Bone and Soft Tissue Pathology in Children and Young Adults

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Edited by

Ali G. Saad

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PREFACE

Pediatric and young adult pathology is a distinct and a rapidly evolving discipline. The diagnosis of pediatric bone and soft tissue tumors can be challenging because of their diverse histological patterns and the lack of diagnostic biomarkers for several examples.

Recent genetic and molecular advances have accelerated our knowledge of various pediatric tumors, and this is particularly true for tumors of bone and soft tissue. These advances have resulted in better understanding of several entities but, most importantly, resulted in further refinement of their classification. Another direct result of these advances is the expansion of previously known family of tumors, such as the Ewing sarcoma family, and the emergence of previously unknown or poorly characterized entities.

The diagnosis of bone and soft tissue tumors demands a team approach. It requires proper communication with the radiologist, the surgeon, and the oncologist. Pathologists are strongly encouraged not to render a final diagnosis, even of benign looking tumors, without being fully aware of the imaging characteristics. Review of the images with a bone radiologist is of great benefit. We are certainly periodically reminded of this in our practice.

This book provides an in-depth review of bone and soft tissue tumors in children and young adults. We made particular effort to highlights, in every section, the most important immunohistochemical markers and molecular characteristics of each entity. We also conformed to the recommendations of the latest WHO classification of bone and soft tissue tumors by incorporating the most recent developments, histological features, and ancillary diagnostic tests. It is my hope that this book will provide practicing pathologists and trainees alike with an additional tool to effectively evaluate a biopsy or resection specimen of bone or soft tissue origin.

CHAPTER 1

CHONDROGENIC TUMOR

ALI G. SAAD

BENIGN CHONDROGENIC TUMORS

SUBUNGUAL EXOSTOSIS

Subungual exostosis is a benign osteocartilaginous lesion of the distal phalangeal bone under the nail bed. It was first described by Dupuytren in 1917 then became known as *Dupuytren exostosis* [1], a nomenclature that we do not recommend using. Approximately 80% of cases involve the dorsal or medial aspect of the tip of the distal phalanx within the big toe but any subungual region of any digit can be affected. The peak incidence is in the 2nd and 3rd decades with a mean age of 24 years. Historically considered a reactive process likely due to trauma, infection, or hereditary abnormality, the consistent identification of t(X;6)(q24-q26;q15-q25) [2] supports it neoplastic origin. The breakpoints are in the *COL12A1* gene on chromosome 6 and near the *IRS4* gene on the X chromosome. *IRS4* gene encodes an insulin receptor substrate, on the X chromosome. This translocation does not result in any fusion transcript but rather results in an increased expression of IRS4 at the mRNA land protein levels [3].

Histological features vary depending on the duration. In its early stages, the lesion consists of fibroblastic proliferation in direct continuity with the nail bed often triggering cartilaginous metaplasia. Over time, cartilage undergoes calcification, increases in thickness, and develops enchondral ossification. The latter gradually transforms into woven bone followed by lamellar bone (figure 1). Eventually the bone forms the base of the lesion and is covered by a typically thick cartilaginous cap. In chronic lesions, the cartilaginous cap may become hypercellular with the presence of binucleated or multinucleated chondrocytes. Similarly, the surrounding myofibroblastic proliferation may become hypercellular. As the reader can imagine, limited biopsy of this peripheral myofibroblastic proliferation may give the illusion of a malignant

neoplasm. The lesion, or the adjacent tissue, may ulcerate and a secondary infection may develop rendering the diagnosis very challenging. However, evaluation of these histopathological features within the context of anatomic location and radiological findings is very helpful.

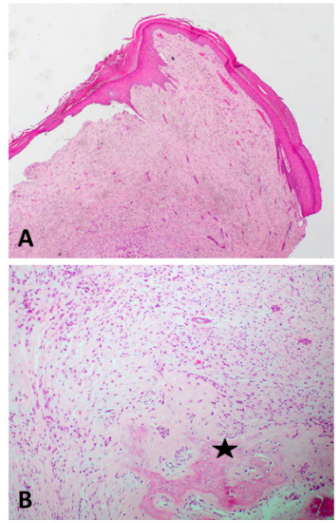

Figure 1. Subungual exostosis. A: The lesion is hypercellular and located underneath the skin/nail. B. It is composed of fibroblastic proliferation. A focus of woven bone is noted (star)

The differential diagnosis includes osteochondroma and bizarre parosteal osteochondromatous proliferation (BPOP). Osteochondromas are rare in small bones of the hands and feet. In addition, the marked proliferative activity and the presence of enlarged binucleated chondrocytes, present in subungual exostosis, distinguish it from osteochondroma. Subungual exostosis can be differentiated from BPOP by the wider anatomic distribution and the frequent presence of distinct blue bone in the latter.

BIZARRE PAROSTEAL OSTEOCHONDROMATOUS PROLIFERATION (NORA LESION)

Bizarre parosteal osteochondromatous proliferation (BPOP) is a benign surface lesion of predominantly the short tubular bones of the hands and feet. Long tubular bones can be affected in about 27% of cases [4]. This lesion was first described by Nora et al. in 1983 [5]. It shares several features

with florid reactive periostitis including the peak incidence and the anatomic sites involved. The etiology of the lesion remains uncertain. BPOP is considered as a part of a histological spectrum encompassing florid reactive periostitis and acquired osteochondroma (either subungual or turret exostosis) [6]. A small percentage of patients report a preceding history of trauma.

Genetics studies have shown recurrent cytogenetic abnormalities including t(1;17) (q32;q21), inv(7), and inv(6) [7] which are different from those seen in subungual exostosis supporting that BPOP is a distinct lesion.

Histologically, BPOP is characterized by a prominent periosteal new bone and cartilage formation and the lesion appears to be composed of a mixture of bone, cartilage, and fibrous tissue (Figure 2). The bone and cartilage can be quiet hypercellular and often display cytological atypia. The latter may show numerous binucleated chondrocytes. Marked hyperchromasia and atypical features are lacking. Scanning at low magnification often discloses a zonal architecture i.e., bony elements located within the central region while the cartilage forms irregular cap-like structures at the periphery. Between the cartilage and bone, a characteristic blue bone (stroma with a basophilic tinctorial quality) can be seen. The intertrabecular space consists of hypervascular fibrous tissue devoid of marrow elements.

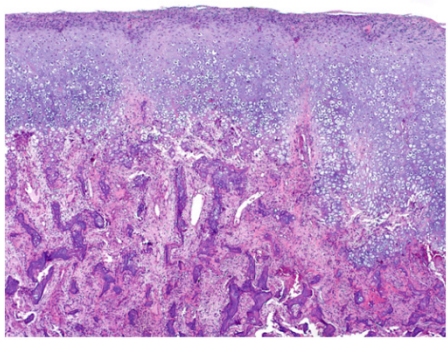

Figure 2. Bizarre Parosteal osteochondromatous proliferation. The lesion is composed of prominent periosteal new osteocartilaginous proliferation (top) with areas consisting of a mixture of bone, cartilage, and fibrous tissue (bottom) (Courtesy AE Rosenberg, MD, University of Miami)

PERIOSTEAL CHONDROMA

Periosteal chondroma is a rare benign cartilaginous neoplasm located on the bone surface beneath the periosteum. The lesion, first described in 1952 by Lichtenstein and Hall [8], commonly involves the small bones of the hands and the long bones of the appendicular skeleton with the proximal humerus representing the most common location with nearly 50% of cases diagnosed at this site [9, 10]. Periosteal chondroma represents <2% of all chondromas and is most common in children and young adults [11]. The M;F ratio is 1.5:1.

Like enchondromas, a subset of periosteal chondromas is caused by mutations in one of the *IDH* genes. Chromosomal aberrations described in periosteal chondroma include loss of chromosome 6 material, rearrangements of 2q37, 4q21-q24, 11q13-q15 and 12q13-q15 [12] as well as genetic rearrangement in chromosome 12 [13].

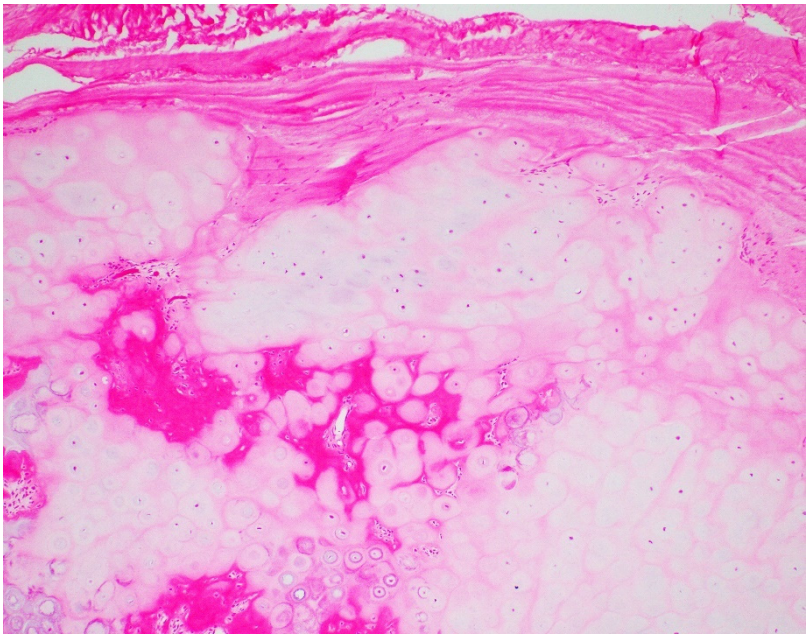

Figure 3. Periosteal chondroma. The tumor is lobulated and is covered by a thin layer of periosteum. The tumor is mildly cellular, and the chondrocytes show no atypia.

Periosteal chondroma shows characteristic histological features. The tumor has a lobulated appearance and is covered by a thin layer of periosteum

(figure 3). The tumor is typically well defined from the underlying cortex which can be eroded but never permeated. The underlying cortex is frequently sclerotic. As mentioned, the tumor is well circumscribed and permeation into adjacent tissue should question the diagnosis. The cellularity of the tumor is moderate at best and cytological atypia is not present.

The differential diagnosis includes enchondromas. As opposed to enchondromas, periosteal chondroma are more cellular and may show greater cytological atypia. The typical size of a periosteal osteochondroma is <5 cm and a size larger than 5 cm favors the diagnosis of periosteal chondrosarcoma. The key distinguishing feature from osteochondroma is the separation of periosteal chondroma from the medullary cavity by intervening cortex.

ENCHONDROMA

Enchondroma is a benign hyaline cartilaginous intramedullary neoplasm representing 10-25% of all benign bone tumors [14]; however, the exact incidence is unknown since a significant proportion of enchondromas are asymptomatic. Stomp et al. reported that the incidence of incidental enchondromas, by MRI of the knee, is about 2% with 84% measuring < 2 cm [15]. The majority of enchondromas are small (<3cm) and solitary. They are asymptomatic and discovered incidentally when they occur in the long tubular bones and they may cause pain, swelling or pathologic fracture when they occur in the short tubular bones of the hands and feet. About 60% of cases involve short tubular bones of the hands and feet (hands more affected than feet; ratio 7:1). Enchondromas may occur at any age with more than 60% of patients are age 10-40 years with a median of 36 years.

In a small subset of patients, the tumor may be multifocal, a syndrome known as *enchondromatosis*. Enchondromatosis encompasses several different subtypes including Ollier disease (enchondromatosis), Maffucci syndrome (enchondromatosis associated with soft tissue hemangiomas), metachondromatosis, genochondromatosis, spondyloenchondrodysplasia, dysspondyloenchondromatosis and cheirospondyloenchondromatosis. Ollier disease and Maffucci syndrome are the most common. Characteristic features of enchondromatosis variants are summarized in table 1.

Histologically, the tumor is composed of mature hyaline cartilage displaying a lobular architecture. Individual lobules may be separated by normal bone marrow with normal hematopoiesis. A characteristic feature is

Table 1. Classification of Enchondromatosis

	Clinical Characteristics	Genetic features
Ollier Disease	Early childhood Mostly short and long tubular bones of extremities	*IDH1, IDH2, PTH1R*
Maffucci Syndrome	Early childhood Bone involved similar to Ollier disease Cutaneous and internal organs hemangiomas	*IDH1*
Metachondromatosis	Early childhood Mostly metaphyses of long bones or lower extremities, iliac crest Osteochondromas of hands and feet	*PTPN11*
Genochondromatosis	Early childhood Symmetric enchondromas in the metaphyses of proximal humerus and distal femur Type 1: above plus enchondromas of clavicle Type 2: Above plus enchondromas of short tubular bones of hands, wrists, and feet	*PTHLH*
Spondyloenchondrodysplasia	Early manifestation: birth or early infancy Vertebral dysplasia and enchondromas of pelvis and long tubular bones Type 1: Classic type Type 2: Neurologic abnormalities: developmental delay, spasticity, and cerebral calcifications	*ACP5*
Cheirospondyloenchondromatosis	Early manifestation: birth or early infancy Symmetrical enchondromas: metacarpals and phalanges resulting in short hands and feet Dwarfism and enlarged joints	Unknown
Dysspondyloenchondromatosis	Early manifestation: birth or early infancy Enchondromas of long tubular and flat bones Bones of hands and feet are spared or minimally involved Facial and spinal malformations with unequal limb length	Unknown

that individual lobules are often encased within a shell of mature lamellar bone (figure 4). In some cases, lobules of cartilage can grow around lamellar medullary bone mimicking the infiltrative growth of the medullary cavity seen in chondrosarcoma. The cellularity of the lobules is generally low, and the cells are typically bland and evenly distributed within the lobules; however, occasionally clustered cells may be encountered. The nucleus of chondrocytes is often round and hyperchromatic resembling a lymphocyte. Prominent myxoid change should not be seen in enchondroma and, when present, it suggests malignancy. Tumors occurring in the small phalangeal bones and in patients with enchondromatosis represent an exception as the lobules may be hypercellular, binucleated chondrocytes, myxoid matrix and stellate or elongated cells.

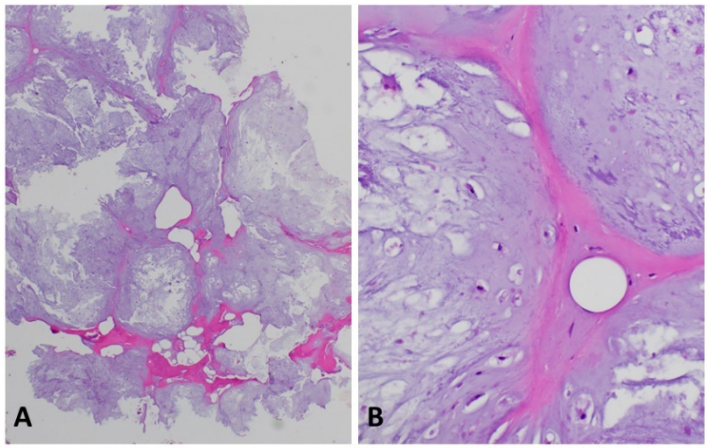

Figure 4. Enchondroma. A: The tumor consists of lobules of mature hyaline cartilage. B: The lobules are encased within a layer of lamellar bone. The chondrocytes show minimal atypia.

The most important differential diagnosis is with chondrosarcoma grade 1. The distinction can be challenging but, in general, a combination of 5 parameters is helpful in making this distinction: host bone entrapment, open chromatic, high cellularity, mucoid matrix degeneration >20%, and age >45 years.

Malignant transformation in solitary enchondroma and enchondromatosis (Ollier and Maffucci) is more common in the long bones of the legs, particularly the femur. Other sites include the pelvis, humerus, scapula and the tibia [16]. The risk of developing secondary chondrosarcoma in solitary

enchondroma is reportedly 4% [17]. In patients with Ollier disease, the risk of malignant transformation is estimated at 10-20% [18].

By cytogenetic studies, enchondromas may show structural aberrations and translocations most often involving chromosomes 6, 12, and 24 [19]. Chromosomal aberrations involving 6q13-21 have been associated with locally aggressive behavior of several benign cartilage lesions, including enchondroma [20]. Recently, isocitrate dehydrogenases 1 and 2 (*IDH1* and *IDH2*) gene mutations mapping to the long arms of chromosomes 2 and 15, respectively, have been identified in solitary enchondromas, chondrosarcomas, and multiple enchondromas of Ollier disease and Maffucci syndrome. *IDH1* or *IDH2* mutations have been demonstrated in approximately 40% of solitary enchondromas and in 80% of multiple enchondromas and hemangiomas associated with Ollier disease and Maffucci syndrome.

OSTEOCHONDROMA

Osteochondroma, or *osteocartilaginous exostosis*, is a common benign cartilaginous neoplasm consisting of an exophytic bony growth on the external surface of the bone and covered by a cartilaginous cap. The average age differs between solitary and multiple osteochondromas; it is 18 for the former while nearly all cases of hereditary osteochondromas are diagnosed before 12 years of age [21]. The tumor occurs in two distinct settings: solitary osteochondroma or as multiple hereditary exostoses. Previously considered a hamartomatous lesion, the presence of chromosomal aberrations involving 8q22-q24.1, where the *EXT1* gene is located or 11p11.2 where the *EXT2* gene is located [22-25] supports the neoplastic origin of this tumor. The cartilage cap in the majority of sporadic and hereditary multifocal osteochondromas consists of a mixture of both mutant and wild-type cells.

Solitary Osteochondromas

Solitary osteochondromas is a very common bone tumor accounting for approximately 35% of benign bone tumors; however, it is likely that the incidence is much higher since a significant number of osteochondromas remain asymptomatic. Osteochondromas arise from bones that are formed by enchondral ossification during skeletal development. The tumor commonly occurs in the metaphyseal regions of the distal femur, proximal tibia, proximal humerus and rarely flat bones.

The gross appearance is characteristic. The overall shape of the tumor can be sessile, cauliflower-like, or pedunculated with a stalk that is variable in

width and length. The cartilaginous cap is covered by a thin perichondrium (fibrous membrane) that is continuous with the periosteum covering the stalk. The cap varies in thickness from 2 mm to 1 cm. This contrasts with adults where the cap is often very thin or even absent. The exact thickness of the cap should be documented. For this purpose, the area of maximum thickness should be selected, and measurement should be done perpendicular to the cartilage-bone junction. A thick (>2 cm) and irregular cap may indicate malignant transformation; however, there is poor correlation between the thickness of the cap and malignancy. The underlying bone may contain foci of calcified cartilage.

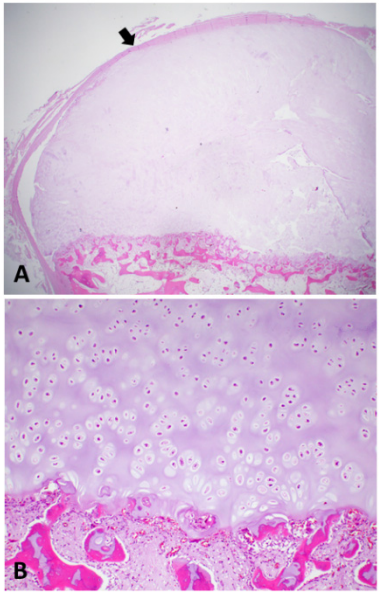

Figure 5. Osteochondroma. A: At low magnification, the three layers of the tumor are identified: the perichondrium (arrow), the underlying cartilage cap and the bone. B. The chondrocytes are arranged in clusters and tend to enlarge closer to the cap-bone junction.

Microscopically, the tumor is composed of three layers: the perichondrium, the cartilage cap, and the underlying bone. The cartilage cap is reminiscent of a disorganized growth plate cartilage. The superficial chondrocytes are arranged in groups or clusters, and those close to the cap-bone junction are larger (figure 5). With age, the thickness and cellularity of the cap decrease. Focal necrosis, binucleated chondrocytes, and cystic degeneration may

occur and do not indicate malignancy. Foci of hypercellularity may be encountered in the cap but, characteristically, these foci do not form distinct nodules but rather they blend with the rest of the cap. Nuclear atypia and mitoses should not be present in osteochondroma. The bone may contain irregular foci of necrotic calcified chondroid.

Multiple Osteochondromas

Multiple osteochondromas is an autosomal dominant hereditary condition where the patient develops multiple osteochondromas. The tumor is caused by mutations in the *EXT1* or *EXT2* gene. Multiple osteochondromas is rarely part of a contiguous gene deletion syndrome including Langer-Giedion syndrome and Potocki-Shaffer syndrome.

Langer-Giedion syndrome, or trichorhinophalangeal syndrome (TRPS) type 2, is a rare gene deletion syndrome with distinct facial features (bulbous nose, prominent philtral area, thin vermilion of upper lip, sparse scalp hair, prominent forehead, mild microcephaly, and broad eyebrows) and bone abnormalities. Oral manifestations include micrognathia, retrognathia, supernumerary teeth, hypodontia, and malocclusion. Like solitary osteochondromas, exostoses involves long and short tubular bones of the limbs which is a differentiation features with TRPS type 1 [26, 27]. The knee region is invariably affected and, therefore, x-ray of the knee joint serves as a good screening tool.

Early diagnosis is important since patients with multiple osteochondromas have a relatively increased risk of progression towards secondary peripheral atypical cartilaginous tumor/chondrosarcoma grade 1 or high-grade chondrosarcoma [28-30].

Potocki-Shaffer syndrome results from loss of genetic material from chromosome region 11p11.2p12 resulting in a continuous gene deletion syndrome. This syndrome encompasses several abnormalities including intellectual disability, developmental delay, central nervous system abnormalities, skeletal and craniofacial abnormalities including multiple exostoses and bilateral parietal foramina, and abnormalities of the genitourinary tract [31, 32].

Multiple osteochondromas are commonly diagnosed during early childhood because of the occurrence of bone deformities and growth disturbances. Pseudo-Madelung deformity is commonly used to describe skeletal deformities of the long tubular bones secondary to multiple osteochondromas.

Gross and microscopic characteristics of multiple osteochondromas are similar to those of solitary osteochondroma.

CHONDROBLASTOMA

Chondroblastoma is a benign tumor of bone characterized by a proliferation of immature cartilage cells (chondroblasts) with islands of eosinophilic chondroid matrix. The tumor represents approximately 1% of all bone tumors. In a large series by Konishi et al. [33]. Ages range from 8 to 61 years with a peak incidence during the 2nd to early 3rd decades of life. Chondroblastomas are rare in the first decade and in older adults; however, Dahlin et al. [34] reported two 5-year-old children with chondroblastoma. It affects males more than females (2:1). It has a predilection for the epiphyseal (subchondral) regions of long bones (approximately 75%) particularly in skeletally immature patients. The tumor has been described in virtually every bone with the femur being the most affected bone. Other sites include the calcaneus, talus, patella, and pelvic bones particularly the acetabulum. Although very rare, chondroblastoma of soft tissue has been reported [35].

Histologically, the tumor is composed of sheets of ovoid to polygonal cells. Some nuclei may appear grooved, and the cytoplasm is eosinophilic. The cells may be packed in sheets imparting a blue cell appearance to the tumor (figure 6). Scattered osteoclast-like giant cells and foci of eosinophilic chondroid matrix are often present. A characteristic feature of chondroblastoma is the presence of a lace-like or chicken wire calcification. Moderate nuclear atypia and mitoses may be present but atypical forms are not seen. In a typical case, the tumor “respects” the adjacent bony end plate, cortex, and bone contour; however, in larger tumors, a reactive periosteal new bone formation may occur. This is particularly prevalent in those cases involving flat bones like the craniofacial, scapula and pelvic bones. Not uncommonly, an aneurysmal bone cyst may coexist with a chondroblastoma. This combination is seen in about 15-20% of cases and is thought to occur more commonly in the tarsal bones [36]. Chondroblastomas very rarely metastasize. In the cohort by Lu et al. [37], only one case developed lung metastasis. In the series by Lin et al. [38], three patients who had recurrence developed distant metastases. We do not recommend the use of the term *metastasis* for these pulmonary lesions but rather *implants* since they display a benign histology and run a benign clinical course. Malignant transformation is exceedingly rare. In the three cases of metastatic chondroblastoma reported by Lin et al. [38], the tumors recurred locally followed by malignant transformation and metastases.

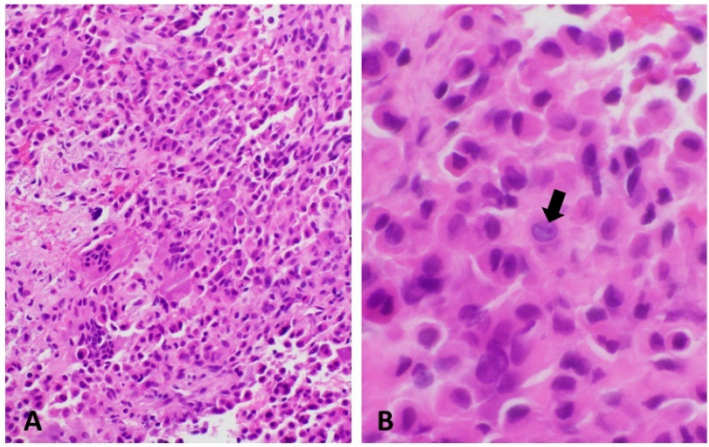

Figure 6. Chondroblastoma. A: In this example, the tumor cells are arranged in sheets imparting a blue cell tumor-like appearance. B. Individual tumor cells have an ovoid to polygonal appearance, some with grooved nuclei (arrow).

Recent studies have identified mutations of Histone-3 in chondroblastomas (and in giant cell tumors of bone) with an estimated incidence of 95% [39]. All the mutations were K36M with a majority in H3F3B and the rest in H3F2A. Substitution with p.Lys36Met in the H3-3B (H3F3B) gene on chromosome 17 is seen in chondroblastoma [39, 40]. These mutations likely represent a dominant driver in the development of these tumors and are rarely detected in other bone tumors. Fang et al. [41] demonstrated that the p.Lys36Met mutations inhibit the H3K36 methyltransferase NSD2 (MMSET) and SETD2 resulting in reduced global H3K36 methylation. A commercially available H3F3 K36M mutant antibody (nuclear stain) is available and is considered a sensitive and specific marker for the diagnosis of chondroblastoma [42].

CHONDROMYXOID FIBROMA

Chondromyxoid fibroma is a benign lobulated cartilaginous tumor composed of immature myxoid mesenchymal tissue, early primitive cartilaginous differentiation and myofibroblasts. The tumor accounts for less than 1% of all bone tumors [43, 44]. It has a male predominance with a sex ratio of about 1.5:1 and has a predilection for patients in the second or third decades of life. Chondromyxoid fibroma can occur at any osseous site but there is a definite predilection for the metaphyseal regions of long bones mostly in the distal femur and proximal tibia. About 25% of chondromyxoid

fibroma occur in flat bones mostly the ileum [45]. Unusual locations, such as in the rib, have been reported [46].

Microscopically, the tumor is typically sharply demarcated from the adjacent non-lesional bone. At low magnification, the tumor displays a general pseudo-lobulated architecture consisting of myxomatous and chondroid areas separated by hypercellular mononuclear cells imparting a lobular appearance with hypocellular centers and hypercellular periphery (figure 7). Multinucleated giant cells may be seen in the hypercellular areas. Distinct tumor nodules separate from the main tumor, can be seen. The cells in the myxoid or chondroid areas are stellate or spindle shaped with indistinct to densely eosinophilic cytoplasm. Cytoplasmic extensions are frequently present. Hyaline cartilage may be seen and has been reported to occur in about 19% of cases [47].

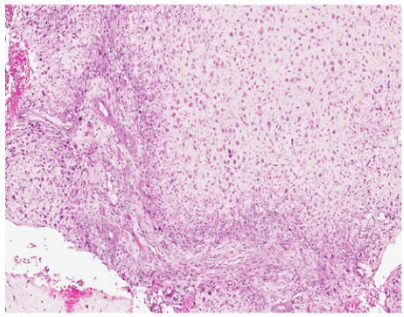

Figure 7. Chondromyxoid fibroma. The tumor has a pseudolobulated appearance. The cells are embedded within a myxoid stroma some of which are hyperchromatic.

Atypical nuclei i.e., enlarged, and hyperchromatic nuclei, have been reported in 20-30% of cases. Mitoses, even atypical mitoses, have been reported [47]. These cases must be differentiated from conventional chondrosarcoma especially when myxoid stromal changes are readily present along with prominent cellularity at the periphery of the lobules. The presence of large amount of well-formed hyaline cartilage matrix is very helpful to make this distinction by virtue of the scarcity of this matrix in chondromyxoid fibroma. In addition, the cells in chondrosarcoma lack the cytoplasmic processes of chondromyxoid fibroma. An exceedingly rare variant of osteosarcoma, the chondromyxoid fibroma-like type, may mimic a chondromyxoid fibroma especially in under-sampled specimens. The distinction relies on the identification of osteoid production by the tumor cells. Luckily, this entity is exceedingly rare [48].

Several studies have identified recurrent chromosome 6 rearrangements in these tumors but the credit for identifying the culprit gene goes to Nord et al. who identified the driver event for chondromyxoid fibroma development. It consists of the recombination of the glutamate receptor gene *GRM1* with several 5' partner genes through promoter swapping and gene fusion events [49]. These rearrangements lead to up-regulated expression of transcripts that include the rearranged coding region of *GRM1*.

The prognosis of chondromyxoid fibroma is excellent and recurrence rates have been reported to occur in approximately 9-15% [50].

OSTEOCHONDROMYXOMA

Osteochondromyxoma is a very rare benign chondroid- and osteoid matrix-producing tumor. The tumor can occur at any age but patients younger than 2 years are particularly predisposed [51-53]. Congenital cases have been reported [52]. The tumor can involve any bone but there is a predilection for the diaphysis of long bones particularly the tibia and the radius as well as the sinonasal bones [54].

Histological features are variable. Typical tumors consist of a mixture of mesenchymal cells, basophilic myxoid material and mucopolysaccharide matrix. While the cells are often arranged in sheets, foci of lobular growth can be identified. The degree of cellularity is proportional to the amount of myxoid matrix [51]. Individual tumor cells are polygonal, stellate, round, and bipolar in shape (figure 8). Cytological features are often bland. The cytoplasm can be vacuolated with occasional inclusion bodies and the nuclei are medium sized with a small nucleolus. Occasional mitotic figures are encountered but atypical forms are seldom seen. Osteoblast-like or chondroblast-like cells are present throughout the tumor.

Osteochondromyxoma is part of the Carney complex, a genetic predisposition syndrome in which most patients carry inactivating mutations in the gene encoding type IA regulatory subunit of PKA, the *PRKAR1A* gene. About 1% of Carney complex patients develop osteochondromyxoma [55]. Pavel et al. [51] postulated that, in Carney complex, the tumor arises from distorted mesenchymal stem cells originally destined to differentiate into osteoblasts.

The prognosis of osteochondromyxoma is excellent when complete excision is achieved. However, this can be challenging when the tumor involves the sinonasal bones. Incomplete excisions are associated with

increased risk or local recurrence. The tumor can be locally invasive mimicking osteosarcoma [56].

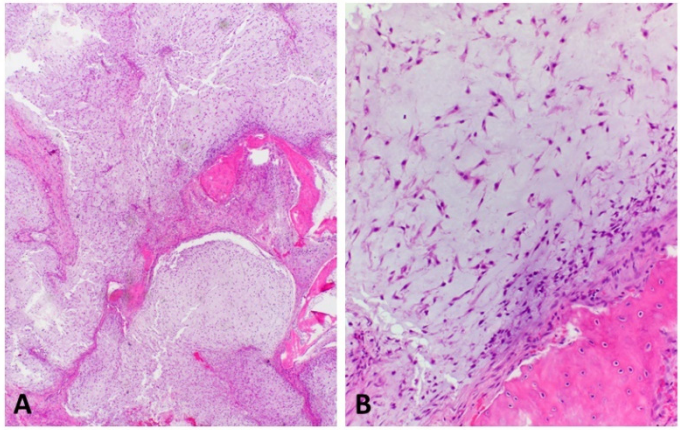

Figure 8. Osteochondromyxoma. A: The tumor may show foci of lobular architecture. B. Individual tumor cells are stellate or bipolar in shape embedded within a myxoid matrix.

SYNOVIAL CHONDROMATOSIS

Synovial chondromatosis is a neoplastic process consisting of multiple nodules of hyaline cartilage. The tumor is commonly intra-articular involving the joint space or subsynovial tissue or extra-articular involving the tenosynovial tissue (tenosynovial chondromatosis). Subsynovial nodules may become detached from the synovium resulting in free floating intra-articular nodules. Any joint can be affected but approximately 60-70% of intra-articular cases involve the knee joint while the hip joint is affected in 20% of cases. The extra-articular subtype commonly arises in the hands and feet [57].

The tumor was first described in 1558 in the knee joint by Ambrose Pare [58], and as loose bodies arising from subsynovial tissues in 1813 by Laennac [59]. Historically considered a metaplastic condition, synovial chondromatosis represents a benign neoplastic process with an estimated incidence of 1.8 cases per 1 million person-years [60]. By fluorescence in situ hybridization, *FN1-ACVR2A* and *ACVR2A-FN1* fusions are identified in more than 50% of benign and malignant cases [61].

Histologically, attached, and loose nodules have similar appearance and consist of clusters of chondrocytes embedded in a matrix of hyaline cartilage. A residual rim of synovial tissue may be present. Chronic lesions may show calcification or endochondral ossification (figure 9). Benign synovial chondromatosis may show atypical cytological features mimicking low-grade chondrosarcoma. One must unequivocally identify marked nuclear enlargement, hyperchromasia and pleomorphism before making this diagnosis. In our experience, the most important feature that correlate with malignancy is the loss of chondrocytes clustering. Additional features such as concentric layers of cartilage and a uniform distribution of chondrocytes within the matrix help identify synovial chondromatosis. Malignant transformation can occur in 5-10% of cases typically in larger tumors and in chronic cases [59]. Malignant tumors may occur de novo as well [62].

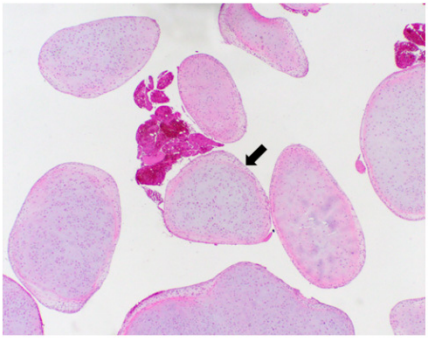

Figure 9. Synovial chondromatosis is composed of nodules of chondrocytes embedded in a matrix of hyaline cartilage. A residual rim of synovial tissue is seen (arrow).

The prognosis of patients with synovial chondromatosis is variable. It has been reported that intra-articular synovial chondromatosis recurs in 15-20% of patients with higher rates reported in patients with extra-articular synovial chondromatosis [60].

MALIGNANT CHONDROGENIC TUMOR

CHONDROSARCOMAS

Chondrosarcomas represent a malignant tumor where the matrix is entirely and uniformly chondroid in nature. Chondrosarcomas are the second most common malignant tumor of bone. They arise throughout the skeleton and