Chordoma of the Head and Neck: A Review

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Abstract Chordoma is a rare malignant bone tumor that can arise anywhere along the central neural axis and many involve head and neck sites, most commonly the skull base. The relative rarity of these tumors, combined with the complex anatomy of the head and neck, pose diagnostic challenges to pathologists. This article describes the pertinent clinical, pathologic, and molecular features of chordomas and describes how these features can be used to aid in formulating a differential diagnosis. Emphasis is placed on key diagnostic pitfalls and the importance of incorporating immunohistochemical information into the diagnosis.

Keywords Chordoma · Chondrosarcoma · Skull base · Brachyury · Head and neck

Introduction

Chordoma is a rare malignant bone tumor that can arise anywhere along the central neural axis [1, 2]. Chordoma is a unique entity in that it is a malignant tumor derived from remnants of the notochord, an embryonic structure that is required for the induction of the neural plate in the embryonic disk. Among head and neck sites, the majority arise in the skull base with a small minority arising along the cervical spine [1–3]. Chordomas have also been reported in extra-axial locations in the head and neck [4, 5], including the nasopharynx, paranasal sinuses, lateral nasal wall,

oropharynx, and the soft tissue of the neck [6–11]. Some extra-axial chordomas of the nasopharynx are associated with a sinus tract extending from the clivus [7, 10]. Males and females are affected equally and head and neck chordomas tend to present one decade earlier than other sites. Chordomas tend to be slow growing tumors and symptoms of head and neck chordomas are related to mass effect including headache, neck pain, diplopia or cranial nerve palsy [12]. Some chordomas in children may be associated with tuberous sclerosis complex although the behavior of these tumors does not appear to differ from their sporadic counterparts [13].

Pathologic Features

The typical chordoma appears grossly as a lobulated mass with a gelatinous or chondroid cut surface. When centered in bone, the tumor typically extends beyond the cortex into the surrounding soft tissue. Microscopically, the conventional chordoma is composed of cords of tumor cells embedded within a myxoid matrix and arranged in lobules separated by fibrous septa (Fig. 1a). The diagnostic “physaliferous” cells have abundant eosinophilic cytoplasm and intracytoplasmic vacuoles, although the relative proportion of these features varies from tumor to tumor (Fig. 1b). Although all chordomas are malignant by definition, cytologic atypia ranges from low grade, with uniform tumor cells and occasional mitoses, to high-grade with significant nuclear pleomorphism and frequent mitoses. Tumor heterogeneity with regards to atypia may be seen. Necrosis is frequent and may be extensive.

Pathologists need to be aware of several distinct histologic subtypes of chordoma that, on initial inspection, lack the typical features of a conventional chordoma. These subtypes include chondroid chordoma, cellular

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Fig. 1 Conventional chordoma. **a** Conventional chordoma consists of cords of tumor cells arranged in lobules, separated by thin fibrous septae and embedded within a myxoid matrix. **b** The tumor cells have abundant eosinophilic cytoplasm and prominent cytoplasmic borders. The characteristic physaliferous cells have vacuolated cytoplasm

Fig. 2 Chondroid chordoma. **a** The tumor cells of chondroid chordoma are identical to conventional chordoma, with cords of tumor cells arranged in lobules and physaliferous cells, however the matrix resembles neoplastic hyaline cartilage. **b** At high power, scattered vacuolated physaliferous cells are seen

chordoma, poorly differentiated chordoma and dedifferentiated chordoma. Chondroid chordoma accounts for 7–63% of skull base chordomas [12, 14]. Like conventional chordoma, chondroid chordoma consists of cords of tumor cells arranged in lobules, with physaliferous cells; however the matrix resembles neoplastic hyaline cartilage (Fig. 2) [15–17]. Cellular chordoma is composed of sheets of tumor cells, including physaliferous cells, with little to no myxoid stroma (Fig. 3) [18]. Poorly differentiated chordomas are composed of tightly packed, small, atypical epithelioid cells arranged nests and sheets with a fibrous background and lack physaliferous cells [18]. Chordomas with rhabdoid cells have been described, and may represent a poorly differentiated chordoma [14, 18]. A conventional chordoma that demonstrates an abrupt transformation into an undifferentiated pleomorphic sarcoma or osteosarcoma is described as a dedifferentiated chordoma [15]. Historically, “atypical chordoma” has been described in the literature, however the criteria are not well established and this group likely contains both cellular and poorly differentiated chordomas and thus, the use of this term is discouraged [18].

Immunohistochemistry

A recommended immunohistochemical panel to aid in the differential diagnosis for head and neck chordomas outlining the most common immunohistochemical profiles is shown in Table 1. All chordomas, including the specific histologic subtypes described above, express cytokeratins (Fig. 4a) and most are immunoreactive for epithelial membrane antigen (EMA) (Fig. 4b) and S100 protein. The most specific marker of chordoma is brachyury, a nuclear protein associated with notochord differentiation (Fig. 4c) [19–22]. While expression of brachyury is highly specific for chordoma, poorly differentiated tumors and dedifferentiated areas may demonstrate loss of brachyury immunoreactivity [14, 19, 20, 22]. Importantly, immunoreactivity for brachyury may also be lost following decalcification and effort should always be made to procure tumoral tissue for immunohistochemistry prior to decalcification. On occasion, chondroid chordoma may demonstrate only focal cytokeratin expression [14]. Interestingly, some studies have reported a loss of SMARCB1/INI1 staining in poorly differentiated chordomas although the significance of this finding is not yet established [23–25].

Fig. 3 Cellular chordoma. **a** Cellular chordoma consists of sheets of typical chordoma tumor cells, including physaliferous cells, but lack either a myxoid or chondroid matrix, and thus can be mistaken for carcinoma. **b** At high power, the vacuolated physaliferous cells are seen scattered throughout the tumor

Differential Diagnosis

Chordoma must be differentiated from a variety of other lesions including chondrosarcoma (Fig. 5a), meningioma (Fig. 5b), myoepithelioma/myoepithelial carcinoma (Fig. 5c), and glioma; and metastatic carcinomas such as mucinous adenocarcinoma and clear cell renal cell carcinoma. Other than involvement restricted to the clivus, seen only in chordoma, the clinical distinction between

skull-base chordoma and chondrosarcoma is difficult and typically requires a biopsy, since both demonstrate similar clinical, CT and MRI findings [26, 27]. Moreover, the histologic similarities between chondroid chordoma and chondrosarcoma may pose a diagnostic challenge, especially on limited and crushed biopsy material that is typical of skull base lesions [14].

Ancillary studies are frequently required for skull base biopsies and the most discriminatory immunostains are combined cytokeratin and brachyury to distinguish chondroid chordoma from chondrosarcoma [14]. EMA is a sensitive marker for chordoma; however, it is not entirely specific since chondrosarcomas may also demonstrate immunoreactivity [14, 28]. A recent study has shown that both D2-40 and SOX-9, a homeobox transcription factor involved in chondrogenesis, can be positive in chordoma and are not helpful in distinguishing chondrosarcoma from chordoma [14].

Although expression of cytokeratins is helpful to distinguish chordoma from chondrosarcoma, it is not helpful in distinguishing conventional chordoma from metastatic mucinous or clear cell carcinomas without immunoreactivity for brachyury and S100 protein [19–21]. Poorly differentiated chordomas may be particularly challenging to diagnose as they consist of small atypical epithelioid cells immunoreactive for cytokeratins and lack the characteristic physaliferous cells and myxoid matrix. Addition of brachyury and S100 immunostains for any skull base tumor is highly recommended.

Co-expression of cytokeratins and S100 protein, along with EMA, will not help distinguish chordomas from myoepithelial tumors, including mixed tumor, myoepithelioma, parachordoma and myoepithelial carcinoma [4, 5, 29]. Distinguishing chordoma from myoepithelial tumors requires immunohistochemical evidence of brachyury expression, in addition to cytokeratins and S100 [4, 5].

Table 1 Immunohistochemical panel to aid in the differential diagnosis for chordoma demonstrating the most frequent immunoprofiles

Entity	Recommended immunohistochemical panel				Other
	Cytokeratin	EMA	S100	Brachyury	
Chordoma	Positive	Positive	Positive	Positive	
Conventional Chondrosarcoma	Negative	Negative/ focal	Positive	Negative	
Chordoid meningioma	Variable	Variable	Variable	Negative	PR
Chordoid glioma	Variable	Variable	Positive	Negative	GFAP
Mixed tumour/myoepithelial-rich tumours	Positive	Positive	Positive	Negative	
Extra-skeletal myxoid chondrosarcoma	Negative	Positive	Negative	Negative	NR4A3 rearrangements
Metastatic adenocarcinoma	Positive	Positive	Negative	Negative	Site specific immunohistochemical markers

EMA epithelial membrane antigen, PR progesterone receptor, GFAP glial fibrillary acid protein

Fig. 4 Conventional chordoma, demonstrating diffuse staining with **a** cytokeratin AE1/3, **b** S100, and **c** brachyury

Extraskelletal myxoid chondrosarcoma shares overlapping histologic features with soft tissue conventional chordoma. Both are soft tissue neoplasms with tumor cells arranged in cords and set in a myxoid background. Although both express S100 protein and extraskelletal myxoid chondrosarcoma may express EMA [29], extraskelletal myxoid chondrosarcoma is negative for cytokeratins and brachyury. In addition, extraskelletal myxoid chondrosarcoma demonstrate rearrangements involving *NR4A3* gene, most commonly *NR4A3-EWSR1* fusion.

Distinguishing chordoma from chordoid meningioma and chordoid glioma can be challenging. Chordoid meningioma and chordoid glioma are so named because both microscopically resemble chordoma. Both tumors consist of cords of epithelioid tumor cells with well-defined cell borders, embedded within a myxoid or mucinous stroma, and tumor cells of chordoid meningioma may be vacuolated.

Fig. 5 Differential diagnosis. Differential diagnosis for chordoma include **(a)** chondrosarcoma, **(b, c)** chordoid meningioma, and **(d)** myoepithelioma. **a** Conventional hyaline chondrosarcoma may have “vacuoles” within the stroma, which at low power may mimic physaliferous cells; however, the tumor cells reside within lacunae, rather than having corded appearance. Although chondrosarcomas are S100 positive and may be EMA positive, they are negative for cytokeratin and brachyury. A chordoid meningioma **(b)** can look identical to a conventional chordoma at low power with vacuolated tumor cells set in a myxoid stroma, but foci of typical meningioma **(c)** are often seen. The typical meningioma areas may be absent on biopsy, but chordoid meningiomas are negative for brachyury. A myoepithelioma **(d)**, with its corded neoplastic cells set in a chondromyxoid stroma, can be confused with a chordoma however physaliferous are not present. Although myoepithelioma are typically immunoreactive for cytokeratins, S100 and EMA, they are negative for brachyury

In chordoid meningioma, traditional meningioma areas are intermixed, aiding with the diagnosis; however, this may be absent on a small biopsy. Cytokeratins, EMA and S100 positivity may be seen in all three tumors; however, only chordoma is positive for brachyury [30]. Chordoid gliomas are

strongly positive for glial fibrillary acidic protein (GFAP), however conventional chordoma and chondroid chordoma may demonstrate focal GFAP immunoreactivity [14, 30].

Molecular Alterations

As a relatively rare tumor, few studies to date have investigated the molecular landscape of chordomas and the studies that have been performed were small. For example a recent study of nine chordomas using ultra-deep sequencing analysis identified hot-spot mutations in the genes TP53, KIT, and KDR and all three of these genes have been shown previously to be involved in chordoma oncogenesis [31]. Decreased expression of *PTEN*, overexpression of *PDGFR-α*, *EGFR*, *Raf-1*, components of the mTOR pathway and activation of the STAT3 pathway have been identified in chordoma and are associated with tumor progression and/or poor prognosis [32–35]. Recent studies have shown down-regulation of various microRNAs implicated in tumor growth, progression and prognosis [36–38]. Recurrent clival chordomas have demonstrated MGMT promoter methylation [39]. Additional studies are required to determine if these markers have the potential to serve as prognostic markers and therapeutic targets in chordoma patients.

Genetic alterations in the gene encoding for brachyury, a transcription factor encoded by *T* gene, have been identified in both sporadic and familial cases. Notably, duplication of brachyury has been described in familial chordomas [40]. In contrast, the much more common sporadic chordoma may demonstrate *T* gene amplification and single nucleotide polymorphism in the coding region of the *T* gene [41, 42]. Cytogenetic studies of chordomas have demonstrated several anomalies, including losses of 1p and 3p, and gains in chromosomes 7 and 19 [43–45].

IDH1 and *IDH2* mutations, which are frequently seen in conventional chondrosarcomas, are not detected in chordomas [46, 47].

Management and Prognosis

The primary treatment modality for chordomas typically consists of surgical resection followed by adjuvant radiotherapy. Chordomas of the skull base are always resected in a piecemeal fashion, which precludes the pathologic assessment of margins. As a result, post-operative imaging is the preferred method for documenting the presence or absence of residual tumor. Unfortunately, complete resection is only achieved in 29% of cases and most tumors recur locally despite adjuvant radiotherapy to the tumor bed [12]. Although skull base chordomas and chondrosarcomas are treated similarly, distinction between the two is important since chondrosarcomas carries a better prognosis [12, 26, 48–51]. The local recurrence rate for

skull base chondrosarcoma is 1.5% (up to 53% without adjuvant radiotherapy), whereas the local recurrence rate for skull base chordoma is 68%. The 5-year and 10-year overall survivals are more favourable for skull base chondrosarcoma (82–88.5 and 50%, respectively), compared to skull base chordoma (63–78.4 and 16–32%, respectively) [12, 26, 48–51].

Traditionally, chordomas are not sensitive to chemotherapy. Early studies assessing the efficacy of *EGFR* inhibitors, as well as imatinib, have been promising, particularly in locally advanced and metastatic chordoma [52–56].

Chondroid chordoma has been reported by some to have a better prognosis [57–59], however most recent studies have demonstrated that conventional and chondroid chordomas have similar outcomes [22, 26, 28, 60–63]. Children under the age of 5 years are diagnosed with a disproportionately high frequency of poorly differentiated chordomas, which is associated with an overall worse prognosis for this age group [18, 25, 62, 64–68]. Indeed, conventional and chondroid chordomas in pediatric patients appears to have similar or better survival when compared to adults [18, 57, 62].

Overall, poorly differentiated and dedifferentiated chordomas are more aggressive tumors with rapid tumor growth and higher rates of metastases. Chordomas most commonly metastasize to the lung, followed by the lymph nodes, bone, liver, and subcutaneous tissues [15, 64, 65]. In adults, sacral and vertebral chordomas are more likely to metastasize than skull base ones with metastatic rates ranging from 3% to almost 50% [15, 66, 69]. Chordomas in children under the age of 5 are much more likely to metastasize (up to 58% of cases) compared to children 5 years of age or older (only 8.5% of cases), reflecting the poorly differentiated histology seen more commonly in very young children [18, 64, 65]. Other adverse prognosticators include older age (≥ 50 years) with conventional or chondroid histology and larger tumor size at presentation (≥ 4.0 cm) [12].

Conclusion

Chordoma is a malignant tumor of notochord origin that can arise in various sites throughout the head and neck. While rare, chordomas are important to recognize as they can easily be confused for other more common entities with very different treatments and prognoses. Pathologists also need to be aware of histologic subtypes of chordoma that can mimic other high-grade sarcomas or carcinomas. Despite optimal medical management, most chordomas recur and future strategies will need to focus on targeted molecular therapies that eliminate residual tumor cells. More large studies are needed to the molecular alterations driving chordoma oncogenesis and growth.

Compliance with Ethical Standards

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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