definition
A diploid pattern with low cell proliferative activity is with rare exception typical of chondromas, as assessed by DNA flow cytometric / cytofluorometric studies and comparative genomic hybridization [36,1190]. Diploid or near-diploid complements with simple structural abnormalities, particularly involving chromosomes 6 and 12, have been detected by conventional cytogenetic analysis [265,856,1870,2106].

Prognostic factors
Enchondromas are successfully treated by intralesional curettage in most cases, and local recurrences are uncommon. Occasionally, an enchondroma will recur many years later, and rarely recur as a low grade chondrosarcoma [411].

Sites of involvement
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Clinical features / Imaging
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Periosteal chondromas have a sharp margin with the underlying thickened cortex. They do not penetrate into cancellous bone. Although the degree of cellularity and the cytological features are similar to other chondromas, occasionally periosteal chondromas can be more cellular and show greater nuclear pleomorphism and more binucleation.

Genetics
One case of periosteal chondroma exhibited structural changes of the same band on both chromosome 12 homologues [1323].
flat bones are also affected. Frequently, the disease is limited to a single extremity or to one side of the body. Many cases, however, have bilateral involvement. In bilateral disease, one side of the body is usually more affected than the other.

**Clinical features / Imaging**
The clinical presentation of enchondromatosis depends on the extent of disease. For example, it can range from a few small lesions in the hand or foot to multiple, widely distributed, sizeable lesions and marked skeletal deformation. Pathological fractures, limb length discrepancies, and bowing deformities are common in severe cases. Change in symptoms and extension beyond the bony cortex herald the development of chondrosarcomas in both Ollier disease and Maffucci syndrome. Malignant transformation occurs in approximately 25-30% of cases (269,1274,1901).

Radiographically, the lesions of enchondromatosis can be radiolucent or mineralized, and can be intramedullary or periosteal in location. Bony expansion is common. Any part of a tubular bone can be affected, including the articular cartilage and the epiphysis (1469). However, the metaphysis is most common. Radiolucent columns that extend from the growth plate into the metaphysis are highly characteristic. In severe cases, the flat bones, particularly the iliac crest, can be affected. In Maffucci syndrome, soft tissue calcifications due to pleboliths within the haemagiomas can be visualised in radiographs.

**Macroscopy**
The gross extent of disease in enchondromatosis is variable. In severe cases, marked expansion and cortical attenuation can be seen even in large bones.

**Histopathology**
The microscopic appearance of lesions in enchondromatosis resembles that described above. However, they can be more cellular and cytologically atypical than typical solitary enchondromas of the long bones.

**Genetics**
A description of molecular alterations identified in enchondromatosis is included within the section on congenital tumour syndromes (see chapter 21).
Chondroblastoma

Definition
Chondroblastoma is a benign, cartilage-producing neoplasm usually arising in the epiphyses of skeletally immature patients.

ICD-O code 9230/0

Synonyms
Calcifying giant cell tumour, epiphyseal chondromatous giant cell tumour.

Epidemiology
Chondroblastoma accounts for less than 1% of all bone tumours. Most patients are between 10 and 25 years of age at diagnosis and there is a male predominance. Patients with skull and temporal bone involvement tend to present at an older age (40-50 years) [2147].

Sites of involvement
Greater than 75% involve the long bones; the most common anatomic sites are the epiphyseal and epimetaphyseal regions of the distal and proximal femur, proximal tibia, and proximal humerus [215,2147]. Equivalent sites within flat bones such as the acetabulum and ilium are not uncommon. Other unusual but classic sites of involvement include the talus, calcaneus, and patella. Within the craniofacial region, the temporal bone is most frequently affected. Chondroblastomas almost invariably involve a single bone but multifocal lesions arising in 2 separate bones have been reported [1795].

Clinical features
The vast majority of patients complain of localized pain, often mild, but sometimes of many years duration. Soft tissue swelling, joint stiffness and limitation, and limp are reported less commonly. A minority of patients may develop joint effusion, especially around the knee. Temporal bone involvement may be associated with hearing loss, tinnitus, and/or vertigo [186,2147]. Radiologically, chondroblastomas are typically lytic, centrally or eccentrically placed, relatively small lesions (3 to 6 cm), occupying less than one half of the epiphysis and are sharply demarcated, with or without a thin sclerotic border. The presence of sclerotic rim, along with the younger age of the patient, helps to differentiate chondroblastoma from giant cell tumour of bone, which generally lacks a sclerotic border and occurs in patients older than 20 years. There generally is no expansion of the bone or periosteal reaction. However, larger lesions involving flat bones or small tubular bones may exhibit a periosteal reaction. Concomitant involvement of the metaphysis is commonly observed [215, 2147]. Although often helpful, matrix calcifications are only visible in about 1/3 of patients [2147].

Macroscopy
Curetted fragments are tan with areas of white colourations. The lesions may be partly cystic.

Histopathology
Histologically, the characteristic cell is a remarkably uniform, round to polygonal cell with well defined cytoplasmic borders, clear to slightly eosinophilic cytoplasm and a round to ovoid nucleus (chondroblasts). The nucleus often displays clefts or longitudinal grooves and contains one or more small to inconspicuous nucleoli. Chondroblasts are packed in pseudo-lobulated sheets often showing a pavement-like pattern. Randomly distributed osteoclast-type giant cells are almost always present. Variably-sized nodules of light-staining, amorphous, bluish to eosinophilic material (chondroid) accompany the chondroblasts [993,2147]. Mature, basophilic-staining, hyaline cartilage is relatively uncommon. A fine network of pericellular calcification defines the so called "chicken wire calcification" seen in many of cases. Individual chondroblasts may exhibit cytological atypia most often represented by large, hyperchromatic nuclei; nevertheless, such features do not adversely affect prognosis [1878, 2015]. Mitoses are observed but atypical forms are never seen. Aneurysmal bone cyst-like changes may be found in up to 1/3 of cases [2147]. Ultrastructural studies reveal deep indentations of the nuclear membrane and features, such as abundant rough endoplasmic reticulum and long cytoplasmic processes, typical of fetal chondroblasts [2025].

Immunophenotype
The chondroblasts generally express S100 protein and vimentin [1493]. The expression of other antigens has been reported with cytokeratin being among the most commonly observed [569,918].

Fig. 10.17 Plain X-ray showing a multiloculated, circumscribed lytic defect with a sclerotic rim involving the greater trochanter. Involvement of the apophysis, such as the greater trochanter, is considered analogous to epiphyseal involvement of a long bone and not uncommon in chondroblastoma.

Fig. 10.18 Plain film radiograph illustrating a multicystic, well-circumscribed lesion involving the patella.
Genetics
Flow cytometric studies have revealed that most chondroblastomas are diploid with low proliferative fractions, however, near-diploid aneuploid populations have been detected in a subset of cases (414, 576,1798,2092). Clonal abnormalities have been described in six benign and one ‘malignant’ chondroblastoma (253, 1333,2068,2184). The observation of recurrent structural anomalies involving chromosomes 5 and 8 suggests that there may be preferential involvement of these chromosomes (2068). Rearrangements of chromosome band 8q21 were detected exclusively in aggressive chondroblastomas (253,2068). Multiple DNA aneuploid populations, and immunohistochemical evidence of TP53 mutation and extensive proliferative activity, were detected in a malignant chondroblastoma (1624).

Prognostic factors
Between 80-90% of chondroblastomas are successfully treated by simple curetage with bone grafting. Local recurrence rates range between 14-18% and occur usually within two years (215,1878,2015,2147). Likely the result of anatomic localization and difficulties of surgical extirpation, temporal bone lesions may recur in up to 50% of cases (186). Huvos et al. (993) documented a higher recurrence rate among chondroblastomas with a concomitant aneurysmal bone cyst component; however, others have not observed this association (2015,2147). The rare development of pulmonary metastases in histologically benign chondroblastoma is well documented (833,1788,2282). However, these metastases are clinically non-progressive and can often be satisfactorily treated by surgical resection and/or simple observation (1788). Unfortunately, there are no reliable histological parameters capable of predicting more aggressive behaviour. The existence of a true “malignant” variant of chondroblastoma is controversial and many investigators propose that most such tumours represent postradiation sarcomas or simply misdiagnoses (2147).

Fig. 10.19  A Chondroblastoma with sheets of mostly uniform-appearing chondroblasts and numerous randomly-distributed osteoclast type giant cells. B Cytologically, the individual chondroblasts are round to polygonal with sharply defined cytoplasmic borders, round to ovoid nuclei, and occasional small nucleoli. Nuclear grooves and indentations are frequently seen.

Fig. 10.20  G-banded karyotype of a chondroblastoma with the karyotype: 47,XY,+5,t(5;5)(p10;p10).
Chondromyxoid fibroma

**Definition**
Chondromyxoid fibroma is a benign tumour characterized by lobules of spindle-shaped or stellate cells with abundant myxoid or chondroid intercellular material.

**ICD-O code**
9241/0

**Epidemiology**
Chondromyxoid fibroma is one of the least common tumours of bone, comprising less than 1% of bone tumours and less than 2% of benign bone tumours (2155). It comprises 2.3% and 2.4% of cartilaginous tumours in children and adults, respectively (1625), and occurs in males more often than females (781, 2300). This tumour presents most frequently in the second and third decades of life (644, 2300).

**Sites of involvement**
Chondromyxoid fibroma occurs in almost any osseous site. It is most frequent in the long bones, most often the proximal tibia (the most common site) and the distal femur. Approximately 25% of cases occur in the flat bones, mainly the ilium. The bones of the feet are also involved, especially the metatarsals. Other sites of involvement include the ribs, vertebrae, skull and facial bones, and tubular bones of the hand.

**Clinical features / Imaging**
Pain is the most common symptom, usually mild and sometimes present for several years (644, 1748). Swelling is noted infrequently, more often in tumours of the bones of the hands and feet. Lesions of the rib or ilium may be discovered as incidental radiological findings (2345). Chondromyxoid fibroma in a long bone is typically metaphyseal, eccentric, sharply margined oval zone of rarefaction with attenuation and expansion of one cortex. The longitudinal axis of the lesion corresponds to that of the involved bone, and the size ranges from 1 to 10 cm with an average of 3 cm (988). In the small bones, fusiform expansion of the soft tissues, but the adjacent periostea is typically intact (1748). Rarely, contiguous bones are affected (282) or the tumour is juxtacortical (1329). Soft tissue extension is best demonstrated with magnetic resonance image studies (1301).

**Macroscopy**
Gross features of chondromyxoid fibroma include an expansile bluish, grey, or white tumour, without necrosis, cystic change, or liquefaction. Typical hyaline cartilage is not present. In flat bones, the tumour is multilobulated and well demarcated from the surrounding bone. The scalloped margins correspond to the trabeculations or septations noted with radiological studies. In rare soft tissue implants, the gross features are identical to the intraosseous tumours.
Histopathology

Chondromyxoid fibroma shows a variety of histological features that are nonetheless quite distinct. The tumour is typically sharply demarcated from the surrounding bone. Rarely there is entrapment of surrounding bone trabeculae by tumour, or lobules of tumour may be separate from the main lesion. The classic features include a lobular pattern with stellate or spindle-shaped cells in a myxoid background [1876]. Occasionally, a more vague lobular pattern is present. Lobules demonstrate hypocellular centres and hypercellular peripheries. Individual cells within lobules have oval to spindled nuclei and indistinct to densely eosinophilic cytoplasm. Cytoplasmic extensions, often bipolar or multipolar, are frequent. Enlarged, hyperchromatic and pleomorphic nuclei are noted in 20-30% of cases. These features may suggest malignancy, but they are usually focal and associated with voluminous cytoplasm as well, sometimes with smudgy or degenerative features, similar to ancient schwannoma [109,2155]. Microscopic cystic or liquefactive change is uncommon and usually focal when present. Hyaline cartilage is present in 19% of cases [2300]. Calcification when present is usually coarse and occurs more frequently in tumours from patients over 40 years of age and in flat bone tumours [2315]. Mitoses are uncommon [644,2300]; atypical mitoses have not been noted. Osteoclast like giant cells are often present at the lobular peripheries. There may be haemosiderin deposition in these regions as well, and inflammatory cells, usually lymphocytes. Aneurysmal bone cyst areas are noted in approximately 10% of long and flat bone lesions [2300].

Fig. 10.24 Chondromyxoid fibroma. Subtle microlobular pattern. Note the myxoid regions among which cells are situated in a sieve-like pattern. The spindle cells show eosinophilic cytoplasm.

Fig. 10.25 Chondromyxoid fibroma. Cellular regions with giant cells are present peripheral to the lobules.

Fig. 10.26 Chondromyxoid fibroma. A This lesion shows more nuclear atypia than the typical case, with densely cellular areas at the periphery of the lobules. B Focal coarse calcification. Note that these elements surround hyaline cartilage. C Moderate nuclear enlargement is present in these cells, and the eosinophilic cytoplasmic processes are prominent.

244 Cartilage tumours
**Immunophenotype**
S100 protein has been reported in chondromyxoid fibroma (213,2345). Immuno-reactivity for smooth muscle actin, muscle actin and CD34 has been noted in regions peripheral to the lobules, but not elsewhere in these tumours (1558).

**Ultrastucture**
Ultrastructurally, the stellate cells have irregular cell processes, scalloped cell membranes, cytoplasmic fibrils and glycogen, features of both chondroblastic and fibroblastic differentiation (1930, 2162). Cells with classic features of chondrocytes, those with myofibroblastic features, and intermediate forms have been described in chondromyxoid fibroma (1558).

**Genetics**
Cytogenetic studies are limited; however, clonal abnormalities of chromosome 6 appear to be non-random (828,870, 1836,1870,2082). In particular, rearrangements of the long arm of chromosome 6 at bands q13 and q25 are recurrent. Expression analysis of matrix components, particularly of collagens, can serve as marker systems for cell differentiation patterns in mesenchymal neoplasms (22,2174). An examination of the matrix composition and gene expression pattern in chondromyxoid fibroma has shown pronounced expression of hydrated proteoglycans (major constituent of the myxoid matrix) and focal expression of collagen type II (a marker of chondrocytic cell differentiation) as well as collagen types I, III, and VI (1980). Importantly, this unique biochemical composition and gene expression pattern in chondromyxoid fibroma has not been detected in other mesenchymal neoplasms, including chondroblastoma, osteochondroma, enchondroma and chondrosarcoma (1980).

**Prognostic factors**
The prognosis for this tumour is excellent, even with recurrence, including soft tissues which occurs in approximately 15% of cases treated with curettage and bone grafting.
Synovial chondromatosis

Definition
Synovial chondromatosis is a benign nodular cartilaginous proliferation arising in the synovium of joints, bursae or tendon sheaths.

Synonyms
Synovial osteochondromatosis, primary synovial chondromatosis, synovial chondrometaplasia.

Epidemiology
Synovial chondromatosis is an uncommon condition, usually occurring in adults, twice as commonly in males (643).

Sites of involvement
Usually only one joint is involved, most often the knee, less commonly the hip, elbow, wrist, ankle, shoulder or temporomandibular joint.

Clinical features / Imaging
Symptoms, where present, are non-specific including recurrent pain, swelling, stiffness or joint locking. Rarely the lesion presents as a painless soft tissue mass adjacent to a joint. Radiography may be negative except for effusion, unless there is calcification or ossification of the nodules. Magnetic resonance imaging demonstrates the cartilaginous or ossific nodules within the joint.

Macroscopy
Lesional tissue consists of multiple glistening blue/white ovoid bodies or nodules within synovial tissue, from less than a millimeter to several centimeters.

Histopathology
The nodules are of variably cellular hyaline cartilage covered by a fine fibrous layer, and sometimes by synovial lining cells. The chondrocytes are clustered, may have plump nuclei with moderate nuclear pleomorphism and binucleate cells are common. Mitoses are uncommon. There may be ossification, sometimes with fatty marrow in intertrabecular spaces.

Genetics
Cytogenetic analyses have disclosed clonal chromosome aberrations in six tumours, all affecting the knee (1426, 1906, 2082). All cases had near-diploid or pseudo-diploid karyotypes, with three showing only simple numerical changes (-X, -Y, and +5, respectively). Among the three cases with structural aberrations, all displayed rearrangement of the bands 1p13-p22.

Prognostic factors
Synovial chondromatosis is self-limiting but may recur locally after excision or incomplete synovectomy, especially in the early phase of the disease. Damage to the joint surfaces may result in secondary degenerative joint disease. Bone erosion with cranial extension from a temporomandibular joint lesion has been reported (1069). Chondrosarcoma may uncommonly develop from synovial chondromatosis (454). A long clinical history of joint symptoms leading to intractable pain may indicate malignant transformation.
Chondrosarcoma

Definition
Chondrosarcoma (CHS) is a malignant tumour with pure hyaline cartilage differentiation. Myxoid changes, calcification or ossification may be present. The term CHS is used to describe a heterogeneous group of lesions with diverse morphologic features and clinical behaviour. This section will deal with primary, secondary and periosteal CHS.

ICD-O codes
Chondrosarcoma 9220/3
Periosteal chondrosarcoma 9221/3

Primary Chondrosarcoma

Primary CHS (or conventional CHS) arises centrally in a previously normal bone and the previous definition is pertinent to all primary CHS.

Epidemiology
Primary CHS accounts for approximately 20% of malignant bone tumours in one large series (2155). It is the third most common primary malignancy of bone after myeloma and osteosarcoma. In the total group of CHS more than 90% are primary (conventional) type.

Age and sex
Primary CHS is a tumour of adulthood and old age. The majority of patients are older than 50 years. The peak incidence is in the fifth to seventh decades of life. There is a slight preference for male patients.

Sites of involvement
The most common skeletal sites are the bones of the pelvis (the ilium is the most frequently involved bone) followed by the proximal femur, proximal humerus, distal femur and ribs. Approximately three-fourths of the tumours occur in the trunk and upper ends of the femur and humerus. The small bones of the hands and feet are rarely involved by primary CHS (1% of all CHS). Chondrosarcoma is extremely rare in the spine and craniofacial bones.

Clinical features / Imaging
Local swelling and pain, alone or in combination, are significant presenting symptoms. The symptoms are usually of long duration (several months or years). Radiographic findings are very important in the diagnosis of cartilaginous tumours. In the long bones primary CHS occur in the metaphysis or diaphysis were they produce fusiform expansion with cortical thickening of the bone. They present as an area of radiolucency with variably distributed punctate or ring-like opacities (mineralization). Cortical erosion or destruction is usually present. The cortex is often thickened but periosteal reaction is scant or absent. MRI can be helpful in delineating the extent of the tumour and establishing the presence of soft tissue extension. CT scans aid in demonstrating matrix calcification.

Macroscopy
The cut surfaces of CHS tend to have a translucent, blue-grey or white colour corresponding to the presence of hyaline cartilage. A lobular growth pattern is a consistent finding. There may be zones containing myxoid or mucoid material and cystic areas. Yellow-white, chalky areas of calcium deposit are commonly present (mineralization). Erosion and destruction of the cortex with extension into soft tissue may be present especially in CHS of the flat bones (pelvis, scapula and sternum).

Histopathology
At low magnification CHS shows abundant blue-grey cartilage matrix production. Irregularly shaped lobules of cartilage varying in size and shape are present. These lobules may be separated by fibrous bands or permeate bony trabeculae.
Chondrosarcomas are hypercellular when compared to an enchondroma. It may vary from field to field, however, the overall picture should be one of increased cellularity. The chondrocytes are atypical varying in size and shape and contain enlarged, hyperchromatic nuclei. The extent of atypia is usually mild to moderate. Binucleation is frequently seen. Permeation of cortical and/or medullary bone is an important characteristic of CHS that can be used to separate it from enchondroma. In some enchondromas, nodules of cartilage may be found in the marrow cavity separate from the main tumour mass. This differs from true permeation of host bone where the tumour fills up the marrow cavity entrapping pre-existing bony trabeculae or invades through cortical bone into soft tissue. Myxoid changes or chondroid matrix liquefaction is a common feature of chondrosarcomas. Necrosis and mitoses can be seen in chondrosarcoma, particularly in high grade lesions.

It is important to stress that the histological guidelines used for a diagnosis of CHS in a small bone of the hand and foot are different. Increased cellularity, binucleated cells, hyperchromasia and myxoid change may all be present in enchondroma in this location. The most significant histological feature of CHS involving the small bones is permeation through the cortex into soft tissue and a permeative pattern in the cancellous bone.

Grading is important in CHS. Several studies have confirmed its usefulness in predicting histological behaviour and prognosis: there are several grading systems. Chondrosarcomas are graded on a scale of 1-3. The grading is based primarily on nuclear size, nuclear staining (hyperchromasia) and cellularity.

Grade 1: Tumours are moderately cellular and contain hyperchromatic plump nuclei of uniform size. Occasionally binucleated cells are present. The cytology is very similar to enchondroma.

Grade 2: Tumours are more cellular and contain a greater degree of nuclear atypia, hyperchromasia and nuclear size. Grade 3 lesions are more cellular and pleomorphic and atypical than grade 2. Mitoses are easily detected.

The vast majority of primary CHS are grade 1 or 2. Rarely grade 3 CHS are reported. Bjornsson et al. [208] reviewing 338 patients with CHS of pelvis, shoulder and tubular bones found that 61% were grade 1, 36% were grade 2, and 3% were grade 3.

Prognostic factors
Several histological parameters are associated with increased risk of recurrence and metastasis including grade, tumour necrosis, mitotic count and myxoid tumour matrix. Analysed in a multivariate fashion, histological grade is the single most important predictor of local recurrence and metastasis [208]. The five-year survival is 89% for patients with grade 1, the combined group of patients with grade 2 and 3 have a five-year survival of 53%. Approximately 10% of tumours that recur have an increase in the degree of malignancy. Occasionally in chondrosarcomas there is the coexistence of various histological grades in the same tumour.
Periosteal chondrosarcoma

Definition
Periosteal chondrosarcoma is a malignant hyaline cartilage tumour, which occurs on the surface of bone.

Synonym
Juxtacortical chondrosarcoma.

Epidemiology
In the SEER data, only 3 of 667 chondrosarcoma were classified as periosteal (538). The tumour occurs in adults.

Sites of involvement
The metaphyses of long bones are involved, especially the distal femur.

Clinical features / Imaging
Patients present with pain with or without swelling. The lesion appears to involve the cortex with indistinct margins. It is generally larger than periosteal chondroma (more than 5 cm) It is a radiolucent lesion with punctate radiodensity (calcification). It is covered by elevated periosteum and it is pasted on the cortical bone showing variable erosion of it.

Macrosopy
A large (more than 5 cm) lobulated mass is attached to bone surface. On the cut section a lucent glistening appearance is often associated with gritty white areas of enchondral ossification and calcification.

Histopathology
Histological features are similar to that of conventional chondrosarcoma. Nodules of tumour invade surrounding soft tissues.

Secondary chondrosarcoma

Definition
Secondary chondrosarcoma is a chondrosarcoma arising in a benign precursor, either an osteochondroma or enchondroma.

ICD-O code 9220/3

Epidemiology
There are no reliable figures about risk of developing chondrosarcoma in the benign precursors which are frequently asymptomatic. Information available is from surgical series which introduces a selection bias. The risk for chondrosarcoma in solitary osteochondroma
has been reported to be 2% and that for osteochondromatosis 5-25% [538]. It is difficult to prove malignant transformation in enchondromas. Patients with Ollier disease and Maffucci syndrome have a 25-30% risk of developing chondrosarcoma [269, 1274, 1901]. Patients are generally younger than patients with primary chondrosarcoma.

**Sites of involvement**
Any portion of the skeleton may be involved. However, the pelvic and shoulder girdle bones are more frequently affected.

**Clinical features / Imaging**
A change in clinical symptoms in a patient with a known precursor lesion heralds the development of chondrosarcoma. Sudden pain or increase in swelling are frequent complaints. In osteochondromas, plain roentgenograms show irregular mineralization and increased thickness of the cartilage cap. In preexisting chondromas, destructive permeation of bone and development of a soft tissue mass are seen. CT and MRI are helpful in delineating the thickness of the cartilage cap and presence of cortical destruction and soft tissue mass.

**Macroscopy**
Chondrosarcomas secondary to osteochondroma show a thick (more than 2 cm) lobulated cartilage cap. The cartilage usually shows cystic cavities. Chondrosarcoma arising in chondromatosis is usually very myxoid and hence appears mucoid. The tissue “runs” when sectioned leaving behind cystic cavities. This contrasts with the solid blue matrix of the areas of chondromatosis.

**Histopathology**
Secondary chondrosarcomas are generally low grade tumors. Invasion of surrounding tissues and marked myxoid change in the matrix are helpful features.

**Prognostic factors**
Patients with chondrosarcoma and osteochondromas have excellent prognosis. Chondrosarcoma in enchondromatosis has the same prognosis as conventional chondrosarcoma and depends on the site and grade of the tumour.

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Secondary chondrosarcoma in Ollier disease and Maffucci syndrome

The secondary chondrosarcoma in these conditions is characterized histologically by increased cellularity and nuclear atypia in comparison to the enchondroma of Ollier and Maffucci diseases. In these two conditions the histology of enchondromas is characterized by hypercellularity and nuclear atypia. So the differential diagnosis between enchondroma and grade 1 CHS on cytology is difficult. The diagnosis needs to be supported by the radiographic and clinical background.

**Genetics**
The cytogenetic data on chondrosarcomas are heterogeneous with karyotypic
complexity ranging from single numerical or structural chromosomal aberrations to heavily rearranged karyotypes. In most cytogenetic reports in the literature, however, no strict distinction between primary conventional, secondary peripheral and periosteal chondrosarcomas is made, resulting in the description of many non-specific structural or numerical aberrations. Although no recurrent structural aberrations are described in these studies, the pattern of changes tends to be nonrandom (253,1315, 2082). Total or partial gains and losses predominate, and the most common imbalances are loss of chromosomes/chromosome segments 1p36, 1p13-22, 4, 5q13-31, 6q22-qter, 9p22-pter, 10p, 10q24-qter, 11p13-pter, 11q25, 13q21-qter, 14q24-qter, 18p, 18q22-qter, and 22q13, and gain of 7p13-pter, 12q15-qter, 19, 20pter-q11, 21q (1315). Loss of material from 13q was found to be an independent predictor of metastasis development, regardless of tumour grade or size (1315). Recent studies have indicated that primary conventional and secondary peripheral (arising within the cartilaginous cap of a preexisting osteochondroma) chondrosarcomas may differ in their genetic make up, as reflected by a clear difference in the loss of heterozygosity (LOH) pattern, LOH incidence, DNA ploidy status and cytogenetic aberrations (236,240). Primary conventional chondrosarcomas are characterized by genetic instability, a high percentage of LOH and a broad range of DNA ploidy. Trisomy 22 was only detected in primary conventional chondrosarcomas (240). Also comparative genomic hybridization studies point to deletions of 9p (1220). The CDKN2A tumour suppressor gene (P16) is a potential target for the deletions in this region. Mutations have not been documented so far (91,236), but CDKN2A methylation has been detected in a substantial number of chondrosarcomas (91).

Fig. 10.41. Chondrosarcoma in a patient with multiple osteochondromas. A Plain X-radiograph and surgical specimen of the tumour of right proximal fibula: Note the thickness of the cartilaginous cap and flaring of the cortex (macro) and the fuzzy indistinct margins with irregular mineralization visible on X-ray. B Discrete peripheral nodules of cartilage are embedded in the soft tissue at the periphery of the lesion. These features explain the irregular margins and the possibility of local recurrence when the lesion is resected with inadequate surgical margins.

Primary conventional chondrosarcomas and enchondromas have been found to occur in high association with the development of breast cancer at early age, not associated with previously recognized breast cancer syndromes (1595). Recently, one somatic and one germline mutation in the gene encoding the PTH/PTHrP type I receptor were identified in a subset of patients with Ollier disease (968). Cytogenetic data on periosteal chondrosarcoma are limited to two cases. No shared breakpoints were found (240).

Fig. 10.42. Multistep molecular genetic model for peripheral secondary chondrosarcoma tumorigenesis.
Dedifferentiated chondrosarcoma

Definition
Dedifferentiated chondrosarcoma is a distinct variety of chondrosarcoma containing two clearly defined components, a well differentiated cartilage tumour, either an enchondroma or a low grade chondrosarcoma, juxtaposed to a high grade noncartilaginous sarcoma. There is a histologically abrupt transition between the two components.

ICD-O code 9243/0

Synonym
Chondrosarcoma with additional mesenchymal component.

Epidemiology
Dedifferentiated chondrosarcoma makes up 10% of all reported chondrosarcomas. The average age of presentation is between 50 and 60 years, and the age range is 29 to 85 years.

Sites of involvement
The most common sites of involvement are pelvis, femur and humerus.

Clinical features / Imaging
The most common presenting symptom is pain, however, swelling, paresthesia and pathological fractures are also common. The tumour usually produces an ill defined, lytic, intraosseous lesion often associated with cortical perforation and extraosseous extension. The pre-existing cartilaginous portion, which may show the ring-like densities seen in enchondromas or other radiologic findings of cartilaginous matrix, is sharply distinct from the lytic permeable and destructive component.

Macroscopy
Typically, both tumour components, cartilaginous and noncartilaginous, are grossly evident in varying proportions.

Histopathology
The cartilaginous component is usually a low grade cartilaginous sarcoma. Malignant fibrous histiocytoma is the most frequent pattern reported in the high grade sarcoma component; however, osteosarcoma, fibrosarcoma and rhabdomyosarcoma are also encountered. There is abrupt demarcation between the two components.

Genetics
Cytogenetic data available at present justify a conclusion that no specific aberrations seem to be associated with dedifferentiated chondrosarcoma. Structural and numerical aberrations are most frequently reported for chromosomes 1 and 9. The non-uniform karyotype is reflecting the wide variety of histology of the "dedifferentiated" part. Based upon mutation analysis of TP53, it was

Fig. 10.43 Dedifferentiated chondrosarcoma. A The distal portion of the tumour has the typical mineralization of a cartilage tumour, whereas the proximal part is lytic and destructive appearing. B There is a central area of calcification associated with large areas of lysis.

Fig. 10.44 MRI of dedifferentiated chondrosarcoma of proximal femur. In addition to large areas of destruction in the medullary cavity, there is a large soft tissue mass medially.
shown that both components – sharing identical and uncommon TP53 mutations – have a common origin, though the apparent numerous additional genetic differences suggest an early division of the two cell clones [237]. Support for this concept comes from combined cytogenetic and immunophenotypic analyses, showing numerical aberrations of chromosome 7 in both components [254]. When considering two subtypes of dedifferentiated chondrosarcoma, i.e., the classical type with a low grade chondroid component and a second type with a more high grade chondrosarcomatous component next to the "dedifferentiated component", the model presented might not be entirely satisfying for both subtypes [23]. This view is supported by studies on the immunohistochemical and ultrastructural levels, as well as based on growth rates of both components. As molecular data on these subtypes separately and more specifically the first mentioned subtype are lacking, the suggestion of two subtypes of dedifferentiated chondrosarcoma with two different genetic routes for tumourigenesis remains speculative.

Prognostic factors
Dedifferentiated chondrosarcomas are aggressive neoplasms and have a dismal prognosis. Despite aggressive therapy, approximately 90% of patients are dead, with distant metastasis within two years.

Fig. 10.45 A Dedifferentiated chondrosarcoma of proximal femur. The medullary part has the appearance of cartilage tumour, whereas a soft tissue mass is fleshy. B Dedifferentiated chondrosarcoma of proximal humerus with cartilaginous areas juxtaposed to fleshy, sarcomatous areas.

Fig. 10.46 Dedifferentiated chondrosarcoma. A Transition between well differentiated or benign-looking cartilaginous tumor and highly anaplastic spindle cell and pleomorphic sarcoma is abrupt without morphologic continuity. B In this lesion, the high grade component has a slightly epithelioid appearance. C Cartilaginous portion of dedifferentiated chondrosarcoma. There is minimal cytological atypia. D Dedifferentiated portion presents as markedly atypical spindle cells with matrix formation.
Fig. 10.47 Multistep model of tumourigenesis of dedifferentiated chondrosarcoma (adapted from J.V Bovee et al. (237)). Genetic analysis provides evidence for a monoclonal origin of both parts, sharing identical genetic alterations. The presence of multiple additional alterations suggest early separation of the cartilaginous and ‘dedifferentiated’ clone.

Fig. 10.48 Dedifferentiated chondrosarcoma. A Typical example with low grade chondrosarcoma juxtaposed to a high grade spindle cell sarcoma. B The low grade chondrosarcoma (left) is juxtaposed to a spindle cell sarcoma with bone formation.
**Mesenchymal chondrosarcoma**

**Definition**
Mesenchymal chondrosarcoma is a rare malignant tumour characterized by a bimorphic pattern that is composed of highly undifferentiated small round cells and islands of well differentiated hyaline cartilage.

**ICD-O code** 9240/3

**Epidemiology**
Mesenchymal chondrosarcoma makes up less than 3 to 10 percent of all primary chondrosarcomas. Although occurring at any age, the peak incidence is in the second and the third decades. Males and females are affected equally [310, 421, 994, 1533, 1881].

**Sites of involvement**
The skeletal tumours show a widespread distribution. The craniofacial bones (especially the jawbones) [1276, 2197], the ribs, the ilium, and the vertebrae are the most common sites [182, 891, 1364].

**Clinical features / Imaging**
The cardinal symptoms are pain and swelling ranging from few days to several years, frequently more than one year in duration [182, 849, 891, 1364]. Oncogenic osteomalacia secondary to mesenchymal chondrosarcoma has been reported [2353]. Radiologically, skeletal lesions are primarily lytic and destructive with poor margins, not significantly differing from ordinary chondrosarcoma in most cases. Mottled calcification is sometimes prominent. Some have well defined margins with a sclerotic rim. Expansion of the bone is frequent, and cortical destruction or cortical breakthrough with extraosseous extension of soft tissue is common. Bony sclerosis, cortical thickening, and superficial involvement of the bone surface are also seen. Imaging features of extraskeletal tumours are also nonspecific, showing chondroid-type calcifications and foci of low signal intensity within enhancing lobules [1927].

**Macroscopy**
The tumours are grey-white to grey-pink, firm to soft, and usually well defined, circumscribed masses varying from 3 to 30 cm in maximum diameter [994, 1533]. Lobulation is rare. Most lesions contain hard mineralized deposits that vary from dispersed foci to prominent areas. Some tumours show a clearly cartilaginous appearance, even in a small section. Foci of necrosis and haemorrhage may be prominent. As evidenced on X-rays, bony expansion with cortical thinning or, more commonly, bone destruction and invasion of soft tissue is frequent.

**Histopathology**
The typical biphasic pattern is composed of undifferentiated small round cells admixed with islands of hyaline cartilage. The amount of cartilage is highly variable. The cartilage may be distinct

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**Fig. 10.49** Mesenchymal chondrosarcoma of the surface of the femur. There is a calcifying neoplasm involving predominantly the cortex and soft tissue. **A** Plain X-ray. **B** CT.

**Fig. 10.50** MRI shows a fairly extensive soft tissue mass attached to the cortex.

Y. Nakashima
Y.K. Park
O. Sugano
Cartilage tumours

from the undifferentiated component or blend gradually with it. In the undifferentiated areas, the small round cells typically simulate Ewing sarcoma, and a haemangiopericytomatous vascular pattern is common. The small cells may be spindle-shaped to some extent. Osteoclast-like multinucleated giant cells may occasionally be seen, and osteoid and even bone may be present.

**Immunophenotype**

Immunohistological studies [508, 513, 827, 958, 1844, 2064] of mesenchymal chondrosarcoma are not specifically helpful in the differential diagnosis among small round cell lesions. The small cell component of mesenchymal chondrosarcomas are positive for vimentin, Leu7 [508,2064], and CD99 [827,958] making differentiation from Ewing sarcoma difficult, whereas cells in the chondroid areas are positive for S100 protein [508, 958, 2064].

**Ultrastructure**

The biphasic nature of neoplastic cells was demonstrated electron microscopically [182,529,727,1342,1358,2026]. In cartilaginous foci, the cells show a chondrocyte-like appearance, as is seen in conventional chondrosarcoma, and in the undifferentiated small cell areas, uniform sheets of round to oval cells with little intercellular matrix are similar to primitive mesenchymal cells.

**Genetics**

Only few cases of mesenchymal chondrosarcoma with chromosome aberrations have been reported [1477]. The observed changes have varied from a pseudodiploid karyotype with a balanced translocations as the sole aberration [1787] to highly complex karyotypes with more than 150 chromosomes and multiple numerical and structural rearrangements [529]. In two cases, a Robertsonian 13;21 translocation was detected [1542]. The 11;22 translocation of the Ewing family of tumours is not seen in mesenchymal chondrosarcoma.

In an immunohistochemical study, nuclear positivity for the TP53 protein was observed in 22-64% of the tumour cells, with positive staining in mesenchymal as well as chondroid components [1659]. PCR analysis revealed that approximately one-fifth of the cases had significantly reduced expression of TP53. However, no mutations resulting in amino acid substitution were found within exons 5-9 of the gene [1659]. Molecular analysis of the CDKN2A tumour suppressor gene revealed low expression levels in 7/33 cases, but single strand conformation polymorphism analysis of the entire coding region did not disclose any mutations [108].

**Prognostic factors**

Mesenchymal chondrosarcoma is a highly malignant tumour with a strong tendency toward local recurrence and distant metastasis which are observed even after a delay of more than 20 years [1533]. The clinical course is frequently protracted and relentless, making long-term follow up mandatory. Mesenchymal chondrosarcoma of the jaw bones appears to have a more indolent course than those in other anatomic sites [2197].

![Fig. 10.51](image1) Gross specimen of mesenchymal chondrosarcoma of the surface of the femur, showing a reasonably well-demarcated lesion involving the cortex and soft tissues.

![Fig. 10.52](image2) A The small cells suggest a diagnosis of Ewing sarcoma. However, the presence of cartilage rules it out. B High power appearance of the small cell malignancy with a haemangiopericytomatous pattern.
Clear cell chondrosarcoma

Definition
Clear cell chondrosarcoma is a rare, low grade variant of chondrosarcoma, which predilects the epiphyseal ends of long bones. It is characterized histologically by bland clear cells in addition to hyaline cartilage.

ICD-O code 9242/3

Epidemiology
Clear cell chondrosarcoma comprises approximately 2% of all chondrosarcomas (1724). Men are almost three times more likely to develop clear cell chondrosarcoma than women. The reported age range is 12 to 84 (209,1014). However, most patients are between ages 25 and 50.

Sites of involvement
Most bones in the skeleton have been reported to be involved by clear cell chondrosarcoma, including skull, spine, hands, and feet. However, approximately two thirds of lesions occur in the humeral head or femoral head.

Clinical features / Imaging
Pain is the most common presenting symptom. Fifty five percent of patients had pain for longer than a year. In some patients (18%) symptoms were present longer than 5 years (209). On occasion, the patient may have an elevated alkaline phosphatase (268). Radiographically, clear cell chondrosarcoma usually presents as a well defined lytic lesion in the epiphysis of a long bone. Occasionally, a sclerotic rim may be present. Some lesions may contain stippled radiodensities characteristic of cartilage. This radiographic appearance overlaps with that of chondroblastoma.

Macroscopy
Lesions range from 2 to 13 cm in maximum diameter. They contain soft but gritty material, sometimes with cystic areas. Gross features characteristic of cartilage are not usually present.

Histopathology
The neoplasm consists primarily of lobular groups of cells with round, large, centrally located nuclei with clear cytoplasms and distinct cytoplasmic membranes. Some cells have a pale pink cytoplasm and resemble the chondroblasts of chondroblastoma. Multinucleated osteoclast-like giant cells may also be present. Mitotic figures are rare. Many lesions also contain zones of conventional low grade chondrosarcoma with hyaline cartilage and minimally atypical nuclei. This cartilage may be focally calcified or ossified. Woven bone may form directly in the stroma, and areas of aneurysmal bone cyst are often present.

Immunophenotype
The clear cells and chondroblastoma-like cells are strongly positive for S100 protein and type II collagen.

Genetics
Only an isolated case report on the karyotype is available (2019). CDKN2A alterations appear to be infrequent (1657).
Prognostic factors
En bloc excision with clear margins usually results in cure. However, marginal excision or curettage provides unacceptable results with an 86% recurrence rate. In these incompletely excised cases, metastases, usually to the lungs and other skeletal sites, may develop, and the overall mortality rate in these cases is 15%. Dedifferentiation to high grade sarcoma has been reported in three cases [1054].