Rare Bone Tumors

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Less than 0.2% of the malignant tumors are primary bone neoplasms. Though they are rare tumors, osteosarcoma and Ewing sarcoma are tumor types typical of children and adolescents. The multimodal treatment of these rare bone tumors combines multiagent systemic chemotherapy and local control modalities as surgery and/or radiotherapy. The treatment of these diseases is defined by structured treatment protocols since more than 40 years. Chondrosarcoma is typically a tumor of the adulthood and is very rare in pediatric age. A wide variety of benign or locally aggressive tumors may affect bone in children: These entities can be classified into different categories according to the matrix, or substance, that they produce: i.e., osteoid or bone-forming tumors, cartilage-forming tumors, and fibrous lesions. Many cases are discovered incidentally; in other cases, they present with localized pain, swelling, deformity, or pathologic fracture. These tumors have characteristic radiographic features (i.e., type of periosteal reaction, calcification, well-defined or sclerotic border, lack of destruction of the cortex, and soft tissue extension) and can be diagnosed with plain radiographs: The evaluation of expert radiologists may avoid in many cases unnecessary invasive diagnostic studies. It is important to refer these cases to experienced orthopedic surgeon: Most cases can be managed with observation. Curettage and bone grafting or excision may be required in more aggressive cases (Fritzsche et al. 2017; Yildiz et al. 2003). However, it is very important to consider that patients with enchondromatoses or multiple osteochondromas have a higher risk of developing chondrosarcoma.

Enchondromas are usually asymptomatic, and the incidence of the development of enchondroma in children, adolescents, and young adults is not well defined. The diagnosis is usually made after imaging for other reasons. Predilection sites are the tubular bones of the hand, where enchondroma is the most frequent bone tumor. Other preferred location is the long bones (especially the femur). Enchondroma can reach considerable extension in the major long bones and may cause pathologic fractures. The neoplasm is frequently central, sometimes eccentric, or intracortical. It is an osteolysis, with rounded, lobulated, well-defined edges with a thin rind of reactive sclerosis. Usually, the lesion contains granular, popcorn, or ring-like opacities that represent calcification and ossification at the periphery of the lobules. The computed tomography scan shows a radiodense lobular or

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multi-island lesion with sharp limits and a clear lack of permeative alterations of the cortex. The pathology appearance is characterized by lobules of cartilage with the typical aspect of hyaline cartilage. The calcified areas appear as granules white-opaque. The chondrocytes are sparse, with small, round, dense nuclei, of relatively uniform size. Enchondromas harbor active hedgehog signaling, which contributes to the inhibition of the growth plate chondrocyte differentiation. Diagnosis can usually be made on the basis of the clinico-radiographic features. The majority of enchondromas do not require biopsy nor surgical treatment, and patients should be followed up by means of standard radiography (Bovee et al. 2010).

Periosteal chondroma is a benign hyaline cartilage neoplasm of bone surface that arises from the periosteum. It prefers the metaphyses of the long bones, particularly the proximal humerus. It may be painful, and some swelling can be observed. The imaging shows a superficial erosion of the bone cortex with regular borders. Such erosion is caused by a hemispherical parosteal cartilaginous mass, usually of small-to-moderate size. In the largest chondromas, the tumor often contains granular or popcorn densities. Histologically, the tumor is very similar to enchondroma, but more frequently it displays features of cell proliferation (high cellularity, nuclear plumpness, and frequent double nucleated cells). Being somewhat painful and causing some swelling in most instances, it usually requires surgical management consisting of either en bloc marginal excision or thorough curettage (Boriani et al. 1983).

45.1 Enchondromatoses (Ollier Disease, Maffucci Syndrome)

Enchondromatoses are rare skeletal disorders in which patients have multiple enchondromas. Enchondromas are defined as benign hyaline cartilage forming tumors. In 10% of patients with enchondromatoses, a mutation in the PTHLH receptor is detected in the tumor tissue. Enchondromatosis manifests itself early in childhood without any significant gender bias. Enchondromatosis encompasses several different subtypes of which Ollier disease and Maffucci syndrome are most common, while the other subtypes (metachondromatosis, genochondromatosis, spondyloenchondrodysplasia, dysspondyloenchondromatosis, and cheirospondyloenchondromatosis) are extremely rare. It has been reported that age at presentation is inversely related to the severity of the disease. *Ollier disease* is a developmental disorder characterized by failure of normal endochondral ossification and production of cartilaginous masses (enchondromas) leading to bone deformity. There is predominant unilateral involvement. About 80% of the patients diagnosed with Ollier disease harbor heterozygous somatic isocitrate dehydrogenase (IDH)1 or IDH2 mutations. In some patients, mutations on the parathyroid hormone receptor 1 are detected (Baumhoer et al. 2019). *Maffucci syndrome* is a non-hereditary disease and combines the features of Ollier disease associated with multiple soft tissue hemangiomas and to a lesser extent lymphangiomas. The lesions occur asymmetrically. In 80% of the patients, the disease develops before puberty, and in 25%, it occurs in the first year of life. The most affected bones are the small tubular bones of the hand and foot, but the enchondromas may present everywhere in the skeleton. Swelling, deformities, and lower limb length discrepancy (even >10 cm) are the dominant symptoms (Pansuriya et al. 2010). Chondrosarcomas may develop in both syndromes (in approximately 25% of cases, after the age of 20–40 years), and there is an increased risk of extraskeletal malignancies, such as breast, liver, and ovarian cancers and brain tumors. Surgical treatment is aimed to relieve symptoms, rather than excise the enchondromas. Skeletal deformities and limb length discrepancy are addressed by osteotomies and/or lengthening procedures. Prognosis is burdened by the incidence of malignant change (Edmondson and Kalish 2015; Albregts and Rapini 1995; Altay et al. 2007; Silve and Juppner 2006). Molecular pathology plays an increasing role in reaching a diagnosis in these rare tumors (Baumhoer et al. 2019).

Osteochondroma (osteocartilaginous exostosis) is a cartilage-capped bony projection arising on the external surface of the bone containing a marrow cavity that is continuous with that of the underlying bone. Osteochondroma is not a neoplasm, but, especially the poliostotic presentation, can go toward a malignant transformation. The diagnosis of osteochondroma is usually performed in the pediatric age with a prevalence for the male gender. The most frequent localization is in the metaphysic of long bones: distal femur, proximal humerus, and proximal tibia. *Multiple osteochondroma* is an autosomal dominant condition. It is genetically heterogeneous and is caused by mutations in one of the exostosin (EXT) genes, tumor suppressor genes located, respectively, at 8q24 and 11p11-p12 (Fig. 45.1). The most important complication of this condition is the malignant transformation in chondrosarcoma. A cartilage cap >1.5 cm, as evaluated by means of magnetic resonance imaging, should be regarded with caution as a possible radiographic marker of malignant transformation (Bovee et al. 2010; Ahmed et al. 2003).

Chondrosarcoma Primary chondrosarcoma is a tumor of adulthood and old age. The majority of patients are older than 50 years with a peak incidence in the fifth to the seventh decades of life. Chondrosarcomas are graded on a scale of 1–3 (based on nuclear size, nuclear staining, and cellularity), from moderately cellular tumors similar to enchondroma to pleomorphic and atypical lesion with high mitotic rate. The majority of primary chondrosarcomas are grade 1 or 2.

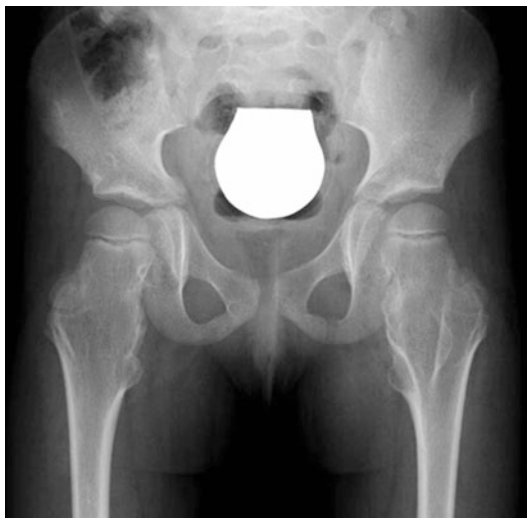

Fig. 45.1 Multiple osteochondromas in a 4-year-old girl. (Courtesy Dr. Annette Schmitz-Stolbrink, Pediatric Radiology, Dortmund, Germany)

Secondary chondrosarcoma arises from, in a benign precursor, either osteochondroma or enchondroma. The risk to develop chondorsarcoma has been reported around 2% for solitary osteochondroma and 10–25% for multiple osteochondromas 5–25%. Patients with secondary chondrosarcoma are generally younger than patients with primary tumor. The pelvic and shoulder girdle bones are frequently affected. Changes in symptoms (sudden pain, increase in swelling) and radiological findings (increased thickness of the cartilage cap, destructive permeation of bone, development of soft tissue mass) in a patient with a known precursor lesion herald the development of chondrosarcoma. Secondary chondrosarcomas are generally low-grade tumors. About 60% of chondrosarcoma harbor a IDH1 R132 or IDH2 R172 mutation and, if present, are diagnostic for chondrosarcoma; they are not detected in mesenchymal chondrosarcoma or osteosarcoma. Heterozygous somatic IDH mutations are also found in patients with Ollier disease (Baumhoer et al. 2019).

Mesenchymal Chondrosarcoma Mesenchymal chondrosarcoma (MCS) is a rare malignancy characterized by a biphasic histologic pattern of small undifferentiated round cells intermixed with islands of well-differentiated cartilaginous matrix. Because of its aggressive clinical behavior, MCS should be always regarded as a high-grade sarcoma. MCS is a rare tumor. In comparison to the most frequent classic chondrosarcoma, generally affecting patients who are >50 years old, MCS typically occurs in young adults; it is highly malignant and has a high proportion of extraskeletal tumors (about one-third of MCS occur in soft tissues, whereas extraosseous classic chondrosarcoma accounts for <1% of all cases). In the SEER database (1973–2006),

only 24 children with MCS are recorded (and 142 adults). Tumor locations are bone and joints (n = 9), soft tissue (n = 7), nose/nasal cavity (n = 2), eye/orbit (3), cranial nerves (1), lung (1), and kidney (1). A German retrospective study reported on 15 cases aged 0–25 years, 4 osseous and 11 extraosseous. Tumor sites were the head/neck (6 cases), paravertebral (3), pelvis (3), limbs (2), and kidney (1). Actuarial 10-year event-free and overall survival rates were 53% and 67%, respectively (Dantonello et al. 2008). Emerging cytogenetic data have raised the idea that this tumor may be closely related to extraskeletal Ewing sarcoma; patients with MCS should be probably treated with multimodal regimens, following Ewing sarcoma protocols. The prognosis may be slightly inferior compared to Ewing sarcoma (Frank et al. 2017).

Chondroblastoma is a benign rare tumor of the second decade of life, usually epiphyseal, located distally in long bones. Pain is usually present and, relatively common, also joint effusion. The radiographic appearance is characterized by a round or oval radiolucent lesion, small-to-moderate in size within the epiphysis or an apophysis or even extending across the plate. The margins are sharp with a sclerotic rim. The cortex may be expanded but preserved in most cases. Usually no periosteal reaction can be detected. Calcification inside the defect is observed in 30–40% of cases. Histologically, chondroblastoma shows a combination of mononuclear cells and giant cell. The typical cell is uniform, round to polygonal cell with well-defined cytoplasmic borders, clear to slightly eosinophilic cytoplasm, and a round to ovoid nucleus (chondroblasts). Chondroblasts are packed in pseudo-lobulated sheets often showing a pavement-like pattern. Chondroblastoma is molecularly characterized by a H2F3 p.K36 mutation and in rare cases by a H3F3A mutation. The mutations are diagnostic. The malignant cell in this disease is the stromal mononuclear cell (Baumhoer et al. 2019). Chondroblastoma has a slow course and may be surgically treated with curettage. The incidence of local recurrence is <20% and is related to the site of the tumor. Lung metastases can exceptionally complicate the course of the disease, but they can be effectively surgically removed.

Chondromyxoid fibroma is a benign tumor made by lobulated, fibromyxoid, and chondroid tissue, typical of the second and third decades of life, arising in the metaphysis of long bones (preferred sites are the proximal tibia). Mild-to-moderate pain is generally associated with local swelling. Radiographically, it appears as a small, metaphyseal, and eccentric radiolucent defect, usually with the long axis parallel to the bone of origin, sharply marginated for a sclerotic rim. There may be cortical destruction with extension to the soft tissue with absent or minimal periosteal reaction (Fig. 45.2).

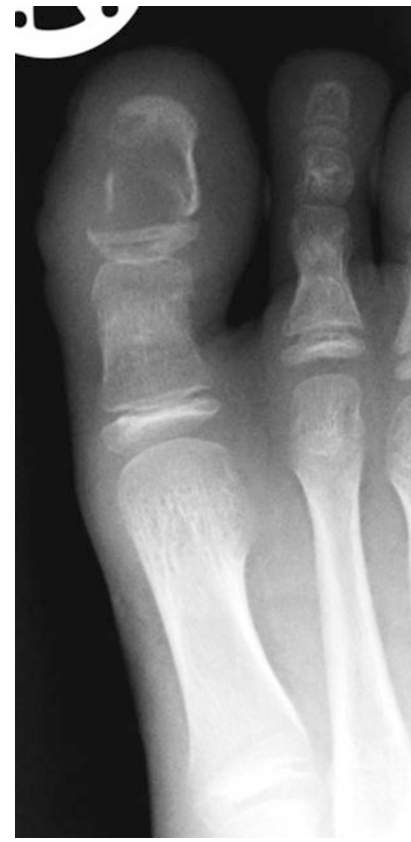

Fig. 45.2 X-ray of a chondromyxoid tumor of the toe in a 12-year-old boy. (Courtesy Dr. Annette Schmitz-Stolbrink, Pediatric Radiology, Dortmund, Germany)

Osteoblastoma is a benign tumor, made of osteoblasts producing osteoid and woven bone, arising in the second to third decades with an evident predilection for the posterior arch of the vertebral column and the sacrum. The tumor shows a rearrangement in the AP-1 transcription factor, either FOS on chromosome 14 or FOSB on chromosome 19 (Baumhoer et al. 2019). Signs of root compression may be present. Osteoblastoma is an osteolytic tumor well circumscribed and confined by a shell of reactive bone. Most of the tumors are of small size. In larger tumors, cystic spaces can be detected with radiographic appearance similar to an aneurismal bone cyst. Microscopically, the tumor consists of large osteoblasts producing osteoid and woven bone spicules and thin trabeculae. The surgical curettage is curative in most of the lesions. In selective cases, arterial embolization may be useful to reduce hemorrhage during surgery, and postoperative radiation therapy can be added to improve the local control (Greenspan 1993).

Osteoid osteoma is a small benign tumor, made of osteoid and woven bone, surrounded by reactive bone. The tumor usually affects patients in the pediatric age. It mainly occurs in the appendicular skeleton (femur in particular), while it is rare in the trunk, with the exception of the spine (mostly localized in the posterior arch). The almost constant symptom is pain, with a typical tendency to increase during the night, relieved by nonsteroidal anti-inflammatory drugs. When localized near a joint, limited motion and chronic synovitis can be observed. In the spine, it may cause muscular spasm with stiff scoliosis. The basic radiographic element is a small (1–2 cm) rounded area of osteolysis ("nidus"), surrounded by a halo of bone sclerosis. Left untreated, it increases very slowly. Surgery, up to the late 1990s, has been historically the mainstay of treatment. Nowadays, computed tomography-guided percutaneous radiofrequency or laser ablation is considered the treatment choice. Success rate of this approach is usually more than 90% based on pain relief. The main risk factor for symptomatic recurrence is female sex (Baal et al. 2019). Surgery remains an option in cases refractory to percutaneous ablation (Kaweblum et al. 1993; Kneisl and Simon 1992).

Giant cell tumor of bone is a relatively rare tumor (high incidence rates are reported in Asia) characterized by a benign but locally aggressive behavior. The tumor is molecularly characterized by a H3F3A p.G34W mutation (Baumhoer et al. 2019). Rare cases of metastases are reported, as well as transformations to a malignant sarcoma phenotype. Giant cell tumor of bone usually affects young female, arising in long bones. The tumor presents as an osteolytic lesion, characterized by the presence of multinucleated giant cells (osteoclast-like cells) and stromal cells that express RANK ligand, a key mediator of osteoclastic activation. Radiologically, the tumor may show a non-sclerotic and sharply defined border and a characteristic "soap bubble" appearance. Substantial skeletal morbidity may occur. Surgery is the treatment of choice. In unresectable cases, therapy with bisphosphonates may be used in order to induce apoptosis and prevent osteolysis. More recently, denosumab (a monoclonal antibody targeting the RANK ligand) showed to be significantly active (86% of tumor response was reported in a phase II trial on 37 patients with recurrent or unresectable disease) and may represent an important treatment option (Baal et al. 2019; Balke and Hardes 2010; Palmerini et al. 2019).

Adamantinoma is a slow-growing primary malignant tumor of the long bone. The tumor may be characterized by a wide range of morphological patterns, the most common of which consists of circumscribed masses or tubular formations of what appear to be epithelial cells surrounded by spindle-celled fibrous tissue. Immunohistochemically, the epithelial cells show co-expressions of keratin, especially basal epithelial cell keratins (CKs 5, 14, and 19) and vimentin. The cells of origin and the pathogenesis of the disease are still unknown. Adamantinoma is a very rare disease. Though the real number of cases may be underestimated in a cancer registry, only 15 cases under 20 years of age and 42

older cases are reported in the SEER database (1973–2006). A comprehensive literature review was able to identify 119 pediatric cases (Van Rijn et al. 2006). The term "adamantinoma" derives from the Greek word "adamantinos," which means "very hard." The typical presentation of adamantinoma is a painless swelling on the anterior side of the tibia. On conventional imaging, adamantinoma initially appears as a cortical lytic lesion without significant periosteal reaction, but in advanced cases, the tumor consists of a bubbly multiloculated sharply delineated lesion, with cortex disruption and soft tissue component.

Surgery is the mainstay of treatment. However, tumors may present in advanced stage, and conservative-wide resection with free margins is often unfeasible. Amputation might be required in more aggressive cases. Chemotherapy and radiotherapy do not have a role in the treatment of this tumor. The overall outcome is relatively good. In the pediatric review (Van Rijn et al. 2006), 13% of cases developed metastases (mainly in the lungs), and 10% of cases died of tumor. However, amputation was necessary in around 30% of cases.

45.2 Osteosarcoma

Although rare, osteosarcoma or osteogenic sarcoma is the most common malignant bone sarcoma. Osteosarcoma occurs most frequently in teenagers and young adults but may be diagnosed in younger children and older adults, in the latter often as secondary malignancy after previous radiotherapy. In the classical age group, there is a predominance in males. Osteosarcoma is associated with cancer predisposition syndromes, as Li-Fraumeni syndrome (mutated p53 gene), hereditary retinoblastoma (mutated RB1 gene), osteochondromatoses, Rothmund-Thomson syndrome, Bloom syndrome, Werner syndrome, and Diamond-Blackfan anemia. High-grade osteosarcoma is histologically described as osteoblastic, chondroblastic, fibroblastic, small cell, telangiectatic, or high-grade surface. Very rare are malignant soft tissue osteosarcomas. Treatment of these malignant osteosarcomas follows recommendations by specialized groups or is performed within clinical trials and consists of chemotherapy with common used agents as high-dose methotrexate, anthracyclines, cisplatin, and surgery. Radiation therapy is less effective in osteosarcoma, though the use of new improved radiation techniques, such as proton beam or heavy ion therapy, is currently studied. The clinical management is usually well known by pediatric and medical oncologists in specialized sarcoma centers. Parosteal, periosteal, and low-grade surface osteosarcoma are of low or intermediate malignancy and have thus no tendency to spread and treated by local treatment modalities only (Baumhoer et al. 2019; Bielack et al. 2016; Strauss and Whelan 2018).

45.3 Ewing Sarcoma

Ewing sarcoma is a very rare malignant bone or soft tissue sarcoma that tends to occur in children, adolescents, and young adults. It is more common in males. Risk factors for Ewing sarcoma are unknown. Interestingly, it occurs significantly more frequent in the Caucasian population. EWS is a small blue round cell sarcoma and is characterized by tumor-specific chromosomal translocations, in which ETS transcription factors are fused with a member of the FET gene family. The most common tumor-specific chimeric transcription factor EWSR1-FLI1 is composed of Ewing sarcoma breakpoint region 1 (EWSR1) protein and an ETS-family gene such as Friend leukemia integration 1 transcription factor (Fli1) (Delattre et al. 1992; Sand et al. 2015). Cooperative group clinical trials have demonstrated that multidrug treatment and treatment intensity are important factors of therapy and that intensity of chemotherapy is important for outcome. Modern protocols consist of intense induction chemotherapy with vinca alkaloids, alkylating agents, and anthracyclines. Local control in Ewing sarcoma comprises surgery and/or radiotherapy. The outcome in patients with localized disease has constantly improved

over the past. In patients with disseminated disease or relapse the outcome remains poor and novel treatment approaches are needed (Grunewald et al. 2018; Pappo and Dirksen 2018).

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