CHAPTER 11

Osteogenic Tumours

Osteogenic tumours are defined as neoplasms that produce an osteoid or bony matrix. According to their biological behaviour, they are divided into benign and malignant lesions. Benign bone-forming neoplasms very rarely undergo malignant transformation. Osteomas are not considered neoplasms and, therefore, are not included in this volume.

Osteoid osteomas and osteoblastomas share many clinical and roentgenographical similarities. They cause severe pain which, however, is effectively alleviated by aspirin.

Osteosarcomas are the most frequent bone tumours and are almost always highly malignant. Most arise in the long bones of children without a recognizable precursor lesion, but about 15% arise in adults secondary to a pre-existing condition, such as Paget disease. Although all osteosarcomas produce osteoid or bone, they represent different entities based on clinical, roentgenographic, or histological features. Advances in the clinical management of osteosarcomas have lead to a significant increase in 5-year survival rates, which in most centres now exceed 50%.

Osteoid osteoma

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Definition
Osteoid osteoma is a benign bone-forming tumour characterized by small size, limited growth potential and disproportionate pain.

ICD-O code   9191/0

Epidemiology
Osteoid osteoma usually affects children and adolescents, although it is occasionally seen in older individuals. It is more common in males.

Sites of involvement
Osteoid osteoma has been reported in virtually every bone except for the sternum, but it is most common in the long bones, particularly in the proximal femur.

Clinical features / Imaging
The usual presenting complaint is pain. The pain, at first intermittent and mild with nocturnal exacerbation, eventually becomes relentless to the point of interfering with sleep. On the other hand, it is characteristic for salicylates and non-steroidal anti-inflammatory drugs to completely relieve the pain for hours at a time. Patients usually have become aware of this prior to seeking treatment, and about 80% report this characteristic feature {922}.

On physical examination, there is often an area of exquisite, very localized tenderness associated with the lesion, and there may be redness and localized swelling. There are sometimes unusual clinical manifestations that are site dependent. When lesions are located at the very end of a long bone, patients may present with swelling and effusion of the nearest joint. When osteoid osteoma arises in the spine, it usually affects the neural arch, and patients may present with painful scoliosis due to spasm of the spinal muscles {1126}. When the tumour occurs in the fingers, the persistent soft tissue swelling and periosteal reactions may result in functional loss that leads to numerous surgeries, large en-bloc excisions {1983} and even ray amputations.

Osteoid osteoma near or within joints may cause a reactive and inflammatory arthritis that can result in secondary osteoarthritis and in ectopic ossification {1579,2078}.

On plain films, the lesion is characterized by dense cortical sclerosis surrounding a radiolucent nidus. The cortical sclerosis may be so pronounced that the dense bone obscures the lesion. In those uncommon cases in which the centre of the lesion has ossified, the lesion can appear like a target, demonstrating central sclerosis within an area of circumscribed radiolucency. When plain x-rays demonstrate dense cortical sclerosis, particularly if it is eccentric and fusiform, osteoid osteoma should be suspected. The area containing the actual tumour may be visualised with a Technetium-99 bone scan if it can not be seen on a plain radiograph. Atypical and even misleading radiographic findings may be associated with osteoid osteomas in certain locations. Subperiosteal osteoid osteoma may produce a misleading degree of periostitis, while surface osteoid osteomas arising within joints may be virtually invisible on plain radiographs {1923}. The best imaging study to demonstrate osteoid osteoma is a CT scan {93}. The CT scan must be performed using bone windows, and it is essential to prepare the actual slices at 1 mm intervals rather than at conventional 5 mm or 1 cm intervals. The reason is that the standard CT slices may very easily cut above and below a small lesion. MRI may be useful in demonstrating medullary or periarticular lesions and peritumoural oedema {2014}.

Macroscopy
Osteoid osteoma is a small cortically based, red, gritty or granular round lesion surrounded by (and sharply circumscribed from) ivory white sclerotic bone.

Histopathology
Osteoid osteoma has a limited growth potential. Even though it may be present

in a patient for several years, the lesion seldom exceeds 1 cm in greatest diameter. In fact, the term osteoblastoma is usually applied if a lesion of identical histology exceeds 2 cm in diameter; the implication is that lesions of this size are not limited in growth potential.

The tumour consists of a central area of vascularised connective tissue within which differentiating osteoblasts are
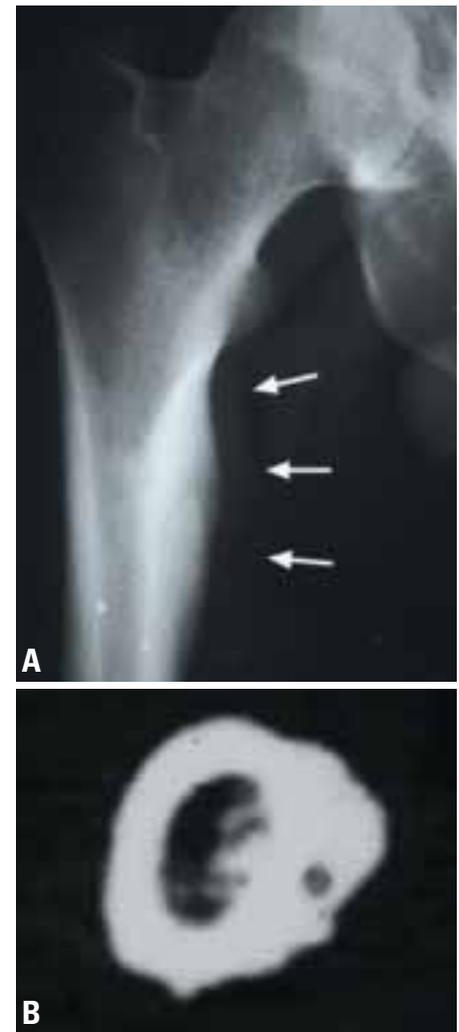

Fig. 11.01 **A** Osteoid osteoma of proximal femoral diaphysis, presenting on X-ray as dense, continuous fusiform sclerosis of the medial femoral cortex (arrows). **B** CT of the same lesion shows a circular radiolucency (nidus) in the outer portion of the thickened medial cortex.

Fig. 11.02 Osteoid osteoma. **A** The lateral X-ray shows a radiolucent nidus with an unusual radiodense centre just medial to the olecranon fossa of the humerus. The surrounding bone demonstrates very dense reactive sclerosis. **B** On the CT scan, the target-shaped centrally dense nidus is very clear.
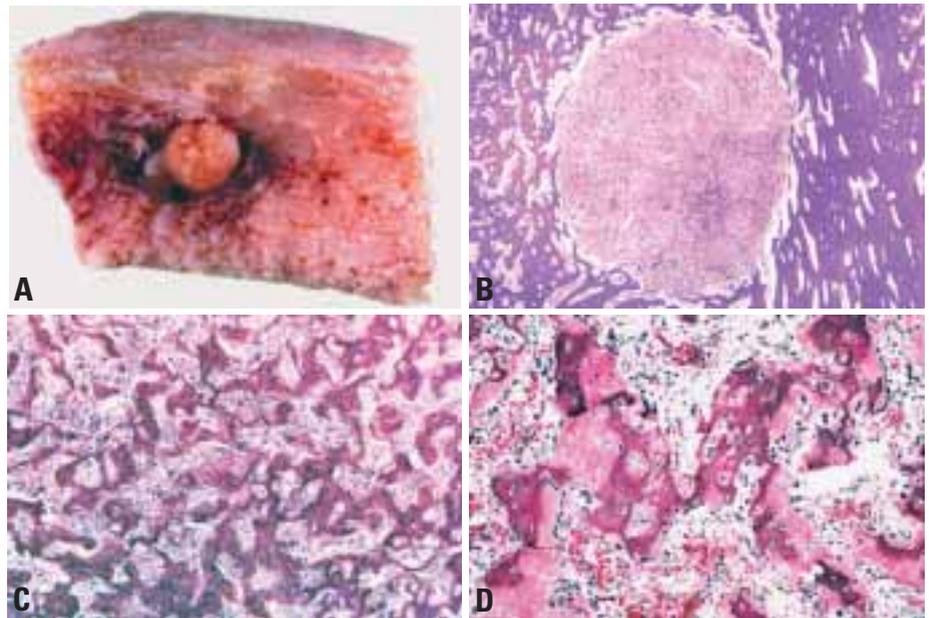

Fig. 11.03 Osteoid osteoma. **A** Grossly, the nidus is 5mm in diameter and has a hypervascular zone within the surrounding sclerotic cortex. **B** Very sharp circumscription of nidus near cortical surface showing dense cortex to the right and reactive neocortex above, below, and to the left of the lesion. **C** The histology of an undecalcified section from the centrally dense nidus shows interconnected, ossified bone trabeculae. **D** Clear ossification of osteoid trabeculae is seen (dark blue) as well as appositional osteoblast activity.

engaged in the production of osteoid and sometimes of bone. If actual bone is present, osteoclasts may also be seen engaged in remodelling, but the essential feature in the central portion of the lesion, or nidus {1024}, is the presence of differentiated osteoblastic activity. The osteoid may be microscopically disposed in a sheet-like configuration, but very often it is organized into microtrabecular arrays that are lined by plump appositional osteoblasts. It is this latter feature that helps to distinguish its pattern of bone formation from osteosarcoma. Additionally, nuclear pleomorphism is absent in osteoid osteoma. Cartilage is usually absent in osteoid osteoma. Surrounding the tumour, there is almost always an area of hypervascular sclerotic bone. This osteosclerosis tends to be more pronounced as lesions become closer to the bone surface and less pronounced in medullary lesions. The interface between osteoid osteoma and the surrounding reactive bone is very abrupt and circumscribed. When it can be demonstrated histologically, this interface provides very strong histological evidence of indolent local behaviour.

Even when the interface between tumour and reactive bone is not demonstrable in sections, the diagnosis becomes apparent by correlating the histological findings with satisfactorily prepared imaging studies.

Genetics
Only three osteoid osteomas, all with near-diploid karyotypes, have been described. In two cases each, involvement of chromosome band 22q13 and loss of the distal part of chromosome arm 17q were detected {136}.

Prognostic factors
The prognosis of osteoid osteoma is excellent. Recurrences are rare. Some lesions have been reported to have disappeared despite the lack of surgical therapy.

Osteoblastoma

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Definitions

Osteoblastoma is a rare benign bone forming neoplasm which produces woven bone spicules, which are bordered by prominent osteoblasts.

ICD-O code   9200/0

Synonyms

Ossifying giant cell tumour, giant osteoid osteoma {427}.

Epidemiology

Osteoblastoma is rare, accounting for about 1% of all bone tumours and is more common in males (2.5:1) and affects patients in the age range of 10-30 years, with extremes of 5–70 years old. It is a disease of male teenagers and young adults.

Sites of involvement

Osteoblastoma is one of the few neoplasms that predilects for the spine, particularly the posterior elements, and the sacrum (40–55% of cases). In the appendicular sites, the proximal femur, distal femur and proximal tibia are the most frequent. Osteoblastoma less commonly involves the tarsal bones (talus and calcaneous). The cementoblastoma of the jaws is considered an osteoblastoma and is attached to the root of a tooth, particularly the lower molars, and therefore the jaws are also common sites. The vast majority of cases are intra-osseous (medullary) but a small percentage can occur on the surface of the bone in a periosteal (peripheral) site.

Clinical features

Osteoblastoma of the spine has similar symptoms and signs to that of osteoid osteoma namely back pain, scoliosis and nerve root compression {1547}. Jaw lesions produce tooth pain and/or swelling. The appendicular tumours also produce pain and/or swelling but these symptoms may be vague enough to last for months before the patient will see a clinician. Aspirin does not relieve the pain after prolonged therapy.

Imaging

An osteoblastoma is generally a lytic well circumscribed oval or round defect almost always confined by a periosteal shell of reactive bone. In the spine such an X-ray pattern gives rise to an aneurysmal bone cyst-like (ABC) picture. Limb tumours are metaphysical lytic defects with a thin periosteal bone shell. Large tumours also produce ABC – like changes. Some tumours may arise in a subperiosteal location but are still confined by a thin reactive bone shell. Most osteoblastomas are totally lytic and less than 30% may have focal areas of calcification indicative of tumour bone mineralisation {1292}.

The size of osteoblastomas varies from small (2-3 cm) to enormous dimensions of 15 cm or more. Most are in the 3–10 cm range. In those cases with secondary ABC changes, the tumours are generally larger.

Macroscopy

Osteoblastoma has an extremely rich vascular supply and, therefore, it is red or red brown and often with a gritty or sandpaper consistency due to the tumour bone. The tumour is usually round to oval with a thinned cortex and always with a thin periosteal reactive bone shell if the cortex is destroyed. In cystic lesions, blood-filled spaces simulating an ABC are prominent. The border between the tumour and medullary cavity is sharp, often with some reactive bone. The tumour has a "pushing" border rather than a permeative or infiltrative border against the endosteal cortical surface and trabecular bone of the marrow.

Histopathology

Osteoblastoma has identical histological features to osteoid osteoma {720,1022}. The tumour is composed of woven bone spicules or trabeculae. These spicules are haphazardly or chaotically arranged and are lined by a single layer of osteoblasts. The vascularity is rich, often with extravagated red blood cells. Osteoblasts may have mitoses but they are not atypical. Diffusely scattered osteoclast-type multinucleated giant cells are often present which may mimic giant cell tumour. In very rare cases, hyaline cartilage may be present and may represent micro callus formation. In some cases, the tumour woven bone may be in aggregates or nodules and in such cases careful scrutiny must be done to exclude osteosarcoma.

In some cases the tumour may have foci of large blood filled spaces which are not lined by endothelial cells. The walls of such spaces are composed of fibrovas-
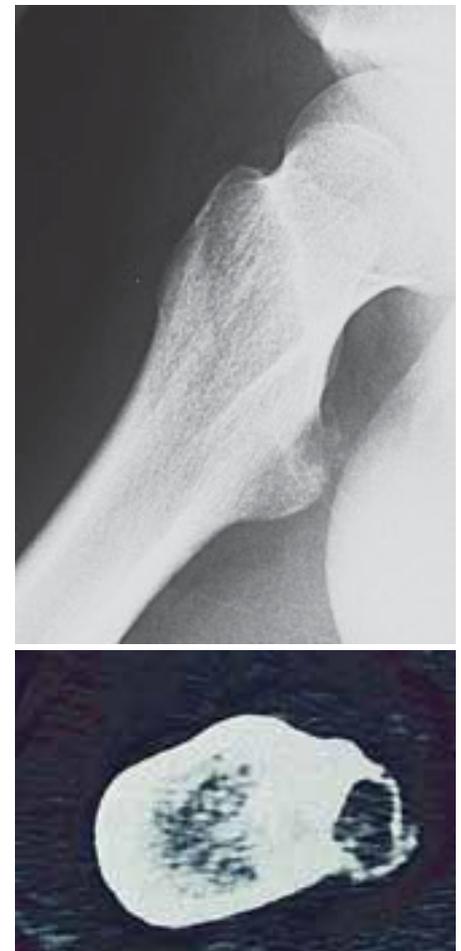

Fig. 11.04 A Osteoblastoma. Expanded radiolucent lesion of lesser trochanter in a 22 year-old male. **B** CT scan of same osteoblastoma showing a thin intact rim of encasing periosteal new bone.

Fig. 11.05 Osteoblastoma. Plain X-ray of large expansile lesion of cervical vertebra.

Fig. 11.06 Osteoblastoma. Excised specimen of femoral lesion showing a well-demarcated fleshy tumour.

Fig. 11.07 Osteoblastoma. The centre of the tumour shows vascularity and irregular osteoid with osteoblasts and giant cells.

cular tissue with longer woven bone spicules usually in a parallel arrangement indicating reactive bone rather than tumour bone. Such foci are indistinguishable from an ABC and therefore more typical foci should be sought to confirm the diagnosis of osteoblastoma.

The pathologist, especially in large tumours, should definitely sample the border between pre-existing cortex or marrow trabeculae. Osteoblastomas do not infiltrate and isolate pre-existing lamellar bone structures as does osteosarcoma.

In some cases of osteoblastoma large, plump osteoblasts with a prominent nucleus and nucleoli, some with mitoses, may be present. The term epithelioid osteoblastoma has been used for this {541,1089}.

Genetics

Chromosomal rearrangements have been described in four cases, with chromosome numbers ranging from hypodiploid to hyperdiploid {443,1348, 1743}. No consistent aberration has been detected among them. In comparison with osteosarcomas, the total number of genetic alterations is rather low in osteoblastomas {1743}. Nevertheless, there are some hints that cell cycle dysregulation is correlated with the aggressive potential of these tumours. *MDM2* amplification was reported in one case {1743}, and *TP53* deletion at a splice region was demonstrated in an aggressive osteoblastoma {1184}.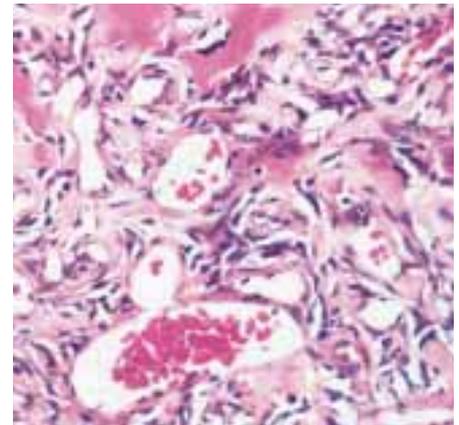 In accordance with the mostly benign character of osteoblastomas, they do not show telomerase activity {1100}, Overexpression of the hepatocyte growth factor receptor (MET/HGF receptor), a transmembrane tyrosine kinase encoded by the *MET* protooncogene, has been detected by PCR but not by Western blotting {653}. Serial analysis of the DNA content in one case of aggressive osteoblastoma showed that the appearance of aneuploidy could be demonstrated before malignancy was morphologically evident {824}.

Prognostic factors

Osteoblastoma should be treated by curettage. Large lesions may have to be excised. The prognosis is excellent and recurrences are unusual and more likely in those cases, which were curetted from a bone, which has difficult surgical access.
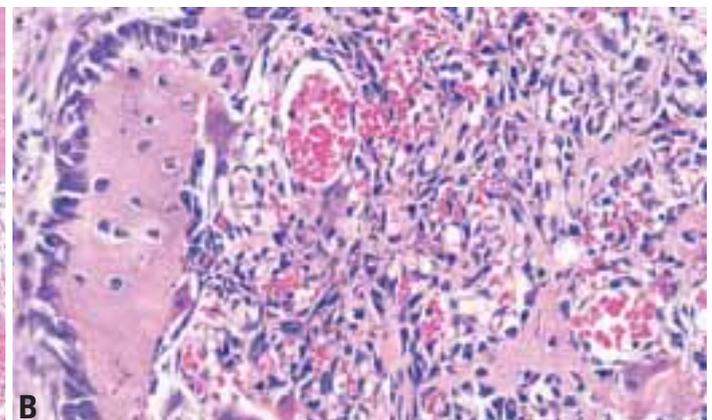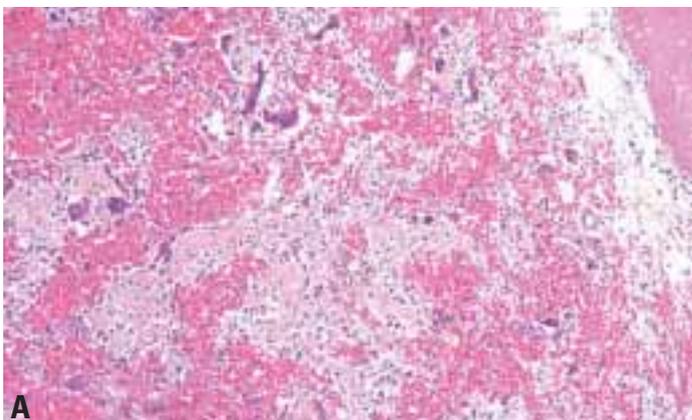

Fig. 11.08 Osteoblastoma. **A** Irregular osteoid, osteoblasts and giant cells, ectactic blood vessels and a reactive shell of periosteal new bone. **B** Classic osteoblastoma which is indistinguishable from an osteoid osteoma with small irregular islands of osteoid, osteoblasts and osteoclast-like giant cells and blood vessels.

Conventional osteosarcoma

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Definition
Conventional osteosarcoma is a primary intramedullary high grade malignant tumour in which the neoplastic cells produce osteoid, even if only in small amounts.

ICD-O codes
Osteosarcoma,
  not otherwise specified   9180/3
Chondroblastic osteosarcoma   9181/3
Fibroblastic osteosarcoma,
  osteofibrosarcoma   9182/3
Central osteosarcoma,
  conventional central osteosarcoma,
  medullary osteosarcoma   9180/3
Intracortical osteosarcoma   9195/3

Synonyms
Conventional osteosarcoma, classical osteosarcoma, osteogenic sarcoma, osteosarcoma not otherwise specified, osteochondrosarcoma, osteoblastic sarcoma, chondroblastic osteosarcoma, fibroblastic osteosarcoma, osteofibrosarcoma, central osteosarcoma, central osteogenic sarcoma, conventional central osteosarcoma, medullary osteosarcoma, sclerosing osteosarcoma.

Epidemiology
Osteosarcoma is the most common, non-haemopoietic, primary malignant tumour of bone; estimated incidence of 4-5 per million population. There does not appear to be significant association with ethnic group or race. Conventional osteosarcoma is largely a disease of the young {537}. It most frequently occurs in the second decade with some 60% of patients under the age of 25 years. Although 30% of osteosarcomas occur in patients over 40 years of age, the possibility of a predisposing condition should always be considered in older patients (e.g., Paget disease of bone, post-radiation sarcoma) {986,988}. Conventional osteosarcoma affects males more frequently than females in a ratio of 3:2. This gender selection is even more pronounced in patients under 20 years of age and tends to become less dramatic with increasing age.

Sites of involvement
Conventional osteosarcoma shows a profound propensity for involvement of the long bones of the appendicular skeleton; in particular, the distal femur, proximal tibia, and proximal humerus. It tends to be a disease of the metaphysis (91%) or diaphysis (<9%). Primary involvement of the epiphyses is extraordinarily rare {1765}. Although the long bones remain the most frequent sites of primary conventional osteosarcoma, the relative incidence in non-long bone (i.e., jaws, pelvis, spine, and skull) involvement tends to increase with age. Osteosarcoma arising in bones distal to the wrists and ankles is extremely unusual {1472,1601}. Because of unusual clinical factors, imaging features, histological findings and/or unique treatment problems, tumours arising in certain sites (e.g., jaws, skull, spine, pelvis, intra-cortical, multicentric, and skip metastases) deserve special consideration {586,670, 857,995,1165,1196,1310,1578,1852, 1943,2113,2189}.

Clinical features / Imaging
Symptoms generally develop over a period of weeks to a few months. Early symptoms may wax and wane and thereby be difficult to interpret; eventually, they become unremitting. Although relatively non-specific, pain, with or without a palpable mass, is the cardinal symptom of conventional osteosarcoma. Pain is usually described as deep, boring and severe.
Findings on physical examination may be limited to a painful, tender mass. Other findings may include: decreased range of motion, limitation of normal function, oedema, localized warmth, telangiectasias and bruit on auscultation. A sudden dramatic increase in tumour size is generally attributable to second-

Fig. 11.09 Osteosarcoma presenting as mixed lytic / blastic lesion involving the distal femoral metaphysis of a skeletally immature patient. The radiodensity pattern is "cumulus cloud-like".

Fig. 11.10 Osteoblastic osteosarcoma with sunburst configuration involving the proximal tibial diaphysis. Such a location makes a patient a relatively ideal candidate for limb-sparing surgery.

ary changes such as intra-lesional haemorrhage. Pathological fracture occurs in 5-10% of patients. Laboratory findings are limited, although elevation of certain serum markers (e.g., alkaline phosphatase and lactic acid dehydrogenase) may be present and have been used to monitor disease status.

The overall radiographic appearance of conventional osteosarcoma is extremely variable. It may be purely osteoblastic or osteolytic {505}. In most cases, it is a mixed lytic/blastic lesion accompanied

Fig. 11.11 Osteosarcoma. MRI, T1 weighted image. Decreased intramedullary signal intensity corresponds to area of pathology. Care must be taken not to over-interpret images; superimposed reactive changes (e.g., oedema, inflammation) may lead to an overestimation of the extent of tumour.

by cortical destruction and tumour extension into soft tissue. Tumours tend to be eccentric and the linear growth within the medullary cavity tends to stay ahead of its soft tissue counterpart. Rarely, non-contiguous intra-medullary growth within the parent bone or across adjacent joints may take place (i.e., "skip metastases") {586}. Soft tissue masses tend to be variably mineralized with the least calcification at the periphery. Tumour / periosteal interaction may lead to a variety of manifestations secondary to periosteal elevation (e.g., Codman's triangle) and periosteal reactive bone formation {538, 988}. Although involvement of true soft tissue eventually occurs, the radiographic soft tissue masses are frequently confined beneath the periosteum until late in disease evolution.

CT scan and MRI may be helpful in delineating the extent of the tumour preoperatively. {789,1378,1614,1768}. The latter studies are of paramount importance now that most patients have a potential for limb-salvage.

Tm99 radionuclide bone scan, may provide information regarding skip-metastases, multicentricity and systemic disease. Although not universally employed, the arteriogram can provide information pertaining to tumour response, or lack of response, to preoperative therapy. Osteosarcoma is a hypervascular lesion, with response to preoperative chemotherapy there is a decrease and elimination of tumour neovascularity {308,1183,1764}.

Aetiology

The precise aetiology of conventional osteosarcoma remains unknown. Although a history of trauma is frequently elicited, it is felt that trauma draws attention to the tumour rather than causing it. Paget disease of bone and radiation exposure have long been associated with an increased incidence of osteosarcoma {883,2263}. Although a wide variety of other tumours (e.g., osteoblastoma, osteochondroma, and fibrous dysplasia) and non-neoplastic conditions (e.g., osteomyelitis, and metal endoprosthesis implantation) have been linked with osteosarcoma, the extreme rarity of these associations suggests that any cause-and-effect relationship is tenuous {271,1164,1822}.

Macroscopy

Osteosarcoma is often a large (over 5 cm), metaphyseally centered, fleshy or hard tumour which may contain cartilage. It frequently transgresses the cortex and is associated with a soft tissue mass.

Some osteoblastic osteosarcomas may appear grey-tan and randomly granular (pumice-like), while others become denser, sclerotic and more yellow-white. Chondroblastic osteosarcomas tend to be white to tan, and variably calcified with a fish-flesh or rope-like cut surface.

Histopathology

As a sarcoma, conventional osteosarcoma is frequently referred to as a "spindle-cell" tumour; a reference which over-simplifies its cytological appearance. It tends to be a highly anaplastic, pleomorphic tumour in which the tumour cells may be: epithelioid, plasmacytoid, fusiform, ovoid, small round cells, clear cells, mono- or multinucleated giant cells, or, spindle cells. Most cases are complex mixtures of two or more of these cell types.

The diagnosis of osteosarcoma is predicated on the accurate identification of osteoid. Histologically, osteoid is a dense, pink, amorphous intercellular material, which may appear somewhat refractile. It must be distinguished from other eosinophilic extra-cellular materials such as fibrin and amyloid. Unequivocal discrimination between osteoid and non-osseous collagen may be difficult, and at times somewhat arbitrary. Non-osseous collagen tends to be linear, fibrillar, and compresses between neoplastic cells. In contrast, osteoid is curvilinear with small nubs, arborisation, and, what appears to be abortive, lacunae formation. The thickness of the osteoid is highly variable with the thinnest referred to as "filigree" osteoid. Osseous matrix also has a predisposition for appositional deposition upon previously existing normal bone trabeculae (i.e., "scaffolding"). When neoplastic cells are confined within large amounts of bone matrix, they frequently appear as small, pyknotic, minimally atypical cells, a feature referred to as "normalisaton." An under-appreciated architectural feature is the tendency for conventional osteosarcoma to grow in an angiocentric fashion which imparts an overall "basket-weave" or "cording" pattern to the tumour.

Conventional osteosarcoma can also produce varying amounts of cartilage and/or fibrous tissue. Many investigators further subdivide conventional osteosarcoma in terms of the predominant matrix {426,430,1764,1857,2155}. The algorithm is: identify the presence or absence of matrix and, if significant matrix is present, determine the matrix form. This system divides conventional osteosarcoma into three major subtypes: osteoblastic (50%), chondroblastic (25%), and fibroblastic (25%) osteosarcoma. Classification is a function of the primary tumour. There is a tendency for metastases to mimic the primary, but exceptions are frequent and there is a higher-than-expected incidence of fibroblastic differentiation in metastases.

Osteoblastic osteosarcoma

Bone and/or osteoid are the predominant matrix in osteoblastic osteosarcoma. The extremes of matrix production are thin, arborising osteoid (i.e., filigree) to dense, compact osteoid and bone (i.e., sclerotic).

Fig. 11.12 Osteosarcoma. X-ray shows an ill defined radioopaque lesion involving the distal metaphysis and epiphysis with a hint of additional pathology in the more proximal femoral diaphysis.

Fig. 11.13 Osteosarcoma. Surgical specimen demonstrating the presence of both primary tumour in the distal and skip metastases involving more proximal part of the femur.

Fig. 11.14 Osteosarcoma. Tm99 bone scan. There is significant concentration of isotope at the primary lesion. Also, a second, discontinuous lesion is shown within the more proximal diaphysis.

Chondroblastic osteosarcoma
Chondroid matrix is predominant in chondroblastic osteosarcoma. It tends to be high grade hyaline cartilage, which is intimately associated, and randomly mixed, with non-chondroid elements. Myxoid and other forms of cartilage are uncommon, except in the jaws and pelvis. Grossly, an overt chondroid appearance is rare. This is probably secondary to the cartilage component being less well-formed, high grade, and mixing with non-chondroid elements resulting in a lack of large areas of pure chondroid differentiation and its attendant blue-grey lobulated appearance.

Fibroblastic osteosarcoma
A high grade spindle-cell malignancy with only minimal amounts of osseous matrix with or without cartilage is the hallmark of fibroblastic osteosarcoma. In general, the overall histological appearance is similar to fibrosarcoma or malignant fibrous histiocytoma. However, its loose definition (i.e., minimal matrix) makes fibroblastic osteosarcoma a de facto default classification.
There are many additional unusual morphological forms of osteosarcoma (Table 11.01), but lacking unique biological properties, they are merely considered forms or subtypes of the three major

groups {116,139,990,1166,1765, 1877, 2133}. In many cases the lack of significant amounts of osteoid, bone or cartilage relegates them to subtypes of fibroblastic osteosarcoma.
Historically, there has been little, if any, prognostic significance to such subtyping of conventional osteosarcoma. Rather, it has been an arguably artificial method of imparting some order to conventional osteosarcoma. However, recent data appear to indicate that there are some predictable survival differences between subtypes when contemporary multi-disciplinary therapy is employed {909}.
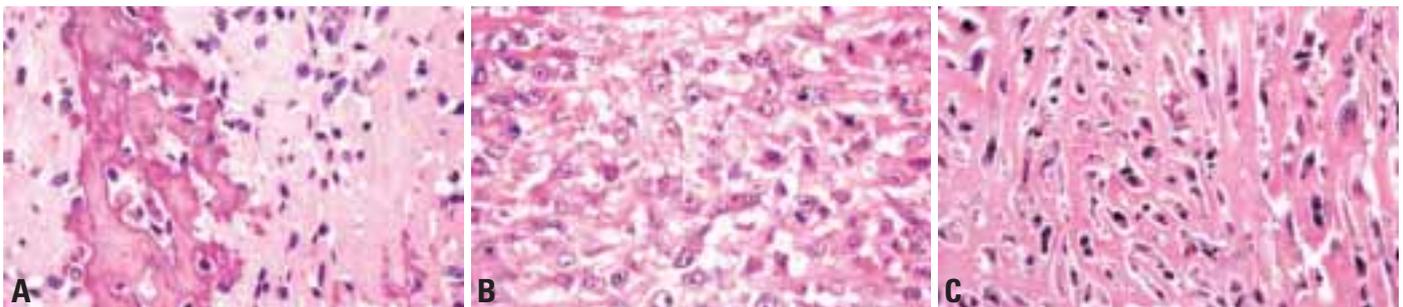

Fig. 11.15 Osteoblastic osteosarcoma. **A** Osteoid and bone. Osteoid is unmineralized bone matrix that is eosinophilic, dense, homogeneous and curvilinear and becomes bone as a result of mineralization (blue areas). **B** Filigree osteoid comprises thin, randomly arborizing lines of osteoid interweaving between neoplastic cells. **C** Osteoid seams may be flat and thick.
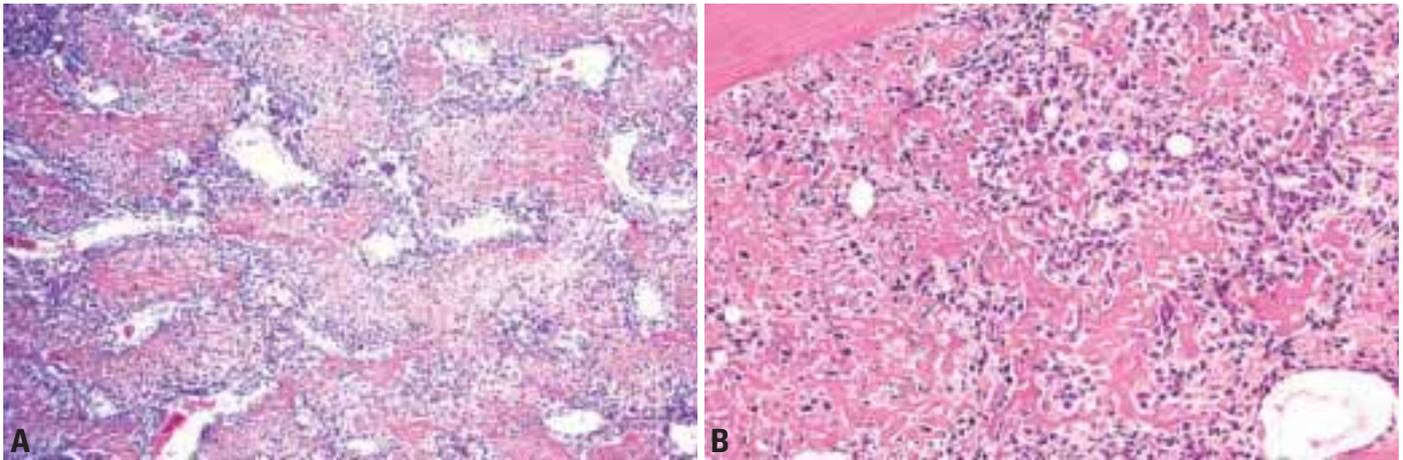
Fig. 11.16 Osteosarcoma. **A** Frequently occurring angiocentric pattern of growth may impart a basket-weave appearance while combined with abundant osteoid production. **B** Appositional osteoid/bone deposition of matrix onto previously existing normal bone trabeculum, a feature referred to as "scaffolding."

Management and interpretation of the post-chemotherapy, operative specimen is of critical importance since it yields an important prognostic determinant: response to pre-operative chemotherapy {1704,1763,1764}. The tumour-bearing bone is cut in the longitudinal axis in the plane that will demonstrate the greatest volume of tumour. The resulting cut-surface is sectioned and completely submitted (i.e., "mapped"). The orientation of these sections can be recorded by a number of techniques (i.e., specimen X-ray, and photocopy). Additional "non-mapped" sections from suspect areas should also be submitted for histological analysis. Response to therapy is recorded in terms of "tumour necrosis." The hallmark of osteosarcoma tumour necrosis is the absence of neoplastic cells (so-called "cell drop-out") in the face of residual tumour-produced matrix. Loose granulation tissue, fibrosis, and small numbers of inflammatory elements replace the cellular component of the tumour. The results of this analysis is generally reported in terms of percent tumour necrosis {988,1704,1764,2205,2292}.

Immunophenotype
The absence of reproducible evidence of specific findings minimises the use of both immunohistochemistry and electron microscopy in osteosarcoma {650,817, 893,1613,1666,2272}. In both cases their primary utility lies in their ability to exclude other diagnostic possibilities such as metastatic sarcomatoid carcinoma, and synovial sarcoma. Certain potential pitfalls exist. Osteosarcoma may be immunoreactive for cytokeratin and is frequently immunoreactive with antibodies to smooth muscle actin. Osteosarcoma usually has diffuse moderate to strong intra-cytoplasmic staining for CD99. Osteocalcin and osteonectin have sometimes been used to highlight osteoid.

Genetics
Cytogenetics
Most, if not all, osteosarcomas contain clonal chromosomal aberrations. The aberrations are complex, comprising an abundance of numerical and structural alterations {191,263,688,965,1428, 2090}. The modal chromosome number is highly variable. Multiple clones are common and may be related or unrelated. Diploid ploidy pattern by DNA cytofluorometry has been reported to be a poor prognostic sign {1191}.
Although no specific translocation or any other diagnostically consequential structural alteration has been assigned to

Fig. 11.17 Osteoblastic osteosarcoma is typically a radioopaque lesion, which may be purely blastic or mixed lytic / blastic. The tumour involves the metadiaphyseal region of the distal femur of a skeletally immature boy and has an overall "sunburst" configuration.

Fig. 11.18 Osteoblastic osteosarcoma presenting as dense, granular to sclerotic grossly bone-producing lesion. Note the deposition of tumour-produced bone on previously existing matrix and the well defined matrix within the soft tissues.

Table 11.01

Osteosarcoma: unusual histological forms*
- Osteoblastic osteosarcoma - sclerosing type
- Osteosarcoma resembling osteoblastoma
- Chondromyxoid fibroma-like osteosarcoma
- Chondroblastoma-like osteosarcoma
- Clear-cell osteosarcoma
- Malignant fibrous histiocytoma-like osteosarcoma
- Giant cell rich osteosarcoma
- Epithelioid osteosarcoma

*These forms are not associated with a specific biological behaviour that differs from conventional osteosarcoma. Therefore, these lesions are viewed as forms or subtypes of conventional osteosarcoma.

conventional osteosarcoma, involvement of certain chromosomal regions is recurrent. Chromosomal regions 1p11-13, 1q11-12, 1q21-22, 11p14-15, 14p11-13, 15p11-13, 17p and 19q13 are most frequently affected by structural changes, and the most common imbalances are +1, -6q, -9, -10, -13, and -17 {220,263}. Homogenously staining regions (hsr) and double minutes (dmin), cytogenetic manifestations of gene amplification, are frequently seen in conventional osteosarcomas {1404}.

Fig. 11.19 Osteosarcoma. The infiltrative quality of the tumour becomes apparent on closer inspection of the gross specimen. Also note thickening of pre-existing bone trabeculae caused by appositional deposition of matrix by the tumour.

DNA copy numbers

Comparative genomic hybridization analysis reveals that chromosomal regions 3q26, 4q12-13, 5p13-14, 7q31-32, 8q21-23, 12q12-13, 12q14-15, and 17p11-12 are most frequently gained {1404,2033,2091}. Gain of 8q23 is seen in 50% of tumours {2033} and seems to be a sign of poor prognosis {2089}. Increased copy number of the *MYC* gene localized to 8q24 was detected by fluorescence in situ hybridization (FISH) in 44% of cases {2033}. The 17p amplicon is intriguing as it is rarely seen in other tumour types. The most frequent losses are seen at 2q, 6q, 8p, and 10p {1146, 2091}.

Loss of heterozygosity (LOH)

Chromosome arms 3q, 13q, 17p, and 18q are most frequently involved in LOH {1179}. As the incidence of LOH is high at 3q26.6-26.3, this area has been suggested to harbour a putative suppressor gene {1179}.

Molecular genetics

Target genes of recurrent amplifications
Amplifications at 1q21-23 and at 17p are frequent findings in conventional osteo-sarcoma {1146}. Several genes have been reported to be involved in the 1q21-23 amplicon {708,1435}. Similarly, a variety of genes in the 12q13-15 region are co-amplified {172,711, 1098,1490,1607,1796,1975,2095, 2329}. *MDM2* {1205, 1607} and *PRIM1* {2329} amplifications have been detected in 14-27% and 41% of osteosarcoma cases, respectively. In aggressive osteosarcomas *CDK4* is most consistently amplified, alone or together with *MDM2* {171,710,1307}. The amplification and overexpression patterns of *CDK4*, *SAS*, and *MDM2* appear to differ from those in parosteal osteosarcoma {2305}. Recently, it was shown by FISH analysis that sequences, including *CCND2*, *ETV6*, and *KRAS2*, at 12p and *MDM2* at 12q were differently amplified in low grade osteosarcomas (parosteal osteosarcoma) and high grade osteosarcomas {796}. Amplifications at 12p were seen in 1/5 low grade osteosarcomas in contrast to 9/19 high grade osteosarcomas.

Gene expression

Overexpression of *MET* {652,1804} and *FOS* {2302} has been reported in more than 50% of osteosarcoma cases, whereas *MYC* is overexpressed in less than 15% of cases {130,1208}. *MYC*, *FOS*, and cathepsin L have been shown to be overexpressed in a high proportion of relapsed tumours and metastases {761, 1655}. Bone morphogenetic protein-6 and bone morphogenetic
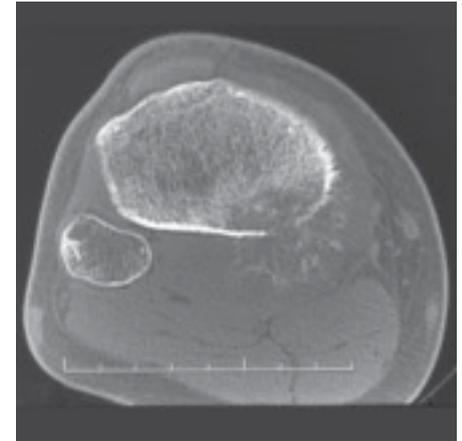

Fig. 11.20 Chondroblastic osteosarcoma. CT shows a mixed lytic / blastic lesion with evidence of ring-like (i.e., chondroid) calcifications.
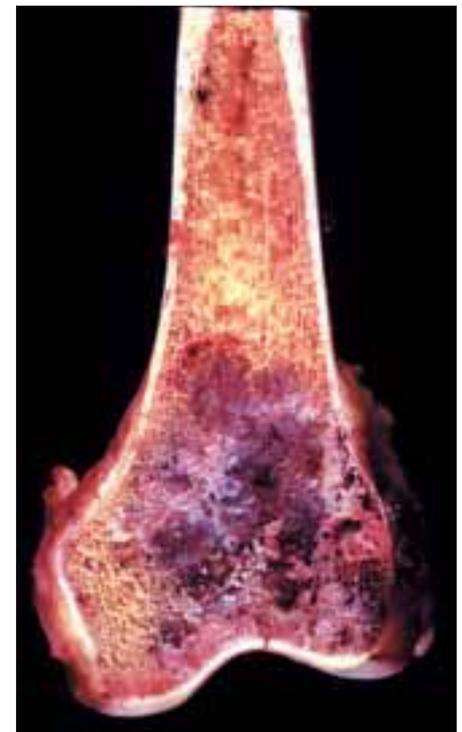

Fig. 11.21 Chondroblastic osteosarcoma. The cartilage component is sufficiently large and well organized to be clearly seen grossly. Note central blue grey cartilage. Peripheral areas with grey-tan tumour infiltrating cancellous bone.
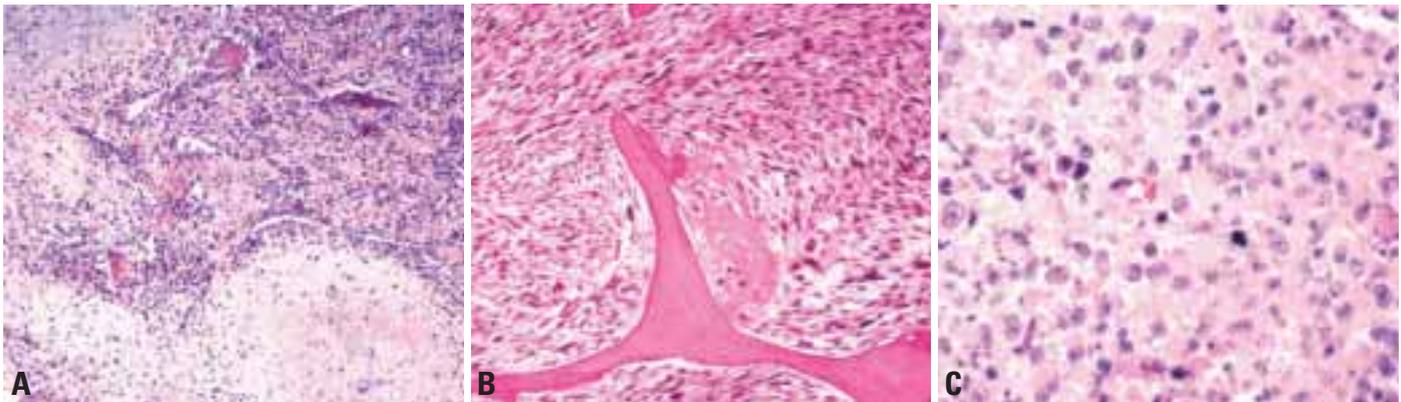
Fig. 11.22 Osteosarcoma. **A** The transition zone between high grade malignant cartilage with adjacent bone-producing spindle cell component. **B** Typically tumour is composed of fusiform spindle cells with minimal osseous matrix. Although anaplastic, cells may have minimal pleomorphism, be organized in herringbone arrangement and mimic fibrosarcoma. **C** Epithelioid osteosarcoma. A densely packed population of neoplastic cells with large eccentric nuclei and abundant eosinophilic cytoplasm imparts an over-all epithelioid or plasmacytoid appearance to the tumour.

ºprotein receptor 2 are expressed in more than 50% of osteosarcomas {858} and the *MAGE* genes in several cases {2050}.

Gene expression profiling

cDNA array analysis of osteosarcoma cell lines and primary tumours showed that *HSP90B* (heat shock protein 90b) and *PABPL1* (binding protein-like 1) were highly overexpressed, whereas *FN1* (fibronectin 1) and *THBS1* (trombospondin 1) were underexpressed {2290}.

Genetic susceptibilty

Hereditary retinoblastoma (RB) patients have a high risk of osteosarcoma development {550}. Such tumours are likely to show LOH at 13q and alterations of the *RB1* tumour suppressor gene. According to several studies, the frequency of *RB1* alterations in sporadic osteosarcoma has been found to vary between 30-40% {75, 1778,2116,2208,2304}. The prognosis for patients with *RB1* alterations seems to be poorer than for patients without *RB1* alterations {2208}.

Li-Fraumeni syndrome patients with a *TP53* germline mutation have an increased risk to develop a variety of tumours, including osteosarcoma. In sporadic osteosarcoma LOH at 17p and *TP53* mutations are seen in approximately 35% of the tumours {58, 313, 1349, 1459,1519,2117,2316}. The event-free survival rate has been reported to be lower in osteosarcoma patients with *TP53* alterations than in those without {2140}.

Prognostic factors

Untreated, conventional osteosarcoma is universally fatal. Aggressive local growth and rapid haematogenous systemic dissemination mark its course. Although metastases may affect many sites, pulmonary metastases are the most frequent site of clinically significant systemic disease. Bone is the second most frequent site of metastases, but this is largely a pre-terminal event.

The identification of prognostic factors has been an additive process in which factors have been investigated, identified and incorporated into an overall therapeutic strategy {1,207,274,426,453, 662,1327,1740,1835,1955,2098,2099}.

Traditionally, age, gender, location, tumour size, stage, and the results of various laboratory tests have been used in an effort to predict prognosis. However, response to pre-operative therapy is currently the most sensitive indicator of survival. At the same time, it is recognized that a single system does not apply to all cases. Unique biological aggressiveness, coupled with an inability to completely resect the tumour at certain sites (e.g., skull, spine) is one example. There are certain sites (e.g., jaw, pelvis) in which response to therapy does not appear to reflect prognosis despite the capacity for complete surgical tumour removal.

When treated by ablative surgery alone, survival is limited. With the development of effective multi-disciplinary therapy, significant changes have been introduced to the management of osteosarcoma.

The death of 80-90% of osteosarcoma patients with pulmonary metastases, despite the use of immediate ablative surgery and pre-surgical, radiographically normal lungs at the time of diagnosis implies that subclinical pulmonary micro-metastases are present in the vast majority of cases at presentation.

Fig. 11.23 Osteoblastic osteosarcoma, after pre-operative chemotherapy. Surgical specimen showing cystification and absence of luster, indicative of non-viable tumour (100% tumour necrosis).

Fig. 11.24 Post-chemotherapy arteriogram. After two courses of therapy, there is almost complete disappearance of neovascularity, indicating a high probability of response to therapy.
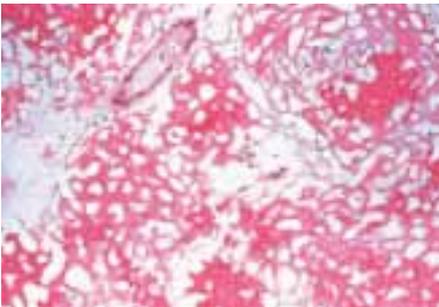

Fig. 11.25 Osteoblastic osteosarcoma after chemotherapy. Tumour-produced osseous matrix is present. There are no neoplastic cells ("cell drop-out"). The cellular component consists of occasional inflammatory cells, granulation tissue and capillaries.

Fig. 11.26 Osteosarcoma. DNA copy number changes in high grade osteosarcoma detected by comparative genomic hybridization. **A** Hybridization of tumour DNA (green) and reference DNA (red) to DAPI (blue) counterstained metaphase chromosomes. Green areas, e.g., at 8q, indicate DNA copy number gain. **B** Green-to-red ratios for each chromosome area are measured using special software. The line in the middle indicates green-to-red ratio 1, and thresholds for losses (0.85) and gains (1.17) are indicated by red and green lines, respectively. Bars show chromosomal areas with copy number changes. Numerous chromosomal imbalances are detected, including amplification of 8q and 15q and loss of 10p and 13q.

Therefore, osteosarcoma must be viewed as a systemic disease at the time of initial diagnosis.

Contemporary therapy is multi-disciplinary, focusing on both local and systemic manifestations of osteosarcoma through the judicious use of multidisciplinary therapy incorporating surgery and chemotherapy. The use of such multi-disciplinary therapy has resulted in disease-free survival of 60-80%, while allowing the use of functional limb-sparing surgery in >80% of patients.

Ultimate survival is directly related to response to pre-operative therapy. In those patients whose tumours have >90% tumour necrosis (i.e., "responders")
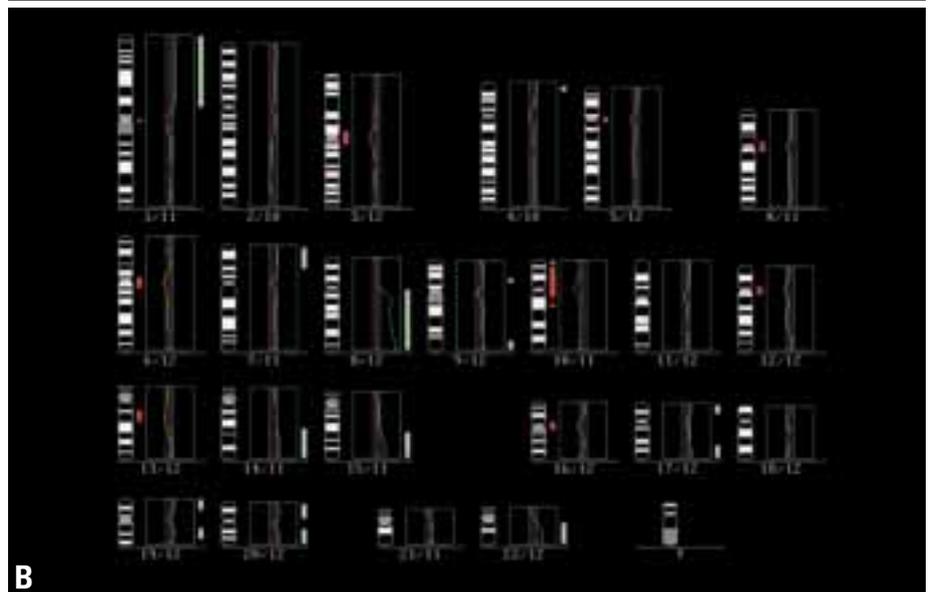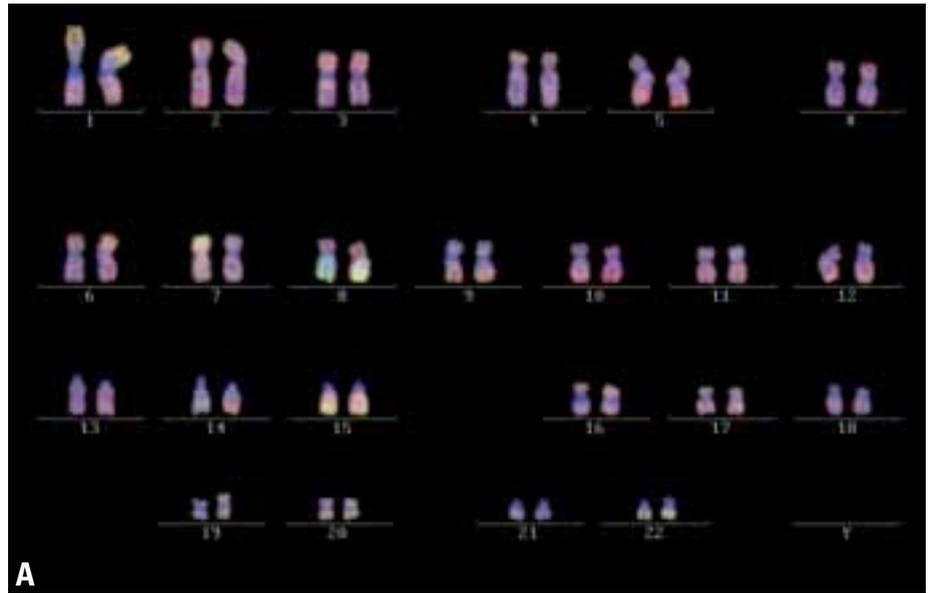
long-term survival is generally 80-90%. In those cases, in which tumour necrosis is <90% (i.e., "non-responders") and there is no change in post-operative therapy, the survival is extremely poor; usually <15%. It has been demonstrated that, with

appropriate changes in post-operative therapy, significant numbers of non-responders can be salvaged and long-term survival in this group may be greatly improved; in some cases approaching that of responders {107,160}.

Telangiectatic osteosarcoma

T. Matsuno
K. Okada
S. Knuutila

Definition

A malignant bone-forming tumour characterized by large spaces filled with blood with or without septa. The roentgenogram typically shows a purely lytic destructive process without matrix mineralisation.

ICD-O code   9183/3

Synonyms

Malignant bone aneurysm, haemorrhagic osteosarcoma, aneurysmal bone cyst-like osteosarcoma.

Epidemiology

Telangiectatic osteosarcoma is a rare subtype, accounting for less than 4% of all cases of osteosarcoma. It most frequently occurs in the second decade of life and has a male predominance (1.5:1 male/female ratio) {2155}.

Sites of involvement

Most tumours occur in the metaphyseal region of long tubular bones. The distal femoral metaphysis is the single most common anatomic site, followed by the upper tibia and proximal humerus or proximal femur {2155}. Rare cases occurring in rib {1357}, skull {2261}, sacrum {1956}, and mandible {325} are reported. Recently, multicentric telangiectatic osteosarcoma has been reported {1658}.

Clinical features / Imaging

Clinical presentation is similar to conventional osteosarcoma. One characteristic clinical finding of this tumour is pathological fracture, being present in one-fourth of the cases {1432}. Massive bone destruction may explain the high rate of pathological fracture. In laboratory data, serum alkaline phosphatase level is elevated in one-third of the cases, being less frequent than in conventional osteosarcoma {106}.

Radiographically, the lesions show purely lytic, large bone destruction without distinct surrounding bony sclerosis. The tumours commonly show extension into soft tissues. Most of the lesions are located in the metaphysis, and usually extend into the epiphysis. The tumours often expand the cortex of bone and/or disrupt the cortex. Periosteal reactions including Codman's triangle and onion skin are frequent. The finding of significant sclerosis within the lesion militates against the diagnosis of telangiectatic osteosarcoma. On magnetic resonance images, a T1-weighted image shows heterogeneous low signal intensity, and a T2-weighted image shows high signal intensity with several cystic foci and fluid-fluid level with an extraskeletal extension of the tumour, similar to aneurysmal bone cyst.

Aetiology

Aetiology of telangiectatic osteosarcoma is unknown. Several cases associated with Paget disease of bone {532,1423} or retinoblastoma {280} have been reported in the literature.

Macroscopy

On gross examination, tumours show a dominant cystic architecture in the medullary space {1357}. The cystic portion of the tumour is filled incompletely with blood clot which is described as "a bag of blood". There is no fleshy or sclerotic tumour bone formation. Extensive irregular cortical erosion and/or complete disruption of cortical continuity with soft tissue mass are occasionally seen.

Histopathology

The tumour contains blood-filled or empty spaces separated by thin septa simulating aneurysmal bone cyst. A few of the tumours are more solid and have smaller cystic spaces. Sections taken at the edges of the lesions shows permeation of

Fig. 11.27 Telangiectatic osteosarcoma. A purely lytic bone destruction is seen in the metaphysis of the distal femur. There is no surrounding bony sclerosis. Note the cortical bone destruction with periosteal reaction (Codman's triangle) and massive extension of the tumour into soft tissue.

Fig. 11.28 Gross appearance of telangiectatic osteosarcoma with dominant cystic architecture, incompletely filled with blood clots ("a bag of blood"). There is no fleshy or sclerotic tumour bone formation. The tumour permeates into the surrounding medullary canal.
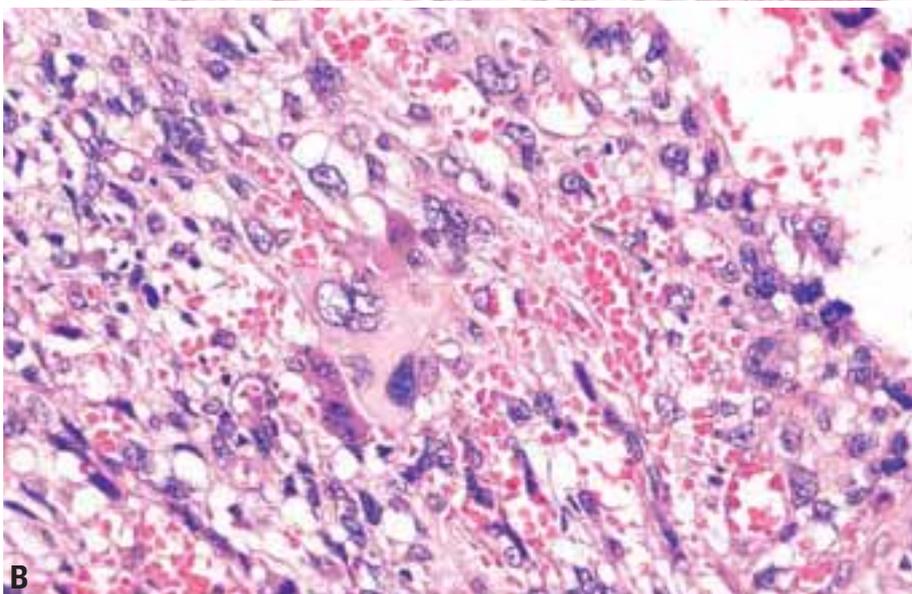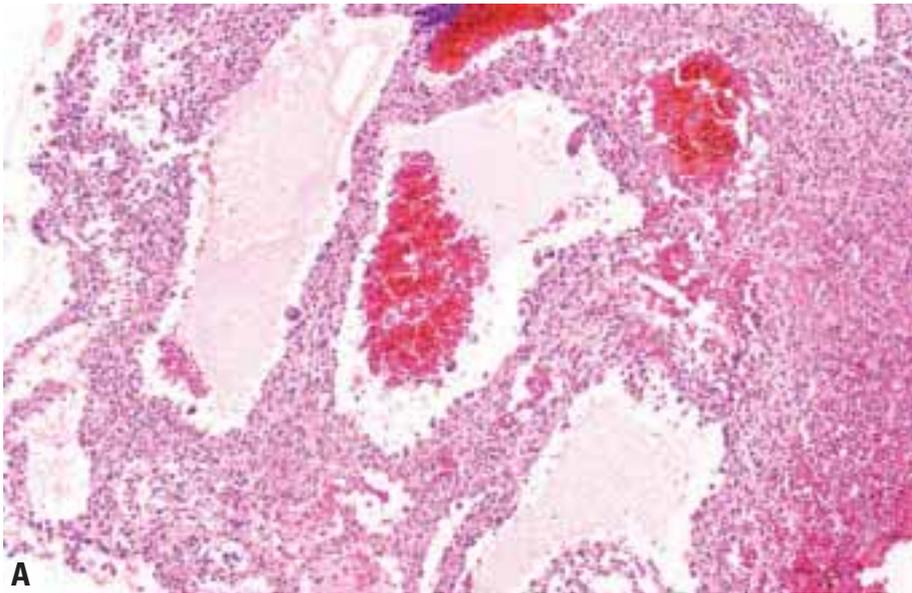
Fig. 11.29 Telangiectatic osteosarcoma. **A** Low-power microscopy reveals blood-filled or spaces separated by thin septa simulating aneurysmal bone cyst. **B** The cystic spaces are lined by benign-looking giant cells without endothelial lining. The septa are cellular and contain atypical mononuclear tumour cells.

Fig. 11.30 Telangiectatic osteosarcoma. Highly malignant tumour cells produce minimal amounts of fine, lace-like osteoid.

the tumour between pre-existing bony trabeculae. Higher-power view shows the cystic spaces lined by benign-looking giant cells without endothelial lining. The septa are cellular, containing highly malignant atypical mononuclear tumour cells. The tumour cells are hyperchromatic and pleomorphic with high mitotic activity including atypical mitoses. 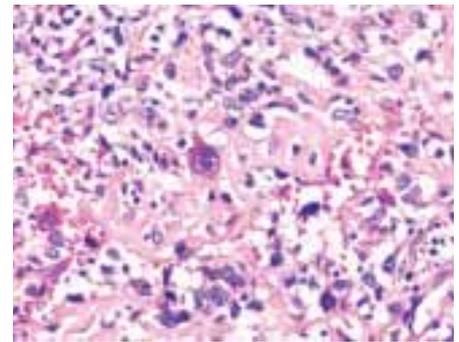Rarely, noncohesive atypical cells are seen in haemorrhagic area. The amount of osteoid varies, but usually fine, and lace-like osteoid is observed in minimal amount. In fact, even if unmistakable osteoid is not seen on multiple sections, these tumours tend to make osteoid matrix when they metastasize. Cellular septe contain many benign looking multi-nucleated giant cells, and these features may lead to a mistaken diagnosis of benign or even malignant giant cell tumour. In small biopsy samples, the only finding may be that of a blood clot with a few malignant cells.

Genetics

Cytogenetic information exists for only four cases {263, 688, 965}. Three had highly complex chromosomal changes, and one had trisomy 3 as the sole change.

Mutations in the *TP53* and *RAS* genes, LOH at the *TP53*, *CDKN2A* and *RB1* loci, and amplification of the *MDM2* and *MYC* genes seem to be rare in telangiectatic osteosarcomas {1743}.

Prognostic factors

Prognosis in the modern era is similar to conventional osteosarcoma. {106,1357, 2155}. Telangiectatic osteosarcoma is exquisitely sensitive to chemotherapy (but this may not reflect an improved survival).

Small cell osteosarcoma

R. Kalil
J.A. Bridge

Definition
An osteosarcoma composed of small cells with variable degree of osteoid production.

ICD-O code   9185/3

Synonym
Osteosarcoma with small cells resembling Ewing sarcoma.

Fig. 11.31 Small cell osteosarcoma of distal femur in a 16 year-old patient. Aggressive roentgenographic image with lytic and blastic tumour tissue at the soft tissue compartment of the lesion and permeative pattern in the bone shaft.

Epidemiology
Small cell osteosarcoma comprises 1.5% of osteosarcomas {98,184,1529}. Patients range in age from 5 to 83, although most are in the second decade. There is a slight predilection for females, 1.1 to 1 {98,184,1340,1529}.

Sites of involvement
Over half of the tumours occurs in the metaphysis of long bones. Rarely multiple skeletal sites are involved {1529, 1953}.

Clinical features / Imaging
Most patients present with pain, swelling or both {1529}.
Symptoms are usually of short duration, but may be prolonged {98,184,1340, 1529}.
Roentgenograms show an aggressive process with destruction of the cortex.

There is always a lytic component, usually admixed with radiodense areas. Mineralized tissue is seen in most tumours, either intramedullary and/or in soft tissue tumour extension strongly suggesting a specific diagnosis of osteosarcoma {98,184,1340,1529}.
Although not distinctive, the diagnosis may be suggested when an osteoblastic tumour extends well down into the shaft of the bone with a permeative pattern {568}.

Macroscopy
The gross features of small cell osteosarcoma are indistinguishable from those of conventional osteosarcoma.

Histopathology
Small cell osteosarcoma is composed of small cells associated with osteoid production. Tumours are classified according to the predominant cell pattern: round cell type or short spindle cell type {98,1529}.

Nuclear diameter of round cells can range in size from very small to medium; the smaller ones comparable to those of Ewing sarcoma and the larger ones to large cell lymphoma {98}. The cells have scanty amounts of cytoplasm.
Nuclei are round to oval and the chromatin may be fine to coarse. Mitoses range from 3 to 5/HPF.
In the less frequent spindle cell type, nuclei are short, oval to spindle, have a granular chromatin, inconspicuous nucleoli and scanty amounts of cytoplasm.
Lace-like osteoid production is always present. Particular care must be taken to distinguish osteoid from fibrin deposits that may be seen among Ewing sarcoma cells.

Immunophenotype
There is no specific immunophenotype for small cell osteosarcoma. Tumour cells may be positive for CD99, vimentin, osteocalcin, osteonectin,
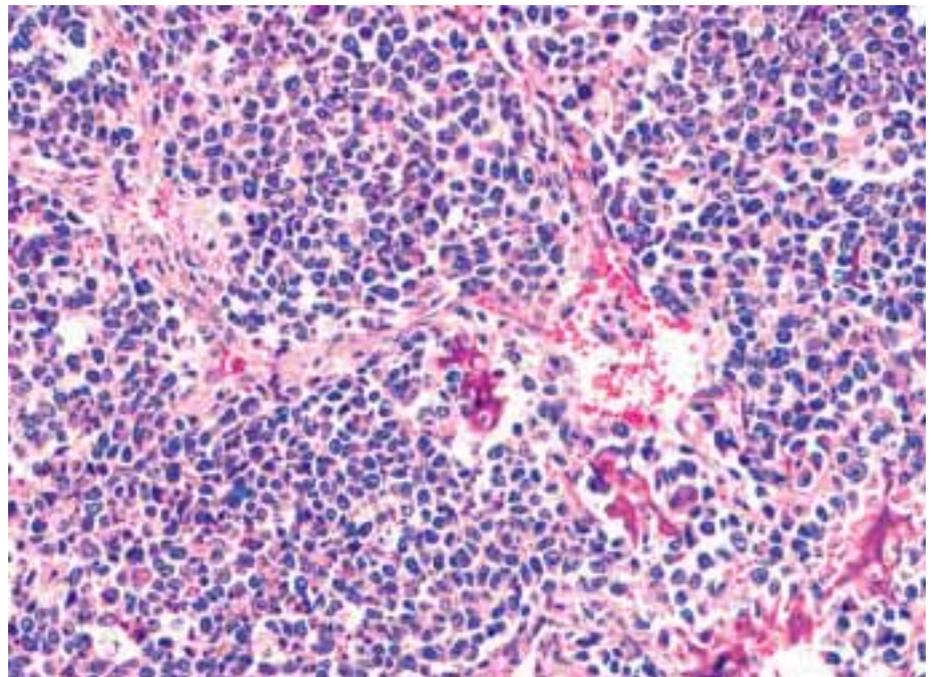

Fig. 11.32 Small cell osteosarcoma, small cell type. Osteoid production at lower right.

smooth muscle specific actin, Leu-7 and KP1 {508,513}.

Ultrastructure

Nuclei may be irregular or have smooth contours and, sometimes, contain large nucleoli. Cytoplasm is poorly differentiated and contains microfilaments, ribosomes, mitochondria and RER in variable amounts. Glycogen is present in 30% of cases. Small junctions are seen in closely apposed cells {518,2218}.

Matrix shows flocculent dense material in close apposition to tumour cell membranes, with subplasmalemmal densities in the adjacent cells, possibly a premineralisation stage of the matrix. These findings may also be seen in chondroid lesions, but never in Ewing sarcoma/PNET group of tumours {1646}

Genetics

The 11:22 translocation of the Ewing family of tumours is not seen in this neoplasm.

Prognostic factors

Aside from the fact that small cell osteosarcoma itself has a slightly worse prognosis than conventional osteosarcoma, there are no particular histological or imaging findings related to prognosis {98,1529}.
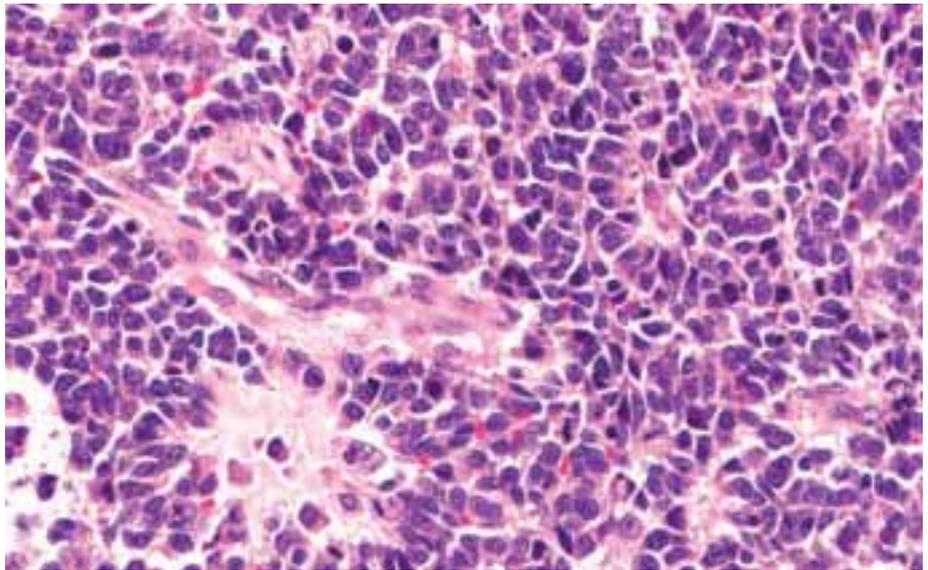

Fig. 11.33 Small cell osteosarcoma, epithelioid-like pattern. Osteoid production at lower left.
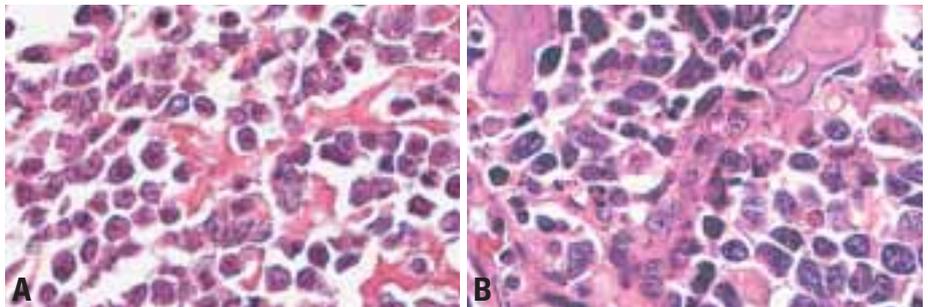

Fig. 11.34 Small cell osteosarcoma. **A** Small cell type. **B** Medium cell type.

Low grade central osteosarcoma

C.Y. Inwards
S. Knuutila

Definition
A low grade osteosarcoma that arises from the medullary cavity of bone.

ICD-O code   9187/3

Synonyms
Well differentiated intramedullary osteosarcoma, low grade intramedullary osteosarcoma, low grade intraosseous-type osteosarcoma.

Epidemiology
Low grade central osteosarcoma accounts for less than 1% of primary bone tumours and only 1-2% of all osteosarcomas {1468,2155,2158}. Males and females are equally affected. The peak incidence is in the second and third decades of life.

Sites of involvement
Approximately 80% of low grade central osteosarcomas are located in the long bones with a distinct predilection for the distal femur and proximal tibia {1186}. The femur is the most frequently involved bone (approximately 50%), followed by the tibia, which is the second most frequently involved bone. Flat bones are uncommonly affected {178,1186,2057, 2312}.

Clinical features / Imaging
Pain and / or swelling are the usual complaints. The duration of pain may be many months or even several years. The radiographic features of low grade central osteosarcoma are variable, however, they are worrisome enough to at least suggest the possibility of malignancy in most cases {345, 581,1186}. Nevertheless, there are examples where aggressive features are subtle or even impossible to detect. They tend to be large metaphyseal or diametaphyseal intramedullary tumours. It is not uncommon to see extension into the end of the bone when the epiphyseal plate is closed. Although the majority of tumours are poorly

marginated, up to one-third may show intermediate or well defined margins suggesting an indolent or benign lesion. Trabeculation and sclerosis are also common findings that reflect the indolent nature of this tumour {345}. The radiographic density is variable, however, low grade central osteosarcomas typically contain areas of heavy mineralisation with regions of amorphous, cloud-like, or fluffy mineralisation {581,1186}. Cortical destruction is the most convincing radiographic feature in support of malignancy. The majority of low grade central osteosarcomas will show some degree of cortical disruption with or without soft tissue extension. Computed tomography and magnetic resonance imaging can be quite useful in delineating the extent of the tumour and identifying cortical abnormalities that are not evident on plain films.

Fig. 11.35 Low grade central osteosarcoma. Mixed lytic and sclerotic lesion involving the distal third of the tibial diaphysis and metaphysis associated with expansion, suggesting a benign or low grade tumour.

Macroscopy
The cut surface of a low grade central osteosarcoma shows a grey-white tumour with a firm and gritty texture arising from within the medullary cavity. Cortical destruction with or without a soft tissue mass may also be seen.

Histopathology
Low grade central osteosarcoma is composed of a hypo- to moderately cellular fibroblastic stroma with variable amounts of osteoid production. The collagen-producing spindle cells are arranged in interlacing bundles that permeate surrounding pre-existing bony trabeculae and bone marrow similar to that of desmoplastic fibroma. While the tumour cells show some degree of cytological atypia, it is usually subtle. Nuclear enlargement and hyperchromasia are generally evident. Occasional mitotic figures are almost always identified.

Fig. 11.36 Low grade central osteosarcoma. Coronal T2 weighted MRI illustrates extensive destruction of the distal third of the tibia and extraosseous soft tissue extension. In contrast, fibrous dysplasia typically would not have such aggressive radiographic features.

Variable patterns of bone production are found in low grade central osteosarcoma. Some tumours contain irregular anastomosing, branching, and curved bone trabeculae simulating the appearance of woven bone in fibrous dysplasia {715}. Others contain moderate to heavy amounts of bone present as long longitudinal seams of lamellar-like bone resembling parosteal osteosarcoma. Small scattered foci of atypical cartilage are occasionally seen. In addition, benign multinucleated giant cells have been reported in up to 36% of low grade central osteosarcomas. In 15-20% of cases progression to high grade spindle cell sarcoma occurs, most commonly at the time of tumour recurrence.

Genetics
The results of a CGH study indicate recurrent gains in minimal common regions at 12q13-14, 12p, and 6p21 {2088}. The low number of chromosomal imbalances in low grade central osteosarcoma is in sharp contrast with the complex aberrations seen in high grade osteosarcoma.
MDM2, *CDK4*, and *SAS* at the 12q13-15 amplicon have been reported to be amplified at frequencies of 35%, 65% and 15%, respectively {1747}.

Prognostic factors
Low grade central osteosarcoma behaves in a much more indolent fashion than conventional osteosarcoma. Nevertheless, it is associated with a high incidence of local recurrence after inadequate resections. Recurrences may exhibit a higher histological grade or
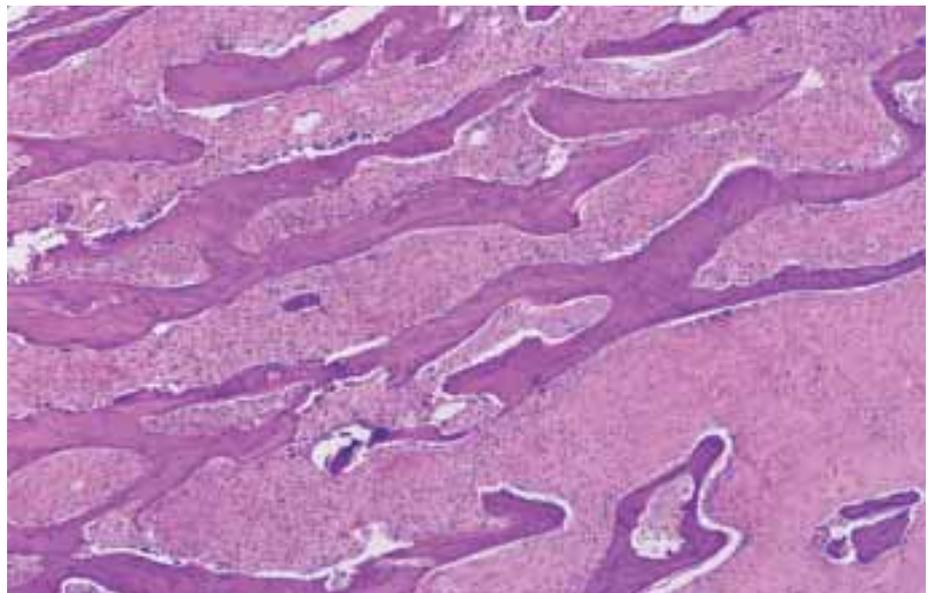

Fig. 11.37 Low grade central osteosarcoma. At low magnification, long, parallel seams of bone surrounded by a hypocellular spindle cell stroma are seen, resembling the pattern of parosteal osteosarcoma.
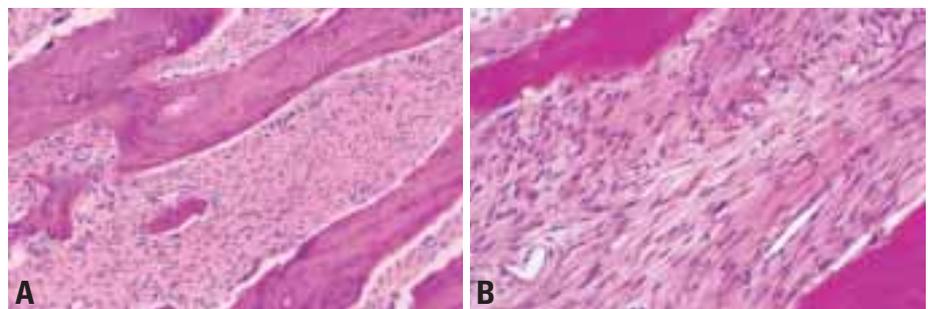

Fig. 11.38 Low grade central osteosarcoma. **A** Irregularly shaped spicules of bone surrounded by a spindle cell stroma with minimal atypia. Distinction fibrous dysplasia requires radiographic correlation. **B** At higher magnification, scattered cells with nuclear enlargement and hyperchromasia occur.

dedifferentiation with the potential for metastases {345,999,1186}. It is metastatic tumour from the higher grade recurrence that can lead to death in patients with low grade central osteosarcoma.

Secondary osteosarcomas

M. Forest
G. De Pinieux
S. Knuutila

Definition
Secondary osteosarcomas are bone forming sarcomas occurring in bones that are affected by preexisting abnormalities, the most common being Paget disease and radiation change, and rarely various other disorders.

ICD-O code   9180/3

Paget osteosarcoma

ICD-O code   9184/3

Synonym
Paget sarcoma.

Epidemiology
Incidence of sarcomatous changes in Paget disease is estimated to be 0.7-0.95%, and osteosarcomas represent 50-60% of Paget sarcomas {867,989, 1879,2263}. In most series, Paget osteosarcoma is more common in men (ratio 2:1), with an overall median age of 64 years: it accounts for more than 20% of osteosarcomas in patients older than 40 years of age.
This complication is usually observed in patients with widespread Paget disease (70%), but can occur in monostotic Paget disease as well.

Sites of involvement
Any bone affected by Paget disease has the potential to undergo sarcomatous change. Except for the high frequency in the humerus and the lower frequency in the vertebrae, osteosarcoma has the same distribution as uncomplicated Paget disease.
Approximately, two-thirds are seen in large limb bones (femur, humerus, tibia), one-third in the flat bones (pelvis, skull and scapula). 10-17% of all Paget osteosarcomas involve the skull.
Most tumours arise in the medulla; few are located near the periosteal surface of bone.
Multifocal osteosarcoma occurs in 17% of cases, usually involving the femur and the skull, superimposed on polyostotic Paget disease and may represent multiple primary tumours or metastatic spread.

Clinical features / Imaging
Clinical symptoms are a change in pain pattern, a swelling, and occasionally pathological fracture (12-20%, more commonly in the femur). Often, there is an elevation of alkaline phosphatase levels above those usually seen in Paget disease. On imaging, tumours with a lytic pattern are more frequent than a blastic or sclerotic appearance {2263}, with cortical disruption and a soft tissue mass. The affected bone shows radiographic features of Paget disease.

Macroscopy
The gross appearance is variable reflecting the patterns seen for conventional osteosarcoma. The non-neoplastic bone shows thickened bone trabeculae and cortical thickening.

Histopathology
Paget osteosarcomas are high grade sarcomas, mostly osteoblastic or fibroblastic osteosarcomas. A great number of osteoclast-like giant cells may be found {1879}. Telangiectatic and small cell osteosarcomas have been reported {2263}.

Genetics
Recent evidence suggests that predisposition to Paget disease may have a genetic component linked to a region of chromosome arm 18q {370,811,883}. In a study of 96 sporadic osteosarcomas frequent LOH was seen at chromosome arm 18q {1546}.

Prognostic factors
The prognosis is poor, especially for tumours located in the pelvic bones and the skull, with a five-year overall survival rate of 11% {2263}. Survival is shorter in cases of multifocal disease. Metastases are present in 25% of patients, at initial presentation (predominantly pulmonary or bone metastases).
There is a small fraction of long-term survivors after aggressive therapy (age less than 60 years, monostotic Paget disease, sarcomas arising in long bones) {867}.

Postradiation osteosarcoma

ICD-O code   9180/3

Synonyms
Postradiation sarcomas, radiation induced sarcoma.

Epidemiology
They constitute 3.4-5.5% of all osteosarcomas and 50-60% of radiation-induced sarcomas. It is estimated that the risk of developing osteosarcoma in irradiated bone is 0.03-0.8% {996,1334}.
Children treated with high-dose radiotherapy and chemotherapy are at the greatest risk. The prevalence of postradiation osteosarcomas is increasing as children survive treatment of their malignant disease {145,2190}.

Sites of involvement
Postradiation osteosarcoma can develop in any irradiated bone, but the most common locations are the pelvis and the shoulder region.

Clinical features / Imaging
The criteria for the diagnosis are well established: the affected bone may have been normal, contain a biopsy proven benign tumour or non-bone forming malignancy; history of prior radiation therapy and tumour developing in the path of the radiation beam; a symptom-free latent period (frequently long but may be as short as two years); a histologically proven osteosarcoma {996}.
The latent period is generally long (median of 11 years), and inversely related to the radiation dosage. Radiation doses are usually greater than 20 Gy; most sarcomas occur in association with doses of approximately 55 Gy.

Common symptoms are pain and swelling.

On imaging, the tumours are densely sclerotic or lytic lesions with a soft tissue mass. Radiation osteitis is present in about 50% of cases (trabecular coarsening and lytic areas in the cortex). Multicentric osteosarcomas have been reported as well as a few parosteal osteosarcomas {2115}.

Macroscopy
Similar to conventional osteosarcoma.

Histopathology
High grade osteosarcomas predominate. Histological changes of radiation osteitis may be present.

Genetics
Cytogenetic and DNA copy number changes are complex and similar to those in conventional osteosarcomas {1427}. Postradiation osteosarcomas frequently exhibit 3p loss cytogenetically {1427}. Sporadic and postradiation osteosarcomas differ in copy number changes by comparative genomic hybridisation {2094}. Whereas gains were more frequent than losses in sporadic tumours, the reverse was seen in radiation-associated sarcomas. Further-more, loss of 1p was rare (3%) in sporadic cases, but frequent (57%) in radiation-associated tumours. In one study, a high (58%) frequency of *TP53* mutations was found {1532}.

Prognostic factors
The 5-year-cumulative survival rate is of 68.2% for patients with extremity lesions, 27.3% for patients with axial lesions {1005}.
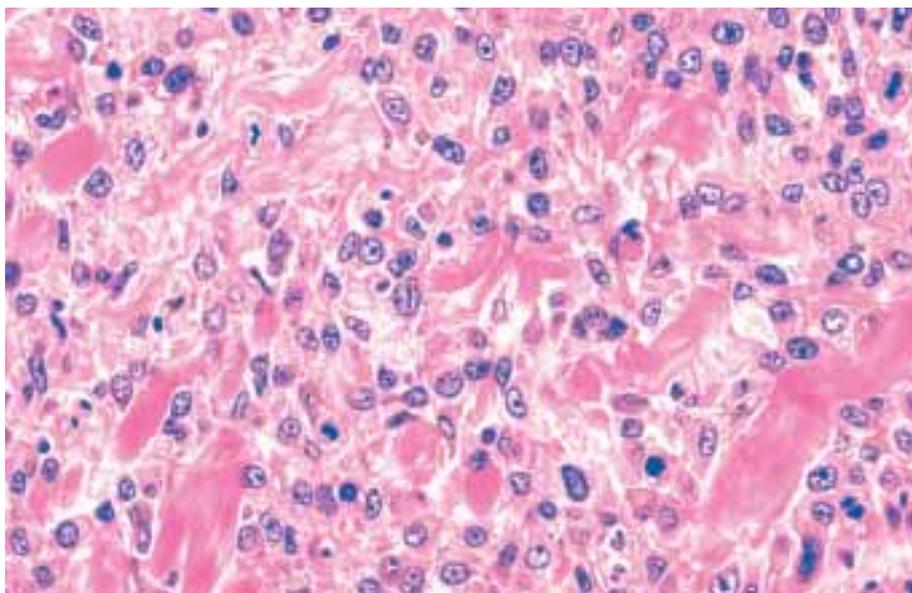The prognosis is worse for pelvic, vertebral and shoulder girdle locations.

Fig. 11.39 Osteoblastic osteosarcoma associated with fibrous dysplasia of the femur.

Osteosarcoma in the course of various bone diseases

Osteosarcoma has been reported in association with a variety of conditions affecting bone. Many of the reports are of rare associations. The three associations deserving special attention are bone infarct, prosthetic joint and fibrous dysplasia. Infarct associated sarcomas most commonly show the histological pattern of malignant fibrous histiocytoma, however a minority are osteosarcomas. It has been suggested that the malignant transformation in large and multiple infarcts arises from the reparative process of osteonecrosis, but this view is disputed {503,2122}. Malignant tumours have been reported at the site of prosthetic replacements as well as at the site of prior internal fixation. The majority of such cases have shown a malignant fibrous histiocytoma morphology, but six cases of osteosarcoma in association with total hip replacements have been reported {271}. Osteosarcoma associated with fibrous dysplasia is most common in the setting of Albright syndrome {992,2074}. Many of the reported cases of osteosarcoma arising in fibrous dysplasia have also been complicated by radiation therapy {992,1822,2074}. There is nothing unique about the pathology or prognosis of secondary osteosarcoma arising in association with bone infarct, prosthesis or fibrous dysplasia.

Parosteal osteosarcoma

K.K. Unni
S. Knuutila

Definition
Parosteal osteosarcoma is a low grade osteosarcoma which arises on the surface of bone.

ICD-O code   9192/3

Synonyms
Juxtacortical osteosarcoma, juxtacortical low grade osteosarcoma.

Epidemiology
Although rare, parosteal osteosarcoma is the most common type of osteosarcoma of the surface of bone. It accounts for about 4% of all osteosarcomas. There is a slight female predominance and most patients are young adults, about 1/3 occurs in the 3rd decade of life {1599}.

Sites of involvement
About 70% involve the surface of the distal posterior femur. The proximal tibia and proximal humerus are also relatively commonly involved. Flat bones are uncommonly affected.

Clinical features / Imaging
Patients generally complain of a painless swelling; inability to flex the knee may be the initial symptom. Some patients complain of a painful swelling.
Roentgenograms show a heavily mineralised mass attached to the cortex with a broad base. The tumour has a tendency to wrap around the involved bone. Computerized tomograms and magnetic resonance images are useful in evaluating the extent of medullary involvement. The outermost portions of the tumour are usually less mineralised {185}. In some cases there may be an incomplete lucency between the tumour and the underlying bone.

Macroscopy
Parosteal osteosarcoma presents as a hard lobulated mass attached to the underlying cortex. Nodules of cartilage may be present. Occasionally, the cartilage will be incomplete cap-like, covering the surface and thus suggesting a diagnosis of osteochondroma. The periphery may be softer and seen to invade skeletal muscle. Invasion of the bone marrow may be seen in 25% of the cases. Soft, fleshy areas, if present, suggest dedifferentiation.

Histopathology
Parosteal osteosarcoma consists of well formed bony trabeculae seen in a hypocellular stroma. The bony trabeculae are arranged in a parallel manner and simulate normal bone {1025}. The trabeculae may or may not show osteoblastic rimming. The intertrabecular stroma is hypocellular. The spindle cells in the stroma show minimal atypia. In about 20% of the cases, the stroma is more cellular and the spindle cells show moderate atypia. About 50% of the tumours will show cartilaginous differentiation. This may be in the form of hypercellular nodules of cartilage

Fig. 11.40 Parosteal osteosarcoma. Plain X-ray shows a heavily mineralised mass attached to the posterior aspect of the distal femur not involving

Fig. 11.41 Parosteal osteosarcoma Anteroposterior view of the knee showing a lobulated, heavily mineralised mass attached to the cortex.

Fig. 11.42 Parosteal osteosarcoma. The formation of large, heavily mineralised masses surrounding the involved bone is common.

Fig. 11.43 Parosteal osteosarcoma. **A** Although much of the tumour is on the surface of the proximal tibia, there is clear-cut marrow involvement. **B** Gross specimen showing large amounts of chondroid differentiation. The marrow cavity, which is free of involvement, is seen at the bottom.

Fig. 11.45 Dedifferentiated parosteal osteosarcoma. The appearance of the lesion on the surface is that of a heavily mineralised mass, typical of parosteal osteosarcoma. There is a very destructive appearing lesion within the medullary cavity, which was the dedifferentiated component.

Fig. 11.46 Parosteal osteosarcoma involving the bones of the forearm. Much of the tumour has the appearance of classical parosteal osteosarcoma with fibrous areas. However, between the bones, there are soft areas representing dedifferentiation.
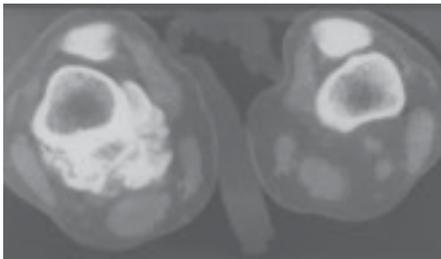

Fig. 11.44 Parosteal osteosarcoma. CT shows a mineralising mass. The marrow is free of involvement. This is the same case as shown in Fig. 11.42.

within the substance of the neoplasm or as a cap on the surface. When present, the cartilage cap is mildly hypercellular, and the cells show mild cytological atypia and lacks the 'columnar' arrangement seen in osteochondromas. There is, however, enchondral ossification as seen in osteochondroma. Unlike fatty and haematopoietic marrow, as seen in osteochondromas, there is spindle cell proliferation between the bony trabeculae. Large areas devoid of bone and rich in collagen similar to

desmoplastic fibroma may be present. About 15% of the tumours will show high grade spindle cell sarcoma (dedifferentiation). This may be at the time of the original diagnosis or, more often, at the time of recurrence {2289}. The areas of dedifferentiation may be osteosarcoma, fibrosarcoma or malignant fibrous histiocytoma.

Immunophenotype
There are no specific features helpful in diagnosis.
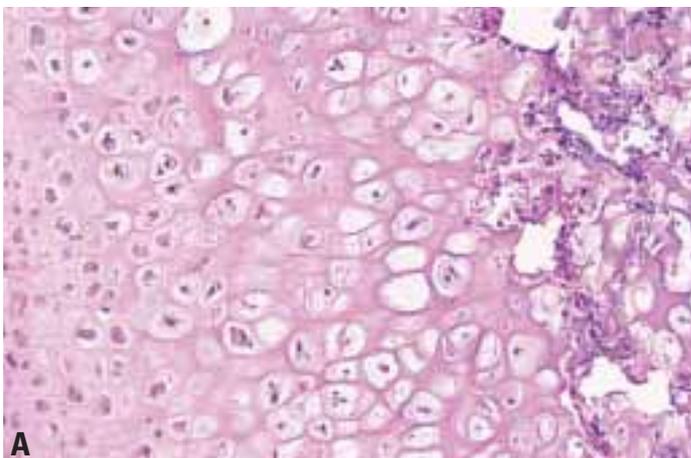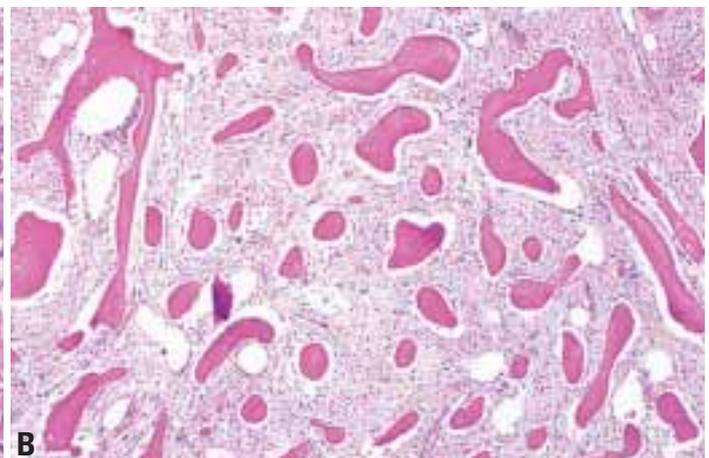
Fig. 11.47 Parosteal osteosarcoma. **A** Extensive cartilagineous differentiation is not uncommon. **B** Well-formed bony trabeculae in a hypocellular spindle cell stroma.
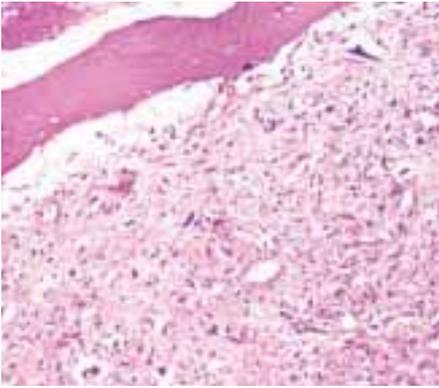
Fig. 11.48 Parosteal osteosarcoma. Area of dedifferentiation with pleomorphic appearing nuclei.
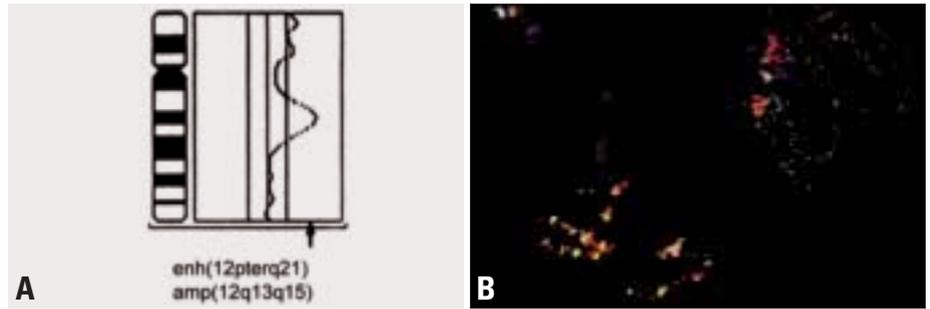

Fig. 11.49 Parosteal osteosarcoma. **A** CGH profile indicating gain at 12pterq21 with amplification 12q13q15. The arrow indicates the cutoff value of 1.5 for amplification (from J. Szymanska et al. {2071}). **B** MS-FISH from the same tumour shows a normal chromosome 12 (top left), ring, and large marker chromosome. FISH shows amplification of *KRAS2*, *CDK4*, and *MDM2*, respectively, whereas no copy number increase could be demonstrated on ETV6 (from D. Gisselsson et al. {796}).

Genetics

Chromosomal alterations in parosteal osteosarcomas are different from those in conventional osteosarcomas. Parosteal osteosarcomas are characterized by one or more supernumerary ring chromosomes, often as the sole alteration {1428, 1634,1961}. CGH studies indicate gain at 12q13-15 as the minimal common region of amplification in the rings {2071}.

The *SAS*, *CDK4*, and *MDM2* genes have been shown to be coamplified and over-expressed in a great proportion of cases {2305} and the incidence of the amplifications of these genes seems to be essentially lower in classical high grade osteosarcoma. Mutations in *RB1* {2208} or microsatellite instability {2087} have not been found to be present in parosteal osteosarcoma.

Prognostic factors

Prognosis is excellent with 91% overall survival at 5 years {1599}. Marrow invasion and moderate cytological atypia do not predict a worse prognosis. If incompletly excised the tumour may reccur and dedifferentiate. The presence of such dedifferentiated areas is associated with a prognosis similar to that of conventional osteosarcoma.

Periosteal osteosarcoma

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Definition

Periosteal osteosarcoma, is an intermediate grade chondroblastic osteosarcoma arising on the surface of bone.

ICD-O code   9193/3

Synonyms

Juxtacortical chondrosarcoma, juxtacortical chondroblastic osteosarcoma.

Epidemiology

Periosteal osteosarcoma {644, 2013, 2155} accounts for less than 2% of all the osteosarcomas {2155,2156}.
Of the surface osteosarcomas, it is more common than high grade surface osteosarcoma, but about one-third as common as parosteal osteosarcoma {644,1600}. The peak incidence of periosteal osteosarcoma is in the second and third decades of life. There is a slight male predominance.

Sites of involvement

Periosteal osteosarcoma has a distinct predilection for the diaphysis or diaphyseal-metaphyseal area of the long bones, with the tibia and femur the most commonly involved bones, followed by the humerus {179,644,874,1792,2013, 2155,2156}. In the long bones, this tumour usually affects the anterior, lateral or medial portions of the shaft, but occasionally may surround the entire circumference of the bone. It can also involve the clavicle, pelvis, mandible, ribs and cranium {179,644,874,1792,2013,2155, 2156}. The case of a bilateral metachronous lesion has also been reported {979}.

Clinical features / Imaging

A painless mass or limb swelling is the most common initial complaint with pain or tenderness later developing in the affected area {179,644,2013,2156}. In most patients the complaints have lasted for less than 1 year and more than half of the patients have been symptomatic for about 6 months {644}.

This tumour, arising on the surface of a bone, displays nonhomogeneous, calcified spiculations that are disposed perpendicular to the the cortex and give an overall sunburst appearance. The lesion decreases in density from the cortical base to the surface, where the tumour has a relatively well demarcated advancing margin. Commonly, the cortex appears thickened as result of the production of a heavily ossified matrix. The bone spicules are variously calcified with fine and coarse calcification. A Codman's triangle is frequently present. Computed tomography and magnetic resonance imaging are very important in the evaluation of tumour size, integrity of the cortex, soft tissue extension and relationship to the neurovascular bundle.

Macroscopy

The tumour arises from the bone surface and may involve part of the bone or the entire circumference {644,2013, 2155,2156}. It has a conspicuous fusiform appearance when it involves the entire circumference of the shaft of a bone. A spiculated pattern arising perpendicular to the cortex is commonly seen grossly, with the longest spicules situated at the centre of the lesion; these

Fig. 11.50 Periosteal osteosarcoma. **A** Plain radiograph of femur shows a large, fusiform surface mass. Perpendicular to the cortex, there are multiple, parallel thin columns of calcified matrix. Focal lytic areas are also present. **B** The upper shaft of the tibia displays a well demarcated tumour arising from the cortical surface of the bone. Fluffy calcifications are present.
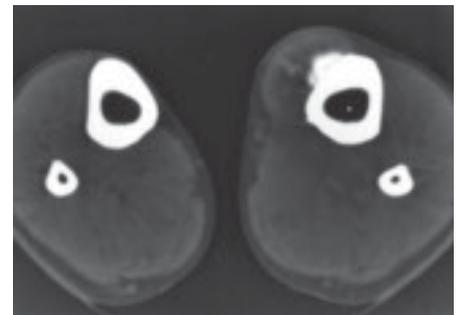

Fig. 11.51 Periosteal osteosarcoma. CT scans show a heavily ossified tibial mass arising from the cortex, covered by a larger, focally or minimally calcified soft tissue mass component.
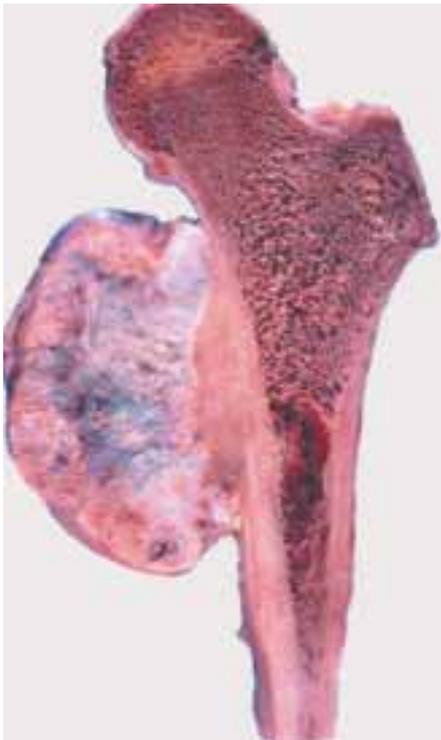
Fig. 11.52 Periosteal osteosarcoma of proximal femur. A broad based, mushroom-like, large surface tumour depicting a thickened ossified area blending in with the cortex. Covering this area there is a large soft tissue component depicting seemingly two layers of tissue. One is whitish-cartilaginous and the other is tan-yellow.

spicules gradually taper from the centre to the outer extremes of the lesion in all directions. A solid ossified mass is commonly seen adjacent to the cortex, while the periphery tends to be uncalcified or minimally calcified. Part of the tumour usually has the glistening, greyish appearance typical of cartilage. The advancing margin is generally well delineated by a capsule/ pseudocapsule that is the product a thickened periosteum. The bony mass merges imperceptibly with the cortex at its base, giving the appearance of a thickended cortex.

Histopathology

Histologically, periosteal osteosarcoma has the appearance of a moderately differentiated chondroblastic osteosarcoma {2155,2156}. The ossified mass is generally found arising from the cortex, to which it is intimately attached, and it is made up of relatively mature bone that has resulted from endochondral ossification. The cartilaginous component predominates, but elements of intermediate grade osteosarcoma are invariably present. The cartilaginous component may show varying degrees of cytological atypia.

The matrix may be myxoid. The bony spicule consists of elongated vascular cores surrounded by a calcified, osseous or chondro-osseous matrix, which in turn may be surrounded by non-calcified cartilaginous growth. The periphery of the tumour generally shows no calcification and is made up of fascicles of spindle cells. In these areas, there may be significant mitotic activity with abnormal figures. These areas may also contain lace-like osteoid.


Fig. 11.53 Periosteal osteosarcoma of femur. These cross sections of the shaft of the femur depict a surface tumour involving the entire circumference of the bone. Calcified spicules impart a sunburst appearance. A glistening non-calcified tumour component covers the entire tumour. The medullary cavity is intact.

Genetics

Among four reported cases, one had +17 as the sole change {263}, and three had complex karyotypic changes {795, 965,2090}.

Prognostic factors

Although periosteal osteosarcoma is associated with a better prognosis than conventional osteosarcoma, it is still a malignant tumour with a tendency to recur and to metastasise {644,2013, 2155,2156}. Medullary involvement by the tumour may portend poorer prognosis. A recurrence rate of 70% has been reported for patients who underwent marginal excision {1341}. The rate of metastasis has been reported to be about 15% {644,1792,2155,2156}.
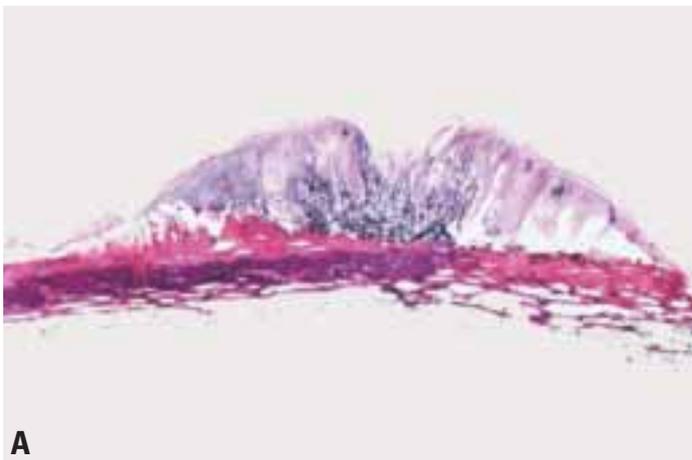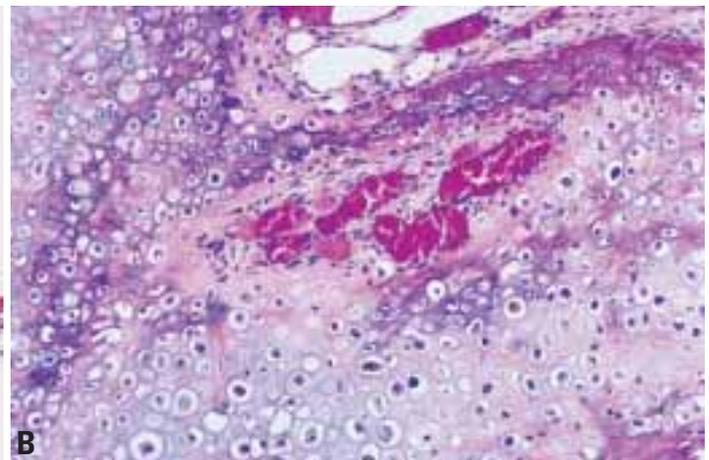
Fig. 11.54 Periosteal osteosarcoma. **A** A cross section of the tibial tumour which shows an ossified mass blending with and thickening the cortex and covered by an uncalcified component. **B** Typical appearance of chondroblastic grade 3 osteosarcoma. There are lobules of malignant-appearing cartilage with bone formation in the centre of the lobules.

High grade surface osteosarcoma

L. Wold
E. McCarthy
S. Knuutila

Definition

A high grade bone-forming malignancy which arises from the surface of the bone.

ICD-O code   9194/3

Synonyms

Juxtacortical osteosarcoma, surface osteosarcoma.

Epidemiology

High grade surface osteosarcoma comprises less than one percent of all osteosarcomas. The peak incidence is in the second decade, and the age distribution of patients at the time of diagnosis is similar to conventional osteosarcoma. There is a slight male predilection.

Sites of involvement

The femur is most commonly affected followed in frequency by the humerus and tibia.

Clinical features / Imaging

Patients with high grade surface osteosarcoma most commonly present with a mass and/or pain in the region of the tumour. The tumour radiographically presents as a surface, partially mineralised, mass extending into the soft tissues. The underlying cortex is commonly partially destroyed, and periosteal new bone is commonly present at the periphery of the tumour. Cross sectional imaging may show minimal medullary involvement, but the tumour is most commonly relatively well circumscribed at its soft tissue margin. The pattern of mineralisation present is variable depending upon the amount of chondroid and osseous matrix produced by the tumour.

Macroscopy

The tumour is situated on the surface of the affected bone and commonly erodes the underlying cortical bone. Tumours vary in consistency depending upon whether they are predominantly osteoblastic, chondroblastic, or fibroblastic. However, all tumours will have "soft" areas in them, a feature which helps separate this tumour from parosteal osteosarcoma. The surface of the tumour is commonly multilobulated, and the colour varies depending upon the amount of chondroid matrix, haemorrhage, and necrosis present.

Histopathology

These tumours show the same spectrum of features seen in conventional osteosarcoma. Regions of predominantly osteoblastic, chondroblastic, or fibroblastic differentiation may predominate. However, all tumours will show high grade cytological atypia and lace-like osteoid as seen in conventional osteosarcoma. Many tumours show regions rich in cytologically atypical spindle cells

Fig. 11.55 High grade surface osteosarcoma in the middle portion of the humerus. The lesion is mineralised where it is attached to the bone but there is also a large unmineralised soft tissue mass.
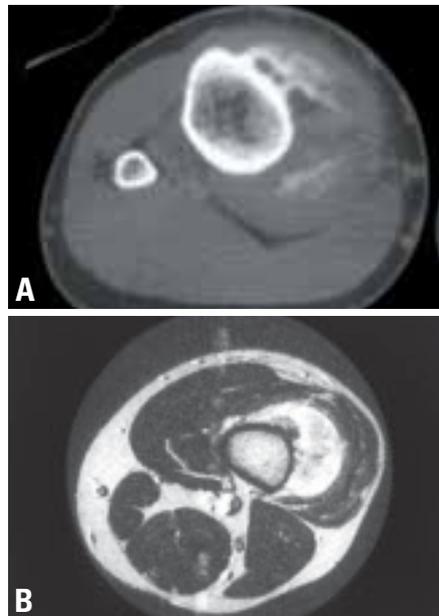

Fig. 11.56 High grade surface osteosarcoma. **A** CT showing focal mineralisation and a large unmineralised soft tissue component. **B** MRI scanning can be very sensitive in evaluating whether there is medullary involvement in surface tumours of bone. There is no medullary involvement in this case.

Fig. 11.57 High grade surface osteosarcoma involving the distal femur. The tumour is soft and fleshy.

with brisk mitotic activity evident in these regions. The pattern of osteoid production and the high grade cytological atypia evident in high grade surface osteosarcoma help to separate it from parosteal osteosarcoma. High grade surface osteosarcomas which show predominant chondroblastic differentiation may be confused with periosteal osteosarcoma. The degree of cytological atypia is greater in high grade surface osteosarcoma than in periosteal osteosarcoma, and the tumours also generally show larger regions of spindle cell morphology. Unlike same dedifferentiated parosteal osteosarcoma, low grade regions of tumour are not identified in high grade surface osteosarcoma.

Immunophenotype
Similar to conventional osteosarcoma.

Prognostic factors
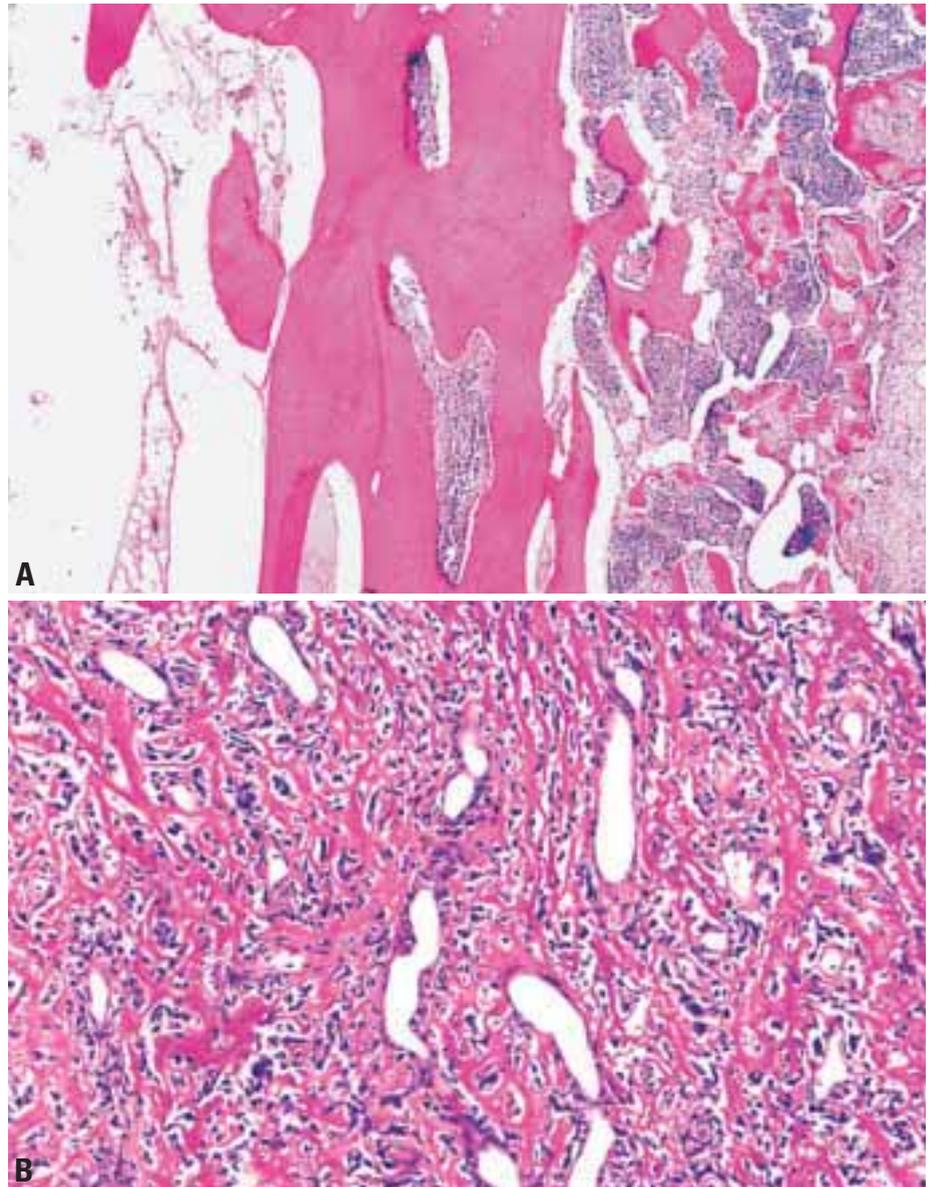As in conventional osteosarcoma the major prognostic feature is the response to chemotherapy.

Fig. 11.58 High grade surface osteosarcoma. **A** The tumour produces large amounts of bone (right). The cortex (middle) and the medullary cavity (left) are uninvolved. **B** Wide vascular spaces bear resemblance to osteoblastoma, but the high grade cytologic atypia and the compact nature of the spindle cell proliferation help to distinguish high grade surface osteosarcoma from osteoblastoma.