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Surface bone sarcomas: an update on current clinicopathological diagnosis and treatment

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- Surface bone sarcomas are rare malignant bone tumours. Osseous and cartilaginous surface bone sarcomas are the most common, with parosteal and periosteal osteosarcomas, periosteal chondrosarcomas and secondary peripheral chondrosarcomas being the most frequent.
- Their clinical symptoms are non-specific and include pain for several months, swelling and limited range of motion of the adjacent joints.
- Prompt diagnosis is important, as biological behaviour, imaging and histopathologic characteristics, treatment and prognosis differ considerably from their conventional intramedullary counterparts. Moreover, their imaging characteristics are not infrequently non-characteristic and may be misinterpreted as juxtacortical benign lesions leading to incorrect diagnosis and treatment, with life-threatening repercussions. Molecular studies and histopathological sampling are essential for accurate diagnosis.
- There are still numerous issues regarding the biology, pathophysiology and treatment options of these entities due to their rarity.

Keywords: juxtacortical tumours; surface bone tumours

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Introduction

Surface bone tumours are neoplasms situated near the bone cortex. They are classified into five different types: osseous, cartilaginous, fibrous, lipomatous and metastatic tumours. The most common types are those producing bone and cartilage.[1–4] Osseous surface bone tumours include benign tumours such as osteoma, osteoid osteoma and osteoblastoma, and the malignant category of surface osteosarcomas (parosteal, periosteal and high-grade osteosarcoma), while the cartilaginous surface tumour category comprises benign tumours such as bizarre parosteal osteochondromatous proliferation (BPOP), periosteal chondroma, chondromyxoid fibroma, osteochondroma and malignant tumours such as periosteal chondrosarcoma and secondary peripheral chondrosarcoma. There are also exceedingly rare descriptions of periosteal Ewing sarcoma.[5]

Regarding clinical symptoms, these are non-specific and include pain, local swelling and limited range of motion of the adjacent joint. Pain is usually present for several months. Although these lesions have similarities to their intramedullary counterparts, their location modifies their imaging characteristics. Imaging characteristics can be either non-characteristic and may be misinterpreted as juxtacortical benign lesions such as myositis ossificans, stress fracture, subperiosteal haematoma or abscess, osteochondromas, or BPOP, leading to wrong diagnosis with devastating consequences. This article aims to discuss the clinicopathological and imaging features, the current treatment and the prognosis of juxtacortical bone tumours.

Surface osteosarcomas

Surface osteosarcomas are distinct clinicopathological entities of osteogenic tumours rather than a subtype of intramedullary conventional osteosarcoma. Prompt diagnosis is important as their biological behaviour, imaging and histopathologic characteristics, treatment and prognosis differ considerably from those of conventional intramedullary osteosarcoma.

Regarding the terminology, the recent World Health Organization (WHO) classification for bone tumours does

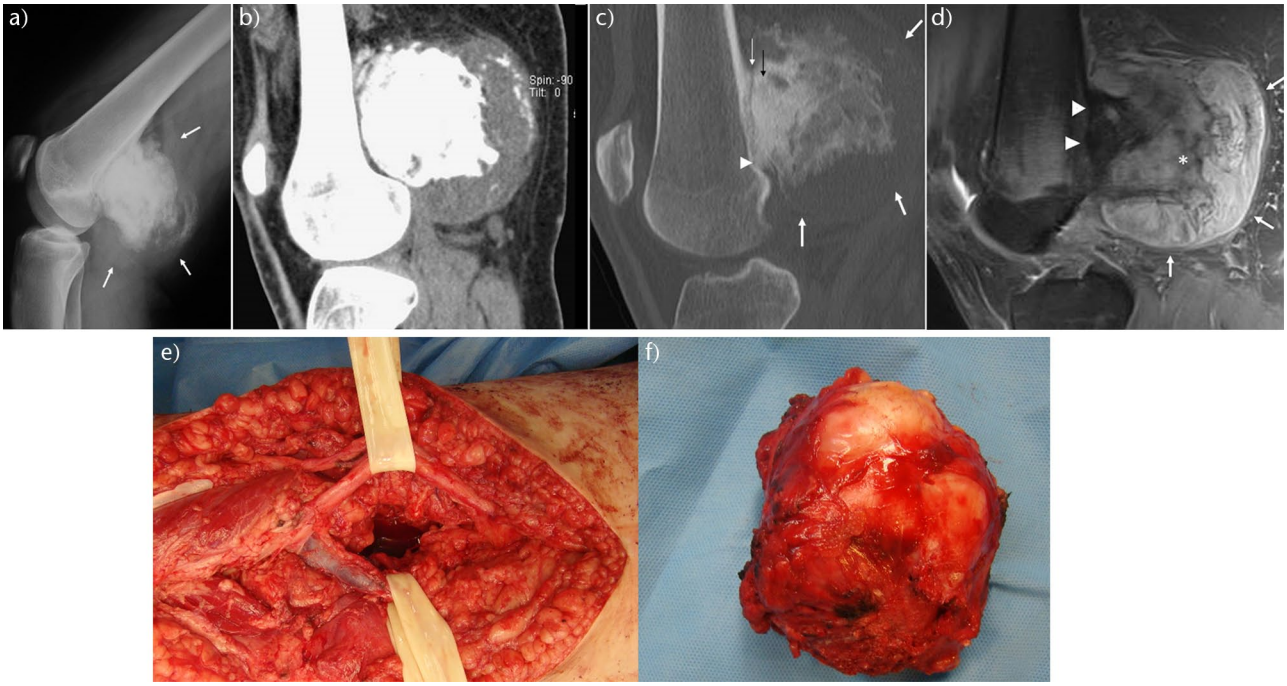

Fig. 1 Parosteal osteosarcoma (PAO) in a 16-year-old female. (A) Lateral radiograph of the knee shows a typical PAO as a large, ossified opacity attached to the posterior cortex of the distal femoral metaphysis. Ossification is mainly central (B&C). Sagittal computerized tomography (CT) reformatted images (B: soft tissue window and C: bone window) exhibit with superior detail the thin separation between the tumour and the intact femoral cortex ('cleft sign' – thin arrow) as well as the ossified thick stuck (arrowhead). Lytic areas are seen within the ossified mass (black arrows) which is surrounded by a thick hypodense rim (arrows) representing cartilaginous tissue. (D) A fat-suppressed T2w magnetic resonance (MR) image shows the densely ossified stuck centrally (arrowheads) the inhomogenous moderately T2 hyperintense mass in the middle (asterisk), and the hyperintense cartilaginous component in the periphery (white arrows). There is no intramedullary extension of the tumour. (E) Intraoperative photograph of the popliteal fossa after the tumour resection. (F) Resected specimen.

not recommend the term juxtacortical osteosarcomas,[6] while the Union for International Cancer Control (UICC) TNM classification (T =tumor extent, N=lymph nodes, M=distant metastases) of malignant tumours does not consider the TNM staging system for bone tumours suitable for surface osteosarcomas.[7] However, other staging systems, such as the American Joint Committee on Cancer (AJCC) TNM system include these tumours in the bone staging system.[8]

Surface osteosarcomas comprise approximately 4–12% of all osteosarcomas.[5,9] They comprise three distinct entities, namely the parosteal (PAO), the periosteal (PEO) and the high-grade surface osteosarcoma (HGSO).[6] The parosteal and periosteal subtypes are more common than HGSO. They tend to affect older patients compared to their conventional intramedullary counterparts.[5] They arise on the outer cortical surface; however, the presence of intramedullary (IM) extension does not rule out a surface tumour as a small percentage have IM extension. They may invade or displace neurovascular bundles, tendons or ligaments in close proximity.[2] Okada et al found that PAO invaded and displaced neurovascular bundles in 22% and 62% of cases respectively in cross-sectional imaging.[10]

These three entities have a spectrum of different biological behaviour, ranging from low-grade (PAO), through intermediate grade (PEO) to high-grade (HGSO). Regarding treatment options, PAOs, as low-grade lesions, can be treated successfully with wide excision, while a combination of chemotherapy and wide excision is the standard of care for HGSO. Currently, the cost–benefit balance concerning the use of chemotherapy in the treatment of PEO has not yet been elucidated, and standardized treatment regimens need to be established to determine its effectiveness.

Parosteal osteosarcoma (PAO)

PAO is the most common surface osteosarcoma (65% of surface osteosarcomas) and represents 4–5% of all osteosarcomas.[11] Peak incidence is at 20–40 years of age[12] with slight female predominance.[13] It is a low-grade malignant bone-forming tumour occurring on the cortical surface of bone,[6] specifically the outer fibrous layer of the periosteum. Most frequent area is the metaphysis of long bones (Fig. 1), but it can also be detected in the diaphysis and metadiaphysis (Fig. 2).[5,14] The most typical location is

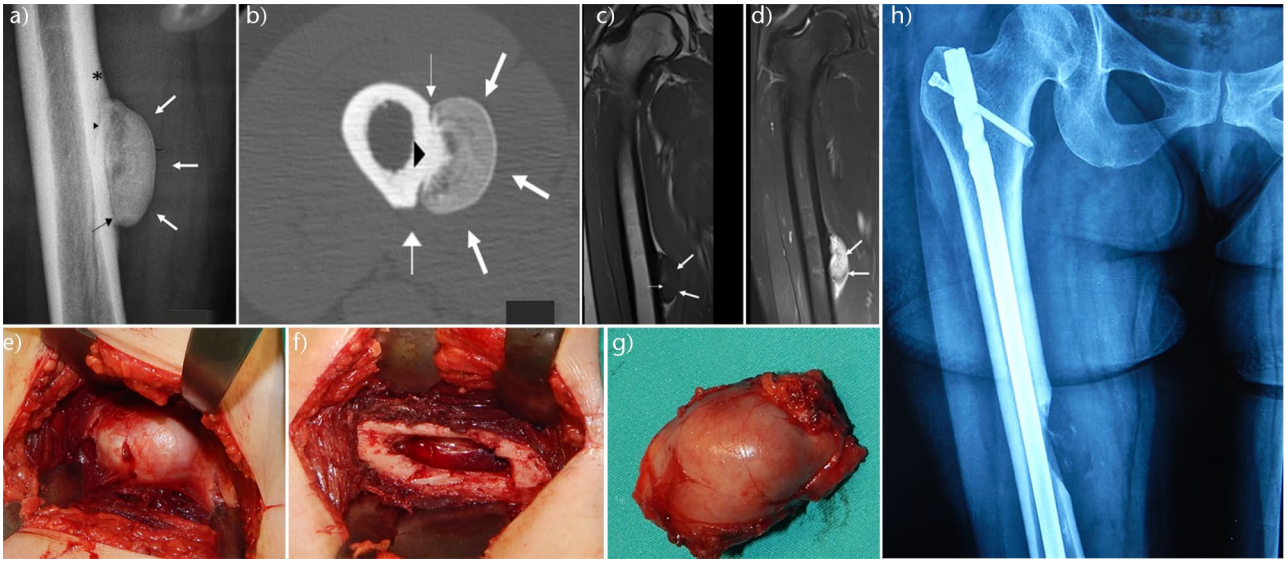

Fig. 2 Parosteal osteosarcoma (PAO) in a 35-year-old female. (A) An X-ray of the right femur shows a smoothly marginated, ground glass density mass adjacent to the medial surface of the of the femoral diaphysis. The presence of the cleft sign inferiorly (thin arrow) and a densely ossified stuck centrally (arrow) help to differentiate this PAO from an atypical osteochondroma or the rare exophytic fibrous dysplasia and cortical osteoma. Benign periosteal reaction (buttressing) is seen in adjacent cortex (asterisk). (B) Transverse computerized tomography (CT) scan image confirms the presence of the broad, of cortical density stuck (arrowhead) and the cleft sign (thin arrows) that separates the ground glass mass (arrows) from the bone cortex. (C) The diaphyseal mass is mildly hypointense to muscles (arrows) on a coronal T1w magnetic resonance (MR) image. (D) On a coronal fat-suppressed T2w MR image the diaphyseal mass is inhomogenously hyperintense. The cortex remains intact with no medullary extension. (E) Intraoperative image of the posterior femur with the parosteal osteosarcoma. (F) The cortex of the posterior femur after tumour resection. (G) The resected specimen. (H) Postoperative radiographs of the femur after resection of the tumour and insertion of an intramedullary femoral nail.

the posterior surface of the distal femoral metaphysis followed by the proximal tibia, fibula and humerus, whereas involvement of the ulna, tarsal and carpal bones has been sporadically described. Symptoms include a painless mass with duration of at least one year.[14] As the mass increases in size, pain worsens. Decreased range of motion might occur if the lesion is adjacent to a joint.[2,13]

The most common radiographic appearance of PAO is that of a large lobulated mass with extensive, mainly central bone formation and a thick mineralized stalk which looks to be 'pasted' onto the bone surface (Fig. 1, Fig. 2).[5,15] The amount of mineralization of the tumour varies from little, rarely, to dense ossification occupying the whole mass. A cleavage plane that partially separates the mass from the underlying bone cortex, the so-called 'cleft sign', is frequently seen (Fig. 1, Fig. 2).

Computerized tomography (CT) confirms the presence of the stalk and the lack continuation of the normal medulla through the stalk (Fig. 1C, Fig. 2B). Furthermore, it provides useful information to the surgeon regarding the degree of circumferential bone involvement.[16,17] Magnetic resonance imaging (MRI) provides superior delineation of the soft tissue component and can be used to visualize the overlying cartilaginous cap that frequently coexists. The soft tissue component is isointense to hypointense on T1w (Fig. 2C), inhomogenous on fluid-sensitive MR images (Fig. 1D, Fig. 2D) and shows inhomogenous enhancement on contrast-enhanced MR images; the cartilage cap is hyperintense on fluid-sensitive MR images (Fig. 1D) whereas the osteoid matrix is hypointense on both T1w and fluid-sensitive MR images (Fig. 1, Fig. 2). Areas with the most vivid enhancement can serve in guiding biopsy.[18] Intramedullary extension of the tumour is not uncommon but does not seem to correlate with prognosis.[15]

Differential diagnosis includes other surface bone sarcomas (Table 1) and benign juxtacortical lesions, the most common of which is myositis ossificans (MO) and rarely diaphyseal parosteal osteoma, parosteal lipoma, bizarre parosteal osteochondromatous proliferation (BPOP) and parosteal exuberant fibrous dysplasia. Regarding the differential diagnosis of BPOP and PAO, BPOP is a rare benign exophytic osteochondromatous lesion that most commonly involves the metatarsals, metacarpals and the phalanges of fingers and toes. Rarely, BPOP can affect large tubular bones, seen as a radiodense well-defined lesion, stuck on the bone cortex simulating a parosteal osteosarcoma. However, unlike PAO, it lacks any cortical erosion, periosteal reaction or intramedullary extension on imaging. On the other hand, to the best of our knowledge, PAO does not affect the small tubulars bones of hands and feet. As regards MO, it is not connected with

Table 1. Demographics, clinical characteristics, imaging, histopathological and molecular findings of surface bone tumors

	PAO	PEO	HGSO	PCS	SPECS
History	Long history (over a year)	Short duration (weeks–months)	Long history	Prolonged clinical course	Longstanding symptoms 1–2 yrs
Demographics	Females > males, 3rd decade	Males = females 2nd decade	Males > females 2nd–3rd decade	Males > females 3rd decade	After skeletal maturation
Clinical presentation	Slowly growing bone tumour, occasionally painful	Swelling and/ or pain, bone tumour	Pain, swelling 5–22 cm	Painless mass, swelling, deterioration of function	Growing painful mass Sudden onset of pain and increase swelling
Location (most common)	Long bones, metaphysis (distal femur)	Diaphysis (femur, tibia)	diaphysis or diaphysis-metaphysis of long bones (femur, tibia)	metaphysis or diaphysis-metaphysis of distal femur or proximal humerus	Malignant transformation of a pre-existing osteochondroma (or of multiple osteochondromas)
X-rays **First line method*	Mineralized juxtacortical mass with broad-based stalk 'Cleft sign' frequent Dense, central mineralization Cleft sign frequent	Broad-based opacity Cortical thickening with saucerization ± perpendicular periosteal reaction within the mass	Broad-based opacity Thickened eroded cortex Intramedullary extension	Broad-based opacity Thin saucerized or thick cortex Chondroid calcification (rings and arcs)	Opacity with chondroid-type calcifications over a pre-existing osteochondroma (OC) Irregular cortex and stuck of OC
CT **Method of choice for calcifications*	STM Confirm broad -based stuck and central mineralization	Same as X-ray, ± STM, additional calcifications	Same as X-ray, ± STM Involvement > 50% bone circumference	Same as X-ray, ± STM Better delineation of chondroid-type calcifications	Same as X-ray
MRI **Method of choice for soft tissues*	Inhomogenous STM with mineralization ± Intramedullary extent, Inhomogenous cartilage cap	STM, ↑↑SI on T2w, nodal/ septal/ peripheral enhancement (chondroid type)	Inhomogenous mass on T2w images Intermedullary extension	T2w hyperintense lobulated mass with hypointense chondroid-type calcifications Exceedingly rare intramedullary extension	Thickened cartilaginous cup > 2 mm Extension to the stalk of OC frequent
IHC markers	SATB2, MDM-2, CDK4	SATB2	MDM-2, CDK4 when developed on PAO	Not relevant	Not relevant
Helpful molecular findings	MDM-2 and CDK4 overexpression	Not relevant	Not relevant	Not relevant	Not relevant

Note. PAO, parosteal osteosarcoma; PEO, periosteal osteosarcoma; HGSO, high-grade surface osteosarcoma; PCS, periosteal chondrosarcoma; SPECS, secondary peripheral chondrosarcoma; CT, computerized tomography; MRI, magnetic resonance imaging; IHC: immunohistochemical; STM: soft tissue mass; SI: signal intensity

the adjacent bone and typically follows a centripetal zonal pattern of ossification, from the periphery to the centre, reverse to the centrifugal pattern of PAO. Moreover, MO is accompanied by extensive oedema of the adjacent muscle in the early and intermediate phase, best visualized on fluid-sensitive MR images.[19,20] Osteochondromas may occasionally be confused with PAO; however, the former are characterized by flaring of the cortex and continuation of the normal medulla within the lesion.[15]

Cytogenetic and molecular studies have depicted one or more supernumerary ring chromosomes which contain a consistent minimal amplification of chromosome 12q13-q15,[6,21,22] which results in targeting the cyclin-dependent kinase 4 (CDK4) gene and the murine double-minute type 2 (MDM-2) gene.[23,24] Amplification of the same genes is noted in about only 10% of conventional osteosarcomas, probably on the grounds of dedifferentiation of low-grade osteosarcoma.[25–29] Consequently, a remarkable increase of protein expression of both CDK4 and MDM-2 is detected in 87–89% and 70–89% of PAO[29,30] by immunohistochemistry or FISH (**Fluorescence in situ hybridization)**.

Histologically, the tumour is composed of hypocellular areas of spindle cells arranged in fascicles in desmoplastic collagenous stroma with parallel trabeculae of well-formed woven bone ('streamer pattern'). Spindle cells are characterized by minimal or, less frequently, moderate atypia and low mitotic activity. Areas of cellular matrix, scattered nodules of chondroid cells with atypical morphology and foci of anastomosing and curved bone trabeculae as in fibrous dysplasia can occur. Its low-grade appearance and positivity for MDM-2 and CDK4 are key features in differentiating it from other juxtacortical sarcomas (Fig. 3).

Dedifferentiation of PAO can occur in about 15–43% of cases at the time of first diagnosis. Dedifferentiated PAO is an aggressive high-grade sarcoma with worse prognosis, metastases and high rates of recurrence usually in the form of HGSO, undifferentiated spindle cell or pleomorphic sarcoma with biological behaviour similar to conventional osteosarcoma.[13,17] Although different, well-differentiated and dedifferentiated areas often coexist.[5] Characteristic imaging findings include tumour size larger than 11 cm, deeper invasion of the medullary canal and

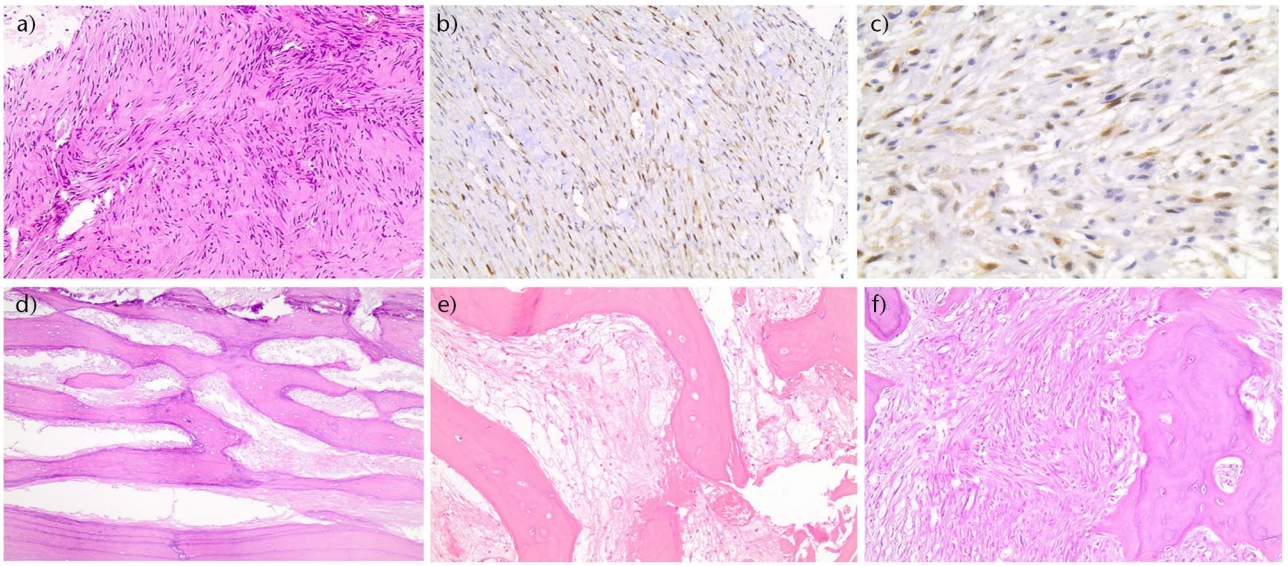

Fig. 3 (A) Hematoxylin-eosin stain (X200): hypocellular tumour composed of mildly atypical spindle cells arranged in fascicles in desmoplastic collagenous stroma. The morphological findings are consistent with parosteal osteosarcoma (PAO). (B) MDM-2 (X400) and (C) CDK4 (X400): the majority of the neoplastic cells show strong nuclear positivity. (D) Hematoxylin-eosin stain (X200): excision specimen of the lesion shown in A, B and C: parallel trabeculae of well-formed woven bone with spindle neoplastic cells in loose stroma. (E) Hematoxylin-eosin stain (X40): the neoplastic population is characterized by mild cellularity and mild cellular atypia. (F) hematoxylin-eosin stain (X40): foci of moderate cellularity and moderate cellular atypia in PAO.

large intralesional radiolucencies on X-rays or CT.[13,17] Moreover, novel evidence suggests that dedifferentiation can be correlated with the amplification and expression status of MDM-2 and CDK4.[31]

The treatment of choice is wide resection with survival rates at five years of approximately 90%.[10] Local recurrence may occur when wide resection is inadequate or in case of dedifferentiation.[32,33] Zaikova et al, in their review of 63 patients, reported a local recurrence rate of 46% following intralesional excision as compared to 20% following marginal and 0% following wide excision.[34] Local recurrence is usually seen as a heavily ossified mass.[33]

Patients of earlier stages are amenable to hemicortical resection with or without prophylactic fixation. Endoprosthesis, extracorporeal irradiation followed by reimplantation or resection arthrodesis could be the alternative methods of surgical reconstruction. Both methods have been found to result in a reasonable functional outcome even in later stages of the disease.[35] The technique of hemicortical resection for treating PAO was first described by Campanacci et al,[36] creating a unicortical window with wide margin. The defect is reconstructed using either bone cement, autograft such as fibular autograft, allograft or pasteurized/autoclaved/irradiated host bone.[37] None of their patients developed local recurrence. Treatment of this aggressive tumour is wide resection. Chemotherapeutic agents offer little or no benefit; however, several authors recommended chemotherapy in cases of dedifferentiation,[17] medullary involvement[17,36] or lung metastasis.[11] The prognosis of PAO is better compared to other surface bone sarcomas and conventional osteosarcoma, with metastasis and recurrence occurring in rare cases.[10,38]

Periosteal osteosarcoma (PEO)

PEO is a chondroblastic, intermediate to high-grade malignant bone-forming tumour, arising from the inner germinal periosteal layer with periosteal reaction.[11] The recent WHO classification does not recommend the term juxtacortical chondroblastic osteosarcoma that has been used in the past.[6]

This surface bone sarcoma is less common than PAO and accounts only for 1.5–2.0% of all osteosarcomas. Slight male predominance is observed, and the tumour mostly affects the second and third decade of life, with peak incidence in the second decade.[39,40] The diaphysis of tibia and femur are the most affected sites, whereas other long and flat bones have been sporadically reported.[40–42] Patients complain of a painful swelling or just pain for a shorter period of time compared to PAO.[6]

Typical radiologic appearance of PEO is a broad-based soft tissue opacity causing a shallow crater of the outer bone cortex; so-called saucerization. Calcified spiculae running perpendicularly from the bone surface within the mass are common and represent periosteal reaction of 'sun burst' type.[5,16] On cross-sectional imaging, the soft tissue mass is well marginated without pseudo-capsule and surrounds approximately 50% of the bone circumference.

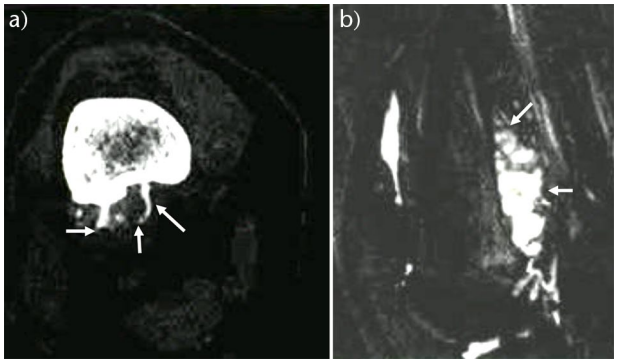

Fig. 4 Periosteal osteosarcoma in a 17-year-old female, presenting with a lytic process at the posterior aspect of the right femur as incidental finding. (A) An axial computerized tomography (CT) image shows a soft tissue mass extending from the posterior aspect of the right distal femur. The typical sunray mineralized spicules are seen within the mass. Distal aspect. (B) A sagittal (left) and an axial (right) fat-suppressed T2w magnetic resonance image show a lobulated, hyperintense mass adherent to the posterior aspect of the femur, with mild cortical erosion. The endosteal surface of the cortex and the medullary cavity appear normal.

Source: With permission from Papagelopoulos PJ, Galanis E, Sim FH, Unni KK. Periosteal osteosarcoma. *Orthopedics* 1999;22:971–974.

On MRI the tumour is predominately hypointense on T1w, hyperintense on T2w images and presents a septonodular pattern of enhancement reflecting its rich cartilaginous content (Fig. 4A–B).[41] Radiological differential diagnosis mainly includes HGSO and periosteal chondrosarcoma (Table 1). The diagnosis is usually confirmed by an image-guided biopsy.[43]

Molecular studies in a small number of cases did not highlight any consistent anomaly, with presence in some cases of complex karyotype and point mutations in TP53, as in high-grade osteosarcoma. The tumour consists of atypical chondroid cells that compose poorly formed lobules intermixed with bone formation and primitive spindle sarcomatous cells. Bone formation is usually central and might be focal. Highly atypical undifferentiated cells are located at the periphery of the tumour. No immunohistochemical expression of MDM-2 or CDK4 is noted.[6] PAO has a low-grade histological appearance and immunohistochemical positivity for MDM-2 and CDK4 that help in its distinction. On the contrary, HGSO is characterized by highly pleomorphic cells throughout the lesion, features not met in PEO.

Management with wide excision surgery is the recommended treatment. The role of neoadjuvant and adjuvant chemotherapy is controversial. Although different protocols are used among different centres, chemotherapy does not appear to influence prognosis or survival,[44,45] on the contrary, it may induce the development of other malignant tumors.[44,46,47] The tumour has a better prognosis compared to conventional osteosarcoma, but worse than PAO. Overall survival rate is approximately 80%. Disease-free survival rates of 89% at five years and 77–86% at ten years have been reported. Local recurrence and metastasis (20% of cases) generally occur within three years after diagnosis.[44] If bone marrow is invaded, a rare event, recurrence is more probable even after surgical resection, and prognosis is worse.[47]

High-grade surface osteosarcoma (HGSO)

HGSO accounts for less than 1% of all osteosarcomas.[11,48] As a high-grade lesion, it bears similarities to conventional intramedullary osteosarcoma regarding its clinicopathological characteristics and biological behaviour. It occurs more frequently in males than females, during the second and third decades of life.[49] It commonly arises in the diaphysis or metadiaphysis of long bones, with the femur, tibia and humerus being the most affected, and usually measures 5 to 22 cm at initial presentation.[39,49] Pain and swelling are the most common symptoms.

Radiographic descriptions are limited and refer to a broad-based surface bone tumour which occasionally may look similar to a PEO, but in contrast to the latter, it surrounds the bone in more than 50% of its circumference, is usually denser and extends to the intramedullary cavity. The soft tissue component is inhomogenous on T2w MR images, featuring a high-grade sarcoma (Fig. 5A-C).[39,50]

The exact pathogenetic mechanisms of HGSO have not been elucidated yet. Cases developed on PAO display amplification of MDM-2 and CDK4.[6] Histologic features are those of high-grade conventional osteosarcoma, with anaplastic-pleomorphic neoplastic cells that show numerous mitoses, including atypical ones, and foci of bone formation in close proximity to the neoplastic cells. Neoplastic population can have plasmacytoid, epithelioid or fusiform appearance or attain a smaller size when closer to bone matrix. Bone formation can take the form of trabeculae composing large sheets of compact bone or more disorganized trabeculae. HGSO may be osteoblastic, chondroblastic or fibroblastic, and typically contains neoplastic cartilage and/or fibroblastic components.[6] It is usually easily distinguished due to its high-grade features (Fig. 6). The tumour should not contain low-grade elements.

The treatment of choice is a combination of wide surgical excision and adjuvant chemotherapy.[10,51] Chemotherapy protocol is similar to conventional osteosarcoma including cases with metastases. The prognosis for HGSO is worse than for the other two types of surface osteosarcoma and is similar to that of conventional osteosarcoma. As a high-grade tumour, it is highly proliferative and may present with satellite lesions and early metastases. Local recurrence is significantly associated with marginal excision.

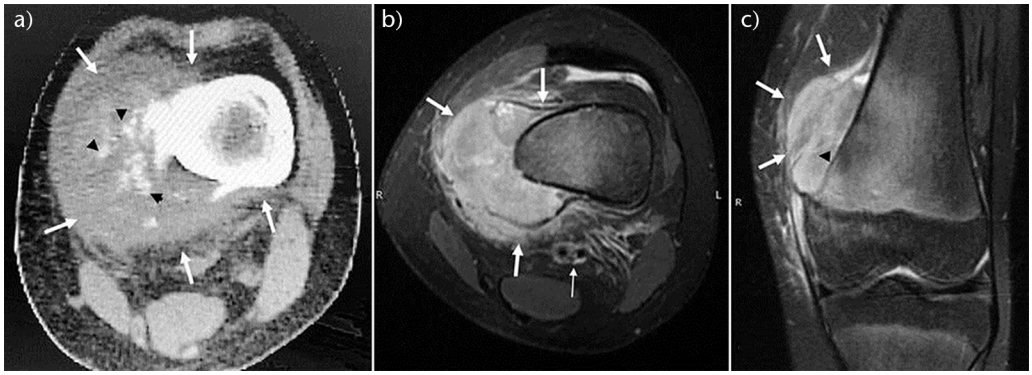

Fig. 5 (A) A computerized tomography (CT) scan shows a cortical broad-based soft tissue mass (arrows) at the distal metaphysis of the left femur which surrounds about 50% of bone circumference. The tumour contains amorphous calcifications, and the adjacent cortex is thickened on this slice. (B, C) An axial (B) and a coronal (C) fat-suppressed T2w magnetic resonance (MR) image demonstrate the bulky tumour (arrows) originating at the medial site of the left femur. The tumour is moderately hyperintense and presents significant intramedullary extension (arrows). At the distal margin of the tumour on the coronal image the bone cortex looks thinned (C). The neurovascular bundle remains intact in B (thin arrow). Note that the calcifications are not apparent on MR images.

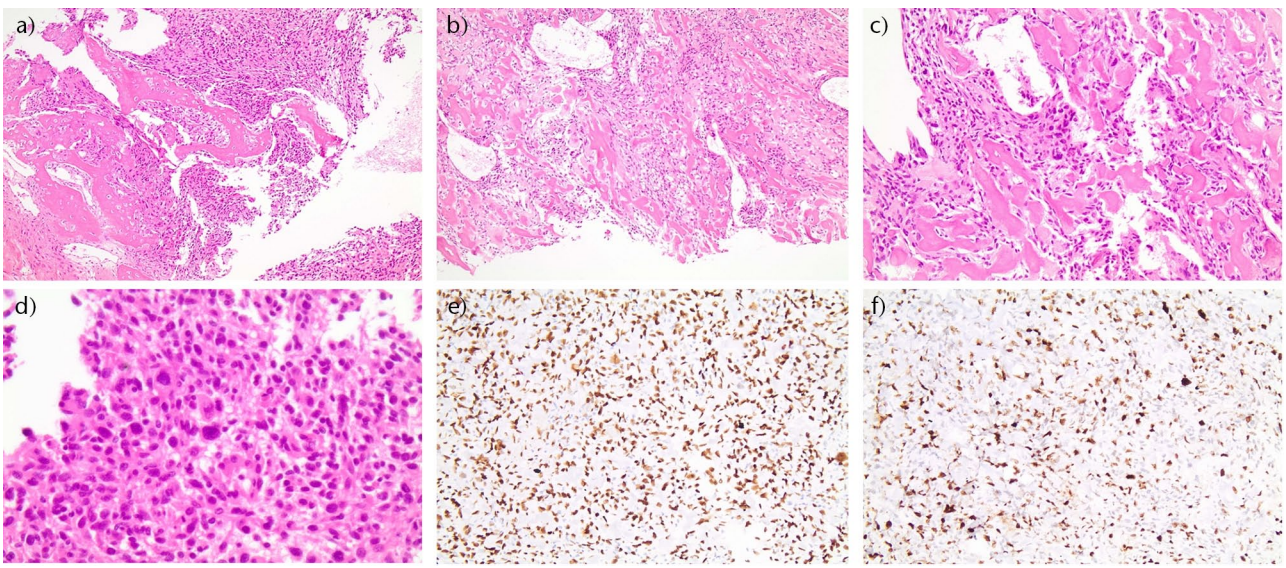

Fig. 6 (A) Hematoxylin-eosin stain (X100): low power view shows pleomorphic neoplastic population being adjacent to and invading bone. (B) Hematoxylin-eosin stain (X100) and (C) hematoxylin-eosin stain (X200): spindle neoplastic cells in close proximity with osteoid formation. (D) Hematoxylin-eosin stain (X400): on high power view, the neoplastic population shows high nuclear pleomorphism and numerous atypical mitoses. Given that the tumour mass is located on bone surface, the morphological findings are consistent with HGSO. (E) SATB2 (X200): the neoplastic cells show nuclear positivity. (F) Ki-67 (X200): proliferation index is high (~50%), consistent with the high mitotic rate.

Note. HGSO, high-grade surface osteosarcoma.

Overall prognosis is affected by the grade of the tumour, by the response to neoadjuvant chemotherapy and by the presence of local recurrence. Medullary involvement is not shown as an independent prognostic factor.[10] Overall five-year survival rate is 62%. Extension to the medullary canal is rare and associated with worse prognosis. The Rizzoli Institute study reports five-year overall survival of 82% and disease-free survival of 70%.[49] Adequate response to neoadjuvant chemotherapy[10] and localized disease without metastasis are factors that favour long-term survival.

Periosteal chondrosarcoma (PCS)

PCSs are malignant hyaline cartilage tumours arising within periosteum,[1] with fibrous pseudo-capsule formation in touch with it[5] and large size, usually greater than 3 cm.[52]

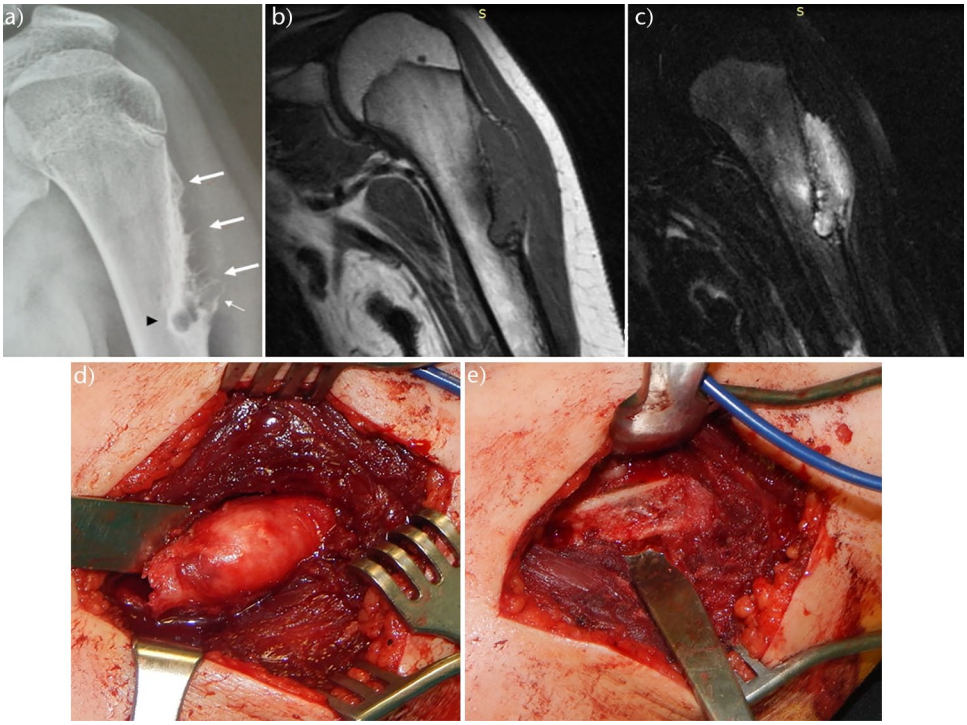

Fig. 7 Periosteal chondrosarcoma (PCS) in a 17 year-old female. (A) Anteroposterior radiograph shows a broad-based soft tissue mass (arrows) at the proximal metadiaphysis of the of the left humerus, causing endosteal scalloping. (B&C) T1w coronal magnetic resonance (MR) image shows a mass (arrows) isointense to muscles (B) and hyperintense with a microlobular contour on a coronal fat-suppressed MR image (C). Cortex seems intact. There is a non-marginated area in the adjacent bone which is hypointense on T1w and hyperintense on fat-suppressed T2w image that corresponds to bone marrow oedema, as no malignant infiltration of the medulla was documented on pathology of the specimen (arrowheads). Barely seen punctuate and curvilinear calcifications at the periphery and within the mass (arrows) signifying cartilaginous matrix. (D&E) Intraoperative photographs showing the periosteal mass before (D) and after resection (E).

It is a locally aggressive, though low-grade, malignant tumour. Histological grading is not applicable.[6]

PCSs represent less than 2–4% of all chondrosarcomas[53] and 0.2% of all bone tumours.[54] The most commonly involved bones are the distal femur at the metaphyseal or diaphyseal-metaphyseal region or the proximal humerus,[5,54–56] followed by the proximal femur, tibia, iliac bones, maxillofacial region, rib, fingers or foot.[53] They usually occur in the second to fourth decade of life,[54] with a peak in the third decade[57] and they are more common in males.[54] Information about PCS is scarce, with the largest published series including 36 patients.[58] Clinical presentation is non-specific, and symptoms include a painless mass, swelling, deterioration of function and a prolonged clinical course.[59]

Radiological features of PCS include a large soft tissue mass with a broad-based, non-calcified attachment to bone surface.[52,54] The lesion is sharply delineated from the adjacent cortex and contains chondroid-type mineralization with ring and arcs. The bone cortex can appear thickened or thinned and saucerized (Fig. 7A). Chronic periosteal reaction, such as buttressing, is frequent, reflecting the slow development of the tumour, but Codman triangles may be occasionally seen. CT can confirm the chondroid type of internal mineralization and additionally show thin interlobular calcifications and a calcified shell that partially surrounds the tumour. MRI demonstrates a cartilaginous-type tumour, isointense to muscles on T1w MR images (Fig. 7B) and typically hyperintense on T2w images with low signal intensity calcifications, multilobulated contour (Fig. 7C) and peripheral and septonodular enhancement. Intramedullary extension or bone marrow oedema are exceedingly rare, unless the tumour is dedifferentiated.[59]

A study about the molecular background of the tumour[57] depicted loss of canonical Wnt signalling and deregulation of pRb signalling by loss of p16 expression. Mutations in IDH1 and IDH2 genes are documented in a number of PCS.

Histologically, variably sized neoplastic chondroid lobules which invade the cortex, with moderate cellularity and no or mild cellular atypia, are the morphologic hallmark. Foci of myxoid matrix, fibrous bands with small vessels, calcification and endochondral ossification may be recognized, along with metaplastic bone formation in the periphery of

the neoplasm. Osteoid or bone formation is not noted. In some cases there is invasion of the bone medulla.

Dedifferentiation of a low-grade PCS may occasionally occur. In this case MR imaging reveals a bulky non-mineralized soft tissue component with mixed-signal intensity on T2w images.[60] Differential diagnosis of PCS predominately includes PEO (Table 1) and periosteal chondroma (PC). PCs are more common than their malignant counterparts and usually appear in a younger age group; both PC and PCS share similar imaging appearances. Robinson et al found that size was the most reliable discriminating feature between PCS and PC: reported size of PC ranged between 1.0 and 6.5 cm, whereas that of PCS ranged between 3 and 14 cm.[52] Histologic evaluation of a periosteal cartilaginous tumour has been advocated for a tumour diameter larger than 3 cm.[52,61] PCSs usually present with invasion of the cortex and in some cases of the bone medulla; findings critical in distinction with PC.

Wide surgical resection is the treatment of choice, whatever the grade of the lesion.[56,58] Smaller tumours (less than 3 cm) can be treated with marginal excision with close follow-up (Fig. 7D, Fig. 7E).[52,54,62] Incomplete excision is associated with local recurrence. In case of medullary involvement, treatment guidelines for central chondrosarcoma should be followed. Goedhart et al recommended follow-up with plain radiographs for the next five years.[58] A baseline MRI can be performed after six months and again at two years.[58] The prognosis of PCS is better compared to conventional chondrosarcoma of the same histologic grade.[63] Invasion of the medullary cavity is unusual. Metastases are rare, occur late and have only been reported in grade II and III lesions.[63] The most common site of metastasis is the lungs, and rarely the lymph nodes and skin. In a retrospective review of 24 patients, Papagelopoulos et al have shown that the overall five-year metastasis-free survival was 83%. However, six out of 24 patients died of pulmonary metastases in a mean follow up of 17 years.[62]

Secondary peripheral chondrosarcoma (SPECS)

SPECSs are malignant cartilage-producing tumours. They develop on the grounds of malignant transformation of a pre-existing osteochondroma, the most common benign cartilaginous lesion of adolescence.[64] They occur as solitary or multiple (hereditary) cartilage-capped bony projections from the metaphysis of endochondral bones adjacent to growth plate.[65] Less than 1% of patients with sporadic osteochondromas[66] may develop SPECS, despite reports of rates as high as 7.3% coming from large referral centers.[67] Of patients with multiple osteochondromas, 1–3% will eventually develop SPECS.[68] Ahmed et al reported that most cases of progression occurred in patients with multiple tumors.[67] Most cases of SPECS are low to intermediate grade, although tumours of higher grade are also possible.

The tumour is far more common after maturity, usually 25 to 45 years of age.[69] The most affected bones are the pelvic bones and the shoulder girdle. Typical presentation is a growing painful mass on an underlying osteochondroma, after skeletal maturation. Sudden onset of pain and increase in the size of the swelling may be hints of malignant transformation.[70] These patients can present with longstanding symptoms lasting between one and two years.

On radiographs, SPECS exhibit lytic areas of the stalk of the pre-existing osteochondroma, irregular surface and an adjacent radiopaque mass with chondroid-type calcifications.[60,67] Cross-sectional imaging can document the exact size and origin of the mass, the type of calcifications and the anatomic relation of the mass with the adjacent soft tissue structures. It is particularly useful to delineate tumours in complex anatomic areas such as the pelvic and shoulder griddle where X-rays are of limited value because of the superimposition of anatomic structures.[59] The soft tissue component is typically lobulated, hypodense on CT and hyperintense on T2w MRI, whereas calcifications are hypointense on all MR sequences (Fig. 8A–C). A painful

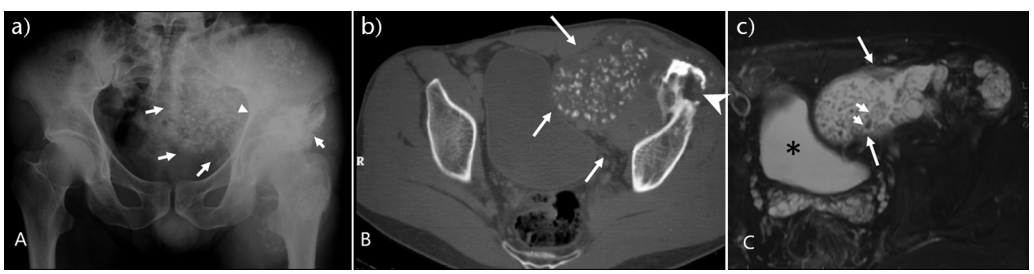

Fig. 8 A 42–year old man with abdominal discomfort and deteriorating left hip pain during the last six months. (A) frontal radiograph of the pelvis shows a bulky soft tissue mass (arrows) with typically cartilaginous rings and arcs calcifications, occupying the left pelvis. A densely mineralized lesion is seen at the left acetabular roof (arrowheads). (B) A computerized tomography (CT) image (bone window) shows an exostosis with lytic areas within it (arrow) of the left innominate bone protruding anteriorly and medially. A space-occupying soft tissue mass with calcified spots (arrows) seems to originate from the osseous protuberance and is displacing the adjacent left wall of the urinary bladder. (C) The mass is typically hyperintense on a fat-suppressed T2w axial image (arrows) and the calcifications are hypointense (arrowheads).

osteochondroma after skeletal maturation, with enlargement of the cartilaginous cup beyond 2 cm should raise the suspicion of SPECS.[60,71] Frequently, a large secondary bursa develops over the top of an osteochondroma, which may share similar imaging features with an abnormally thickened cartilaginous cap;[72] however, a bursa has a more saccular than lobulated shape,[72] whereas application of specific cartilage sequences differentiates between fluid and chondroid tissue.[71]

Recently, Tsuda et al stated that preoperative biopsy correctly predicted the histological grade after excision in only 27% of patients with SPECS, so it was difficult to correctly estimate grading of these tumours prior to surgery.[69] Both types of SPECS show a propensity to develop in patients with multiple osteochondroma syndrome (5% in comparison to 1% in patients with solitary osteochondroma), who carry germline mutations in EXT1 or EXT2. In atypical chrondromatous tumour/chondrosarcoma grade 1 (ACS/CS1), cell population is composed of cells in which EXT1 or EXT2 is biallelically inactivated, which is the characteristic alteration of osteochondroma, and cells that retain at least one functional copy of EXT1 or EXT2, with coexistence of EXT-mutant alleles and EXT-wildtype alleles. In contrast, in high-grade chondrosarcoma the EXT-wildtype cells predominate. Conclusively, data suggest that other factors play their part in tumorigenesis, such as alterations in genes that regulate cell cycle such as CDKN2A in ACS/CS1 or in the p53 and RB1 pathways in high-grade chondrosarcoma, as EXT-wildtype cells are susceptible to progression, given that they are more numerous than the EXT-mutant cells.[6] In ACS/CS1, chondroid cells attain a lobular pattern with histologic features such as cystic changes, necrosis, binucleated cells and increased vascularization being common, but not helpful in the differential diagnosis from osteochondroma. Tumour cell nodules might be seen in the soft tissue, without connection to the main tumour, and calcifications are easily seen. Morphologic signs of the pre-existing osteochondroma are often easily detected. Invasion of the stalk is rare and indicative of progression. Differential diagnosis of osteochondroma, ACS/CS1 and progression of osteochondroma to ACS/CS1 on histologic grounds alone is not feasible and clinical as well as imaging correlation is crucial for correct diagnosis.

Peripheral chondrosarcoma (PECS) grade 2/3 is characterized by lobular configuration and increased cellularity, with evident mitoses, nuclear size variation and prominent nucleoli (Fig. 9). Nuclear condensation and small nuclear size or binucleation may be present. The cartilaginous matrix might show myxoid changes and at the periphery the neoplastic cells can attain spindle morphology. Endochondral ossification may be noted, which is feature of the pre-existing osteochondroma.

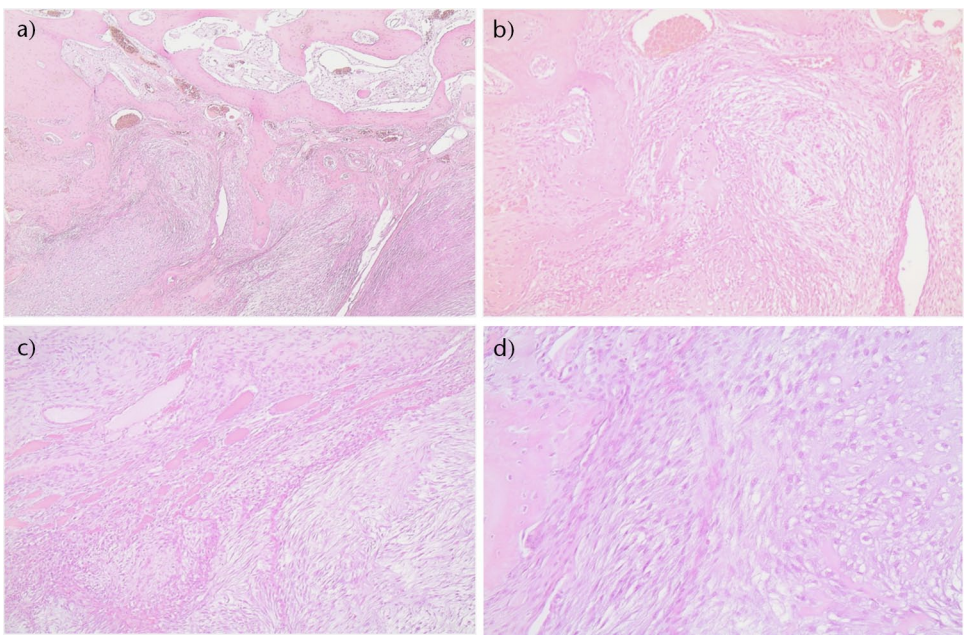

Fig. 9 (A) Hematoxylin-eosin stain (X40) and (B) hematoxylin-eosin stain (X100): the neoplastic population is composed of chondroblastic cells of moderate atypia widely invading bone cortex. (C) Hematoxylin-eosin stain (X100): the neoplastic cells extend to the adjacent soft tissue, invading skeletal muscle. (D) Hematoxylin-eosin stain (X200): on high power view, the chondroblastic neoplastic population is characterized by moderate cellularity and moderate atypia. Reactive bone formation on the grounds of periosteal reaction is noted on the left. Given that the tumour mass is located on bone surface, the morphological findings are consistent with PECS grade 2.

Note. PECS, peripheral chondrosarcoma.

Differential diagnosis from osteochondroma and ACS/CS1 is based on morphologic characteristics of the lesions, as nuclear pleomorphism and mitoses are encountered only in PECS. No osteoid or bone formation is noted, and the lesion is located at the surface of the bone, tumour characteristics that are useful in distinction from PEO and central chondrosarcoma, respectively.[6]

Surgical excision with wide margins is the treatment of choice. Tsuda et al recommend that a secondary chondrosarcoma arising from osteochondroma of the pelvis must be resected with wide/radical resection margins. Resection with wide/radical surgical margins is important to minimize the risk of local recurrence, especially for patients with high-grade tumours and hereditary multiple exostoses. However, the morbidity of surgery and the risk of local recurrence can be balanced in limb secondary chondrosarcomas, which show low risk of death and metastasis. Wide/radical margin was associated with improved local-recurrence-free survival ($p = 0.032$) and local recurrence was associated with worse disease-specific survival ($p = 0.005$).[69] Distant metastasis is uncommon, and prognosis is favourable for most patients. Overall survival at five years is approximately 90%.[73] Local recurrence remains a significant problem for approximately 10–20% of patients. In the study by Tsuda et al, 29% of patients developed local recurrences.[69] However, other authors have reported higher rates of local recurrence (16–52%).[67,68] Patients with SPECS of the pelvis are especially at risk for local recurrence.[73] In the study by Tsuda et al, a total of 51 patients with SPECS occurring from osteochondromas were reviewed. The ten-year disease-specific survival for all patients was 89.4%. Local recurrence occurred in 15 patients (29%), more commonly in pelvic (37%) compared with limb tumours (19%). Four patients with pelvic tumours died from progression of local recurrence. No patient with limb tumour died of disease.[69]

Periosteal Ewing sarcoma

Periosteal Ewing sarcoma (PES) is a very rare surface malignant bone tumour, comprising 3% of all Ewing sarcomas. The male-to-female ratio is 2.2:1 with a peak incidence in the second decade of life. The femur is the most common site of PES. Pain and a palpable mass are the most frequent symptoms. Symptoms and signs similar to those of infection such as fever, leucocytosis, malaise, local reddening, heat, and dilated blood vessels over the palpable mass may be noted. In terms of localization and imaging, it is similar to PEO involving the diaphysis or metadiaphysis of long bones, inciting extrinsic cortical erosion and lacking intramedullary involvement on imaging. Solid periosteal reaction such as Codman triangle type may be seen. However, PES lacks matrix mineralization, which is typical for periosteal osteosarcoma and is moderately hyperintense on water-sensitive MR images, unlike the chondroid-type hyperintensity of PEO.[5]

The histopathologic features of PES are the same as in medullary or extra-skeletal forms of Ewing sarcoma, which are characterized by small round cells with round and centrally located nuclei. CD99 membranous positivity is essential for Ewing sarcoma diagnosis. The tumour is also characterized by presence of FET-ETS fusions.[6] Treatment of PES involves chemotherapy, radiation therapy, and surgical excision with wide excision, although segmental diaphysis removal has been reported.[74]

Conclusions

Surface bone sarcomas are rare. A multidisciplinary approach is essential, as the combination of clinical information, radiological features, molecular studies and histopathological findings leads to correct diagnosis and patient handling. There are still numerous issues regarding the biology, pathophysiology and treatment options. The treatment implications of an accurate and early diagnosis are of paramount importance.

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