Soft Tissue Special Issue: Chondroid Neoplasms of the Skull

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Abstract

Clinically, radiologically, and pathologically, chondroid neoplasms of the skull can be diagnostically challenging due to overlapping features in each of these domains. Compounding the problem for the pathologist, there is also significant morphologic, immunophenotypic, and molecular genetic overlap between benign and malignant cartilaginous lesions, and the majority of these lesions are encountered quite rarely in routine surgical pathology practice. Each of these factors contribute to the diagnostic difficulty posed by these lesions, highlighting the importance of radiologic-pathologic correlation in the diagnosis. This review is intended to provide an update for surgical pathologists on some of the most commonly encountered chondroid neoplasms in the skull, and includes the following lesions: chondromyxoid fibroma, synovial chondromatosis, chondrosarcoma and variants, and chordoma and variants. For each of these lesions, the differential diagnosis and useful ancillary tests will be discussed in the context of a broad range of additional primary and secondary lesions.

Keywords Chondrosarcoma · Chordoma · Chondromyxoid fibroma · Synovial chondromatosis · Anaplastic chordoma

Introduction

Chondroid neoplasms of the skull are challenging because both benign and malignant lesions are often included in the clinical, radiologic, and pathologic differential diagnosis; thus, multidisciplinary input is vital to making the correct diagnosis. Most malignant neoplasms in the head and neck are diagnosed at an earlier stage than their counterparts in other sites, owing to the anatomic constraints of the skull and earlier symptomatology. For benign and low-grade malignant neoplasms, complete resection is often curative. However, anatomic limitations may render this impossible, and malignant neoplasms have a tendency to recur. This article will review the pathologic features and differential diagnoses of some of the most commonly encountered chondroid neoplasms in the skull, including synovial chondromatosis, chondromyxoid fibroma, chondrosarcoma, and chordoma.

Synovial Chondromatosis

Overview

The skull has only two synovial joints with articular hyaline cartilage and synovial tissue, the atlanto-occipital joint and the temporomandibular joint (TMJ); synovial chondromatosis (SC) of the head and neck has only been reported in the latter. Typically, patients demonstrate limited motion of the TMJ, deviation of the mandible, jaw pain, and sometimes swelling in the preauricular region and external auditory meatus [1, 2]. SC may undergo malignant transformation to chondrosarcoma, which has been reported to be as high as 5–10%, but only three cases have been reported in the TMJ [3–8]. SC is postulated to develop through metaplasia of the synovium and is classified as primary or secondary [9]. In primary SC, emerging evidence shows that greater than 50% of cases, as well as 75% of chondrosarcomas arising in SC, show recurrent rearrangements in the *FNI* and *ACVRA2* genes [8]. Secondary SC arises in the setting of arthropathy.

Pathologic Features

Histologically, SC consists of multiple well-differentiated cartilaginous nodules arising from the synovium, with or without loose cartilaginous bodies in the joint space. The

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nodules are composed of bland chondrocytes in lacunae within a chondroid matrix (Fig. 1). Occasionally, a looser myxoid matrix and endochondral ossification may be seen [10]. Atypical features can sometimes be seen such as hypercellularity, increased cytologic detail, hyperchromatic nuclei, scattered binucleate chondrocytes, and even increased mitotic activity (Fig. 1b and c).

Radiologic Features

Imaging of the TMJ space is crucial to the diagnosis. Panorax may show asymmetry of the condylar heads and/or glenoid fossa. In cases with endochondral ossification and/or calcifications, CT scan characteristically demonstrates multiple, small, rounded, radio-opacities superior to the mandibular condylar head [11]. In the absence of calcification/ossification, MRI often yields better visualization and shows numerous chondroid nodules in an expanded joint space and capsule with joint effusions [11, 12]. In more advanced cases of SC, CT scan may demonstrate bony erosion, including of the skull base, and even intracranial extension [13, 14].

Differential Diagnosis

Cartilaginous lesions that involve the TMJ and enter into the differential diagnosis of SC include chondroma, osteochondroma, chondromyxoid fibroma, tenosynovial giant cell tumor, and chondrosarcoma. Chondromas are exceedingly rare in the jaw/craniofacial bones. The diagnosis of chondroma or enchondroma in the head and neck should only be considered if it is a small (< 1 cm), clinically insignificant lesion without any worrisome radiologic features. Osteochondromas of the TMJ have been reported to involve the coronoid and condylar processes of the mandible [15, 16]. These benign lesions present as exophytic outgrowths of the cortical and medullary bone with an overlying cartilaginous cap (Fig. 1d). The microscopic appearance of the hyaline cartilaginous cap is characteristic, with a linear arrangement of chondrocytes mimicking the microscopic appearance of an epiphysis [17]. Radiographically, osteochondromas demonstrate continuity between the base of the lesion and the

Fig. 1 Histologic features and differential diagnosis of synovial chondromatosis (SC). **a** Nodules of mature cartilage underlying the synovium with focal ossification. **b** Mature chondrocytes residing in lacunae with focal mildly atypical features, including binucleation (arrow). **c** Focal hypercellularity mimicking chondrosarcoma. **d** Differential diagnosis: osteochondroma. Well-organized layering (from

top to bottom) of perichondrium, cartilage cap with increasing cellularity towards deeper layers, endochondral ossification resembling growth plate, and medullary cavity. Radiologic imaging reveals continuity between the medullary cavities of the osteochondroma and normal bone. (**a–d**, hematoxylin and eosin)

medullary cavity of the affected bone. Tenosynovial giant cell tumor, which occurs rarely in the TMJ, presents with similar clinical symptoms to SC and may show chondroid metaplasia, entering into the differential diagnosis on a small biopsy in which only the chondroid component is sampled. Clues to the diagnosis may include a proliferation of histiocyte-like mononuclear cells, with or without giant cells, foamy macrophages, and/or hemosiderin [18].

The most important entity in the differential diagnosis of SC is chondrosarcoma due to oft overlapping histologic features such as increased cellularity, enhanced cytologic detail, binucleate chondrocytes, and even occasional mitoses. However, the criteria for malignancy in chondroid neoplasms should only be applied to central chondroid neoplasms in bone. According to Bertoni et al. microscopic features that may be helpful in distinguishing chondrosarcoma from SC include atypical chondrocytes arranged in sheets, myxoid matrix, increased mitotic activity, nuclear crowding, spindling of the nuclei at the periphery of the nodules, necrosis and, most importantly, permeative growth pattern, particularly infiltration of bony trabeculae [19]. Correlation with imaging and recognition of the extraosseous location is also critical to prevent over-diagnosing chondrosarcoma [10]. Ultimately, due to the rarity of these lesions, distinction between SC and synovial chondrosarcoma may be impossible, even with extensive multidisciplinary input [5].

Chondromyxoid Fibroma

Overview

Chondromyxoid fibroma (CMF) is a benign chondroid tumor, accounting for less than 1% of all cartilaginous tumors, which has been reported rarely in the head and neck, involving sites such as the temporal bone, paranasal sinuses, nasal septum, and skull base [20–23]. Depending on the anatomic site involved, the patient's presenting symptoms may include tinnitus, headaches, pain, hearing loss, vertigo, visual disturbances, and sinonasal congestion.

Pathologic Features

Microscopically, CMF consists of a lobular proliferation of uniform spindled or stellate cells with prominent eosinophilic cytoplasm set in a myxoid background (Fig. 2). Often, the neoplastic cells are concentrated at the periphery of the lobules, with the central area appearing hypocellular (Fig. 2a). Osteoclast-like giant cells may also be seen concentrated at the periphery. Scattered coarse calcifications are seen in about a third of cases (Fig. 2c). Despite its nomenclature, true cartilaginous differentiation with hyaline cartilage is rarely seen and if found, is only a focal feature

[24]. Rare atypical cells may be seen; however, significant pleomorphism or high-grade features are not identified [24].

Radiologic Features

Imaging studies typically demonstrate a well-defined, lytic lesion with sclerotic margins and scalloped or lobulated borders. Cortical expansion may be present. Evidence of intralesional calcifications is identified in approximately 10% of cases [25].

Differential Diagnosis

The most important differential diagnoses of CMF are chondrosarcoma and chondroblastoma. Conventional hyaline type chondrosarcoma does not usually enter into the differential with CMF; hyaline cartilage is rarely seen in CMF and if seen, is usually found only focally. However, conventional myxoid type chondrosarcoma may be mistaken for CMF in a limited biopsy. Features that help differentiate the two are the presence of hyaline type cartilaginous areas and aggressive features such as infiltration of bone trabeculae and soft tissue extension in myxoid type chondrosarcoma, versus only rare hyaline cartilage and a circumscribed border with adjacent bone in CMF.

The presence of osteoclast-like giant cells, lack of significant atypia, and minimal or no mature cartilage raises the diagnostic consideration of chondroblastoma, a lesion that occurs most often in the epiphyseal region of tubular bones. However, chondroblastomas contain a uniform population of ovoid cells with clefted or grooved nuclei and distinct cytoplasmic borders, whereas the lesional cells of CMF have spindled or stellate nuclei [26]. Chondroblastomas are also characterized by the presence of “chicken-wire” calcifications, whereas calcifications are coarse and only occasionally seen in CMF (Fig. 2b, c, and d).

Rarely, depending on the anatomic site, phosphaturic mesenchymal tumor, chordoma, and pleomorphic adenoma may enter into the differential diagnosis of CMF. Phosphaturic mesenchymal tumour (PMT) is exceedingly rare, but may enter the differential diagnosis due to the presence of short spindle cells, osteoclast-like giant cells, and calcifications resembling CMF. However, clinical and radiologic correlation may help distinguish the two; PMT are more common in soft tissue rather than bone, and present with osteomalacia in the majority of cases. They also demonstrate a hemangiopericytoma-like vascular pattern and often grungy matrix calcification rather than discrete coarse calcifications of CMF [27]. Most commonly, chordoma demonstrates lobules of tumor cells embedded in a myxoid or chondroid matrix. The tumor cells, including multivacuolated physaliferous cells, are arranged in cords, which is distinct from CMF. Pleomorphic adenoma

Fig. 2 Histologic features and differential diagnosis of chondromyxoid fibroma (CMF). **a** Low power showing lobulation with cellular condensation at the periphery of the lobules. **b** Differential diagnosis: chondroblastoma. Similar lobular configuration but with more conspicuous osteoclast-like giant cells and calcification. **c** Coarse calcification in CMF versus **d** fine, “chicken-wire” calcification in chondroblastoma. **e** Tumor cells of CMF with bland, spindled nuclei and eosinophilic cytoplasm residing in a myxoid stroma. **f** Differ-

ential diagnosis: pleomorphic adenoma (PA). The bland, spindled myoepithelial cells and chondromyxoid matrix resemble those of CMF. Ductal elements (arrow) are sparse in this stroma-rich example, which could be challenging on a small biopsy. Radiologic imaging is crucial to identify location within the bone (CMF) versus within major or minor salivary glands or lacrimal gland in PA. (**a–f**, hematoxylin and eosin)

demonstrates tumor cells embedded in a chondromyxoid stroma however, ductal elements are typically easy to identify, distinguishing it from CMF (Fig. 2f). In addition, both pleomorphic adenoma and chordoma can be distinguished from CMF via immunohistochemical staining with cytokeratins (CK) and in the case of chordoma, brachyury.

Chondrosarcoma

Overview

Chondrosarcoma is the second most common bone sarcoma after osteosarcoma [28–30]. Up to 12% arise in the head and neck, with almost half in the jaw and craniofacial bones,

about a quarter in the ossified cartilages of the larynx, and the remainder in miscellaneous sites [28, 29]. The most common location for gnathic chondrosarcoma is the maxilla; in the mandible, they most commonly involve the symphysis, coronoid process, and condyle, and are rare in the body.

Conventional chondrosarcomas are classified as primary if they arise *de novo*, with no pre-existing lesion [31]. Secondary conventional chondrosarcomas arise from pre-existing lesions including osteochondroma, particularly in the setting of multiple osteochondromas and enchondromas in Ollier disease and Maffucci syndrome, or rarely in synovial chondromatosis, as discussed above. Craniofacial chondrosarcomas tend to occur in younger patients with approximately one-third of cases occurring in patients under the age of 40 [28, 32–34]. Mesenchymal chondrosarcoma, a rare subtype, also occurs in younger patients with peak incidence between the second and third decades [28, 35, 36]. Clinical and pathologic features of chondrosarcoma of the skull are summarized in Table 1 [34, 37–41].

Pathologic Features

On gross examination, conventional chondrosarcoma is a greyish-white lobulated mass that resembles hyaline cartilage, expands the bone, and permeates through the marrow space. There may be areas of cortical breach with infiltration of the adjacent soft tissues. Scattered calcified flecks impart a gritty texture and there may be areas of myxoid and cystic degeneration. Microscopically, conventional chondrosarcoma demonstrates increased cellularity, more than occasional binucleate chondrocytes, a disorganized

arrangement of cartilaginous lobules, and permeation through bone with disruption of the trabeculae or extension beyond the periosteum (Fig. 3a). It shows enhanced cytologic detail compared to normal pyknotic chondrocytes: more abundant cytoplasm and nuclei with open chromatin, visible nucleoli, and irregular nuclear membranes. There are two morphologic variants of conventional chondrosarcoma: hyaline type with atypical chondrocytes residing in lacunae and surrounded by hyaline matrix (Fig. 3b); and myxoid type with stellate atypical chondrocytes floating in a frothy mucinous matrix (Fig. 3c). Grading of conventional chondrosarcomas and variants is summarized in Table 2 [42, 43]. Other histologic variants of chondrosarcoma, including dedifferentiated (Fig. 3d), clear cell (Fig. 3e) and mesenchymal (Fig. 3f), are summarized in Table 3. Immunohistochemistry (IHC) is of little benefit in the diagnosis of chondrosarcoma, except in distinguishing chondrosarcoma from chondroid chordoma, sarcomatoid carcinoma with chondrosarcomatous differentiation, and in the work-up of mesenchymal chondrosarcoma, particularly if the biopsy material consists only of the undifferentiated component. S100 is positive in both benign and malignant cartilaginous tumors.

Complex cytogenetic events characterize conventional chondrosarcoma [31]. Somatic *IDH1* and *IDH2* mutations have been identified in both benign cartilaginous tumors, including enchondroma and periosteal chondroma, and in central and peripheral conventional and dedifferentiated chondrosarcomas [44–46]. A recurrent *HEY1-NCOA2* fusion is characteristic of mesenchymal chondrosarcoma [47].

Table 1 Chondrosarcoma of the Skull [34, 37–41]

Site	Subsite	Age	Gender	Pathologic features	Outcome
Jaw and paranasal sinuses	Maxilla/maxillary sinus: 44.6%	Mean: 41.6 years	1 M:1F	Mean size: 4.0 cm	<i>Conventional:</i> Local recurrence rate: 33.3% Metastatic rate: ~ 5% Overall survival: • 5 year: 80.7% • 10 year: 65.3% <i>Mesenchymal:</i> Local recurrence rate: 34.8% Overall survival: • 5 year: 59.1–82%; • 10 year: 55%;
	Other paranasal sinuses: 41.1% Mandible: 7.7–10.7%	Range: 15–88 years		Majority conventional: • Grade 1: 65% • Grade 2: 30% • Grade 3: 5% Variants: • Clear cell: 1–2% • Dedifferentiated: < 1% • Mesenchymal: 8%	
Skull base	Temporo-occipital junction: 66% Clivus: 28% Sphenothmoid complex: 6%	Mean: 39 years Range: 10–79 years	1 M:1F	Size: > 6.0 cm Majority conventional: • Grade 1: 51% • Grade 2: 49% • No grade 3 Variants: • Dedifferentiated: < 1% • Mesenchymal: 7.8%	<i>Conventional:</i> Local recurrence rate: < 1.5% Overall survival: • 5 year: 82%–99% • 10 year: 50% <i>Mesenchymal:</i> Overall survival: • 5 year: 62% • 10 year: 22%

Fig. 3 Histologic features and variants of chondrosarcoma. **a** Cortical breach and soft tissue extension (arrow) in low-grade conventional chondrosarcoma, diagnostic of malignancy. **b** Low-grade hyaline type conventional chondrosarcoma with frequent binucleated chondrocytes (arrows) and mildly increased cytologic detail. **c** Myxoid type conventional chondrosarcoma (grade 2) with atypical, stellate chondrocytes in a frothy mucinous matrix. Binucleated chondrocytes are seen (arrow). **d** Dedifferentiated chondrosarcoma with an abrupt transition between well-differentiated and dedifferentiated compo-

nents (arrows). The dedifferentiated component is an undifferentiated pleomorphic sarcoma with pleomorphic spindle cells set in a fibrous background (inset). **e** Clear cell chondrosarcoma with prominent cell borders, clear cytoplasm, and spicules of woven bone. **f** Mesenchymal chondrosarcoma with a cartilaginous lobule among undifferentiated “small round blue cells”. This lesion is diagnostically challenging if only the undifferentiated component is sampled. Figure 3f courtesy of Dr. Elizabeth Demicco and used with permission. (a–f, hematoxylin and eosin)

Radiologic Features

Chondrosarcomas present as a radiolucent mass lesion with stippled or coarse “popcorn” calcifications on plain films or CT scans. Invasion of adjacent structures is a

helpful feature that is highly suggestive of malignancy. Any chondroid tumor of the head and neck greater than 1.0 cm in size should be assumed to be a chondrosarcoma until proven otherwise.

Table 2 Histologic grading of chondrosarcoma

Low grade Includes clear cell chondrosarcoma (grade 1) and myxoid chondrosarcoma (grade 2)	Grade 1 (also called atypical cartilaginous tumor)	Atypical chondrocytes with more abundant cytoplasm and most with small dark nuclei; multiple nuclei per lacuna; mild to moderate cellularity; no mitosis; mostly hyaline matrix
	Grade 2	Atypical, moderate-sized chondrocytes with more vesicular nuclei; < 2 mitoses/10 HPFs; greater cellularity; extensive myxoid matrix
High grade Includes mesenchymal chondrosarcoma (grade 3)	Grade 3	Greater cellularity; atypical chondrocytes with pleomorphic nuclei; ≥ 2 mitoses/10 HPFs; myxoid or spindled matrix (peripheral spindling)
Dedifferentiated chondrosarcoma		

HPF high power field

Table 3 Uncommon histologic variants of chondrosarcoma [28, 34–36, 92, 93]

	Dedifferentiated	Mesenchymal	Clear cell
Epidemiology	Arises in 10–15% of central conventional chondrosarcoma, but less than 1% of H&N chondrosarcoma	8.8% of H&N chondrosarcoma	2% of all chondrosarcoma, H&N sites in 5%
Site	<ul style="list-style-type: none"> Same as conventional (maxilla, larynx) 	<ul style="list-style-type: none"> Jaw 1/3 extraosseous (meninges) 	<ul style="list-style-type: none"> Larynx in half of cases
Grade	3	3	1
Low-grade, hyaline-type conventional component	Yes, with non-cartilaginous high-grade sarcoma	Yes, with high-grade undifferentiated component	Some, often lack chondroid matrix
Histologic features	Dedifferentiated component: <ul style="list-style-type: none"> Abrupt transition to non-cartilaginous high-grade sarcoma Most commonly undifferentiated pleomorphic sarcoma or osteosarcoma 	Undifferentiated component: <ul style="list-style-type: none"> Small, round to oval tumor cells with hyper-chromatic nuclei, inconspicuous nucleoli, and minimal cytoplasm Hemangiopericytoma-like vascular pattern 	Clear cell component: <ul style="list-style-type: none"> Sheet-like growth Abundant clear to eosinophilic cytoplasm Well-defined cytoplasmic borders Small, centrally located nuclei with minimal atypia Rare mitoses Irregularly shaped trabeculae of immature woven bone between tumor cells (often)

Differential Diagnosis

Radiologic-pathologic correlation is critical for primary lesions of bone. Distinguishing chondroma from low-grade conventional chondrosarcoma can be challenging on biopsy and curetted specimens, but a permeative growth pattern seen radiologically or histologically confirms a chondrosarcoma. In a biopsy with equivocal histologic and radiologic features, along with borderline size, a diagnosis of “low grade chondroid neoplasm” is recommended. Noting the precise anatomical location by imaging is also important as chondroid chordoma must also be excluded for chondroid neoplasms of the skull base (see section on Chordoma).

High-grade cartilaginous neoplasms of the head and neck are sarcomatoid carcinomas (of cutaneous, mucosal, or salivary origin) or chondroblastic osteosarcoma until proven otherwise, due to the relative commonness of these lesions

compared to high-grade chondrosarcoma. Careful review of the clinical history for prior head and neck carcinomas, adequate sampling to identify a residual well-differentiated or in situ component, and immunohistochemical evaluation for immunoreactivity with CKs and/or p40 are helpful to identify sarcomatoid carcinomas (Fig. 4a and b). A lack of staining with CKs and immunoreactivity for S100, or identification of areas of conventional chondrosarcoma, also eliminate a metastatic clear cell carcinoma in the differential diagnosis for clear cell chondrosarcoma.

Morphologic features that favor chondroblastic osteosarcoma over chondrosarcoma are high grade histology (the majority of gnathic osteosarcomas are high grade); seamless blending of malignant cartilage with osteosarcoma (Fig. 4c), in contrast to dedifferentiated chondrosarcoma where there is an abrupt transition between the differentiated and dedifferentiated components; and mandibular location, especially

Fig. 4 Differential diagnosis of chondrosarcoma. **a** Sarcomatoid carcinoma: this core needle biopsy from bone shows a pleomorphic spindle cell lesion with myxoid stroma, resembling high grade chondrosarcoma. **b** Cocktail immunohistochemistry for cytokeratins 8/18 and AE1/3 is strongly and diffusely positive in the spindle cells from

Fig. 4a. This case was a metastatic sarcomatoid renal cell carcinoma. **c** Chondroblastic osteosarcoma: chondroblastic areas resembling mature cartilage merging seamlessly into osteoblastic areas. **d** Delicate neoplastic osteoid surrounds the chondrocytes in chondroblastic osteosarcoma (arrow). (**a**, **c**, **d**, hematoxylin and eosin)

the body, where osteosarcoma is more common [48]. The identification of malignant osteoid intimately associated with the tumor cells is another key feature to distinguish chondroblastic osteosarcoma from high-grade conventional or dedifferentiated chondrosarcoma (Fig. 4d). The osteoid may be arranged in delicate “filigree” strands, coarse, lace-like patterns, or thick, irregular trabeculae, and it lacks osteoblastic rimming, which helps to distinguish it from reactive new bone formation. Although exceedingly rare in the head and neck, clear cell chondrosarcoma can also be mistaken for osteosarcoma, due to the lack of chondroid matrix and irregularly shaped trabeculae of woven bone.

A core biopsy from a mesenchymal chondrosarcoma can be misleading if only the undifferentiated component is sampled, for which the differential diagnosis includes Ewing Family of Tumors (EFT), lymphoma, rhabdomyosarcoma (RMS), malignant melanoma, small cell osteosarcoma, and poorly differentiated synovial sarcoma.

Unfortunately, due to overlapping profiles with many of these tumors, IHC may not be helpful in some instances. For example, the undifferentiated component is usually positive for CD99, and may also demonstrate focal immunoreactivity with desmin and myoD1, which overlaps with EFT and RMS respectively, although myogenin is usually negative. It is typically negative for CD45, CKs, and HMB45, helping to eliminate lymphoma, carcinoma, and metastatic melanoma from the differential diagnosis [30, 35, 49]. Both components of mesenchymal chondrosarcoma are immunoreactive for SOX-9 making it a somewhat useful marker in distinguishing it from other small round blue cell tumors, although recent literature shows that SOX-9 is also expressed in a majority of synovial sarcoma as well [50, 51]. Ultimately, additional sampling to identify the differentiated cartilaginous component or molecular analysis for the *HEY1-NCOA2* fusion is recommended to confirm a mesenchymal chondrosarcoma.

Important points

- All bone tumors should only be diagnosed in conjunction with radiologic findings
- Low grade cartilaginous neoplasms of the head and neck more than 1.0 cm in size are chondrosarcomas until proven otherwise
- High grade cartilaginous neoplasms of the head and neck are sarcomatoid carcinomas (of cutaneous, mucosal, or salivary gland origin) or chondroblastic osteosarcoma until proven otherwise
- Chondroid chordoma must be excluded in cartilaginous tumors involving the skull base
- A diagnosis of “low grade chondroid neoplasm” is recommended for any low grade chondroid mass of the head and neck with equivocal radiologic findings and borderline size

Chordoma

Overview

Chordoma is a rare malignant bone tumor of notochord origin, arising along the central neural axis [52, 53]. The skull base is the primary site for ~32% of chordomas and the cervical spine for ~5% of chordomas [52–54]. At these sites, it affects males and females equally and tends to present one decade earlier than other sites. Symptoms are related to mass effect including headache, neck pain, diplopia or cranial nerve palsy [37]. Very rarely, chordoma has been reported in extra-axial locations, including sites such as the nasopharynx, paranasal sinuses, lateral nasal wall, oropharynx, and soft tissue of the neck [55–62]. Some extra-axial chordomas of the nasopharynx are associated with a sinus tract extending from the clivus [58, 59]. In rare pediatric cases, there appears to be an association with tuberous sclerosis [63].

Pathologic Features

Grossly, chordomas are lobulated masses that typically extend beyond the cortex and have a gelatinous or chondroid cut surface. Microscopically, conventional chordoma consists of cords of tumor cells arranged in lobules separated by thin fibrous septae and embedded within a myxoid matrix (Fig. 5). The tumor cells have abundant eosinophilic cytoplasm, some with intracytoplasmic vacuoles, referred to as “physaliferous” cells (Fig. 5c, inset). Atypia in chordoma ranges from low-grade, with uniform tumor cells and occasional mitoses, to high-grade with significant nuclear pleomorphism and frequent mitoses, with some cases having areas of both. Necrosis is frequent and may be extensive.

Chondroid chordoma is a distinct histologic subtype that accounts for 7–63% of skull base chordomas [37, 64]. The tumor cells of chondroid chordoma are identical to

conventional chordoma, but the matrix resembles neoplastic hyaline cartilage (Fig. 5b) [38, 65, 66]. Other uncommon histologic types are summarized in Table 4. Dedifferentiated chordoma describes a conventional chordoma juxtaposed to an undifferentiated pleomorphic sarcoma or osteosarcoma [65]. Some authors also recognize sarcomatoid chordomas as a distinct entity in which there is no conventional component or there is a more gradual transition between the conventional and sarcomatoid components, and in which the spindle cell component retains cytokeratin and brachyury expression [67]. Cellular chordoma consists of sheets of tumor cells with conventional cytologic features, including physaliferous cells, without an extracellular myxoid matrix (Fig. 5c) [68]. Poorly-differentiated (anaplastic) chordomas lack physaliferous cells and consist of tightly packed small epithelioid cells with increased nuclear-to-cytoplasmic ratios and irregular nuclei [68]. The tumor cells are arranged in irregular nests and sheets with a more fibrous background. Chordomas with rhabdoid morphology have also been described [68, 69].

Chordomas express CKs by IHC, typically strongly and diffusely, although on occasion, expression may be focal [64]. They are usually positive for EMA and S100. Nuclear expression of brachyury, a marker of notochord differentiation, is highly specific for chordoma (Fig. 5d), although poorly-differentiated and dedifferentiated areas may show loss [64, 69–72]. Decalcification of the tissue may also lead to loss of brachyury expression. Studies have reported loss of INI-1 staining in poorly differentiated chordoma, particularly in children [73–81].

Most chordomas are sporadic; however, a subset appear to be inherited. Duplication of brachyury, a transcription factor encoded by *T* gene, has been implicated in familial chordomas, whereas sporadic chordomas may demonstrate *T* gene amplification or single nucleotide polymorphisms [82–84]. *IDH1* and *IDH2* mutations, which are frequently seen in conventional chondrosarcomas, are not detected in chordomas [44, 85].

Radiologic Features

Chordoma generally presents as an expansile, soft-tissue density mass in the clivus, with lytic destruction of bone and moderate, often heterogeneous enhancement [86]. Distinction from skull-base chondrosarcoma is difficult since both may show similar imaging findings [87, 88].

Differential Diagnosis

The histologic similarities between chondroid chordoma and chondrosarcoma may pose a diagnostic challenge, especially on limited and/or crushed biopsy material typical of skull base lesions [64]. Ancillary studies are frequently required and the most discriminatory immunostains are combined positivity for CK and brachyury to distinguish chondroid

Fig. 5 Histologic features, variants, and differential diagnosis of chordoma. **a** Conventional chordoma with cords of epithelioid cells embedded in a myxoid matrix. **b** Chondroid chordoma, with chordoma cells embedded in a hyaline matrix, closely mimicking chondrosarcoma. **c** Cellular chordoma with sheets of epithelioid cells and little intervening matrix. Abundant multivacuolated physaliferous cells were present in this case (inset, arrow). **d** Immunohistochemis-

try for brachyury with uniform strong nuclear positivity in chordoma. **e** Differential diagnosis: myoepithelioma. Nests and chords of bland myoepithelial cells embedded in a fibromyxoid stroma. **f** Differential diagnosis: chordoid meningioma. Ovoid meningioma cells are arranged more singly within a myxoid matrix. Nuclear pseudoinclusions characteristic of meningioma can be seen (arrow). (**a–c**, **e–f**, hematoxylin and eosin)

chordoma from chondrosarcoma [64]. EMA is not entirely specific since chondrosarcomas may demonstrate immunoreactivity [64, 89, 90]. A recent study has shown that both D2-40 and SOX-9 can be positive in chordoma and are therefore not helpful in distinguishing the two [64].

Although expression of CK is helpful to separate chordoma from chondrosarcoma, it is not helpful in

distinguishing conventional chordoma from metastatic mucinous or clear cell carcinomas [70–72]. In addition, co-expression of CKs and S100 alone will not help distinguish chordomas from myoepithelial tumors, including mixed tumor, parachordoma, myoepithelial carcinoma, and myoepithelioma (Fig. 5e) [55, 56, 90]. Expression of brachyury is critical in these instances as it is consistently

Table 4 Uncommon histologic variants of chordoma [65, 68, 94]

	Cellular	Dedifferentiated	Poorly differentiated/anaplastic
Epidemiology	<ul style="list-style-type: none"> • Rare • Demographics not well-established, likely same as conventional 	<ul style="list-style-type: none"> • Rare • Often seen in recurrences or post-radiotherapy 	<ul style="list-style-type: none"> • Rare • Most commonly occurs in children • Commonly skull base/clival
Pathologic features	<ul style="list-style-type: none"> • Sheets of back to back epithelioid cells with more abundant cytoplasm than poorly-differentiated chordoma • Physaliferous cells present • Little to no intervening matrix 	<ul style="list-style-type: none"> • Differentiated chordoma component with abrupt transition to high-grade sarcoma • High grade component most commonly undifferentiated sarcoma or osteosarcoma • Dedifferentiated component often loses brachyury expression 	<ul style="list-style-type: none"> • Sheets of closely packed small epithelioid cells with increased N:C ratios • Physaliferous cells are absent • Collagenous background • Increased mitotic activity and atypia • Loss of INI1
Prognosis	Same as conventional chordoma	Poor	Poor

expressed in chordoma but negative in these other entities [70].

Distinguishing chordoma from chordoid meningioma and chordoid glioma can be challenging; both entities are so named because they microscopically resemble chordoma (Fig. 5f). Both tumors consist of cords of epithelioid tumor cells with well-defined cell borders, embedded within a myxoid or mucinous stroma, and the tumor cells of chordoid meningioma may be vacuolated. In chordoid meningioma, areas of conventional meningioma are usually intermixed; however, these may be absent on a small biopsy. CK, EMA, and S100 positivity may be seen in all three tumors; however, only chordoma is positive for brachyury [91]. In addition, out of the three tumors, only chordoid glioma is positive for GFAP [91].

Important points

Chondroid chordoma may be misdiagnosed as chondrosarcoma, particularly on a limited biopsy from the skull base

Cellular and poorly differentiated (anaplastic) chordoma may be mistaken for metastatic carcinoma due to the presence of epithelioid tumor cells, lack of matrix and cytokeratin positivity

Extra-axial chordomas may be mistaken for myoepithelial tumors of salivary gland or soft tissue origin

Conclusions

Chondroid neoplasms of the skull may be challenging to pathologists due to their overall rarity and overlapping morphologic features, even between benign and malignant lesions. A conclusive diagnosis may not always be possible on a small biopsy and descriptive diagnoses are an acceptable alternative in these situations, with a deferral to the resection specimen for a final diagnosis. However, to aid in the diagnosis at time of biopsy, careful consideration of the histomorphology in conjunction with the radiologic,

immunohistochemical, and if applicable, molecular pathologic findings, is recommended. Finally, multidisciplinary input, for example in a tumor board setting, may offer the patient and pathologist the best opportunity for a correct and conclusive diagnosis.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to disclose.

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