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The DOI for this manuscript is doi: 10.5858/arpa.2020-0258-RA

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.
Chordoma
A Review and Differential Diagnosis

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The history of notochordal lesions has its origin in 1846, when Virchow observed a small slimy excrescence on the surface of the clivus. He published these findings using the term *echodrosis physaliphora sphen-o-occipitalis* in 1857. Luschka also independently described a similar structure in 1856. As the name implies, at that time it was erroneously believed that the lesion originated from cartilage. The true notochordal nature was pointed out by Müller in 1858, but his theory was disputed until 1895 when it was proved by Ribbert through convincing animal experiments. In 1894 Ribbert suggested using the term *chordoma*, which has been used ever since.

Today, the World Health Organization (WHO) recognizes 3 distinct types of chordoma: conventional chordoma, dedifferentiated chordoma, and poorly differentiated chordoma. All 3 tumor types are malignant, with a high rate of local recurrence and metastasis. The metastatic rate approaches 40% in noncranial cases of chordoma, with the highest rates and the worst prognosis in the dedifferentiated chordoma type.

The common axial skeletal location of chordoma often results in incomplete surgical resection. Attempts at treatment with radiation, proton therapy, and/ or conventional chemotherapy have shown limited efficacy, including limited success with intratumoral chemotherapy. Recent and ongoing studies have improved our understanding of the molecular abnormalities in chordoma, leading to novel clinical trials.

**Epidemiology and Clinical Features**

Chordomas are uncommon malignant neoplasms (0.8 cases per 1 million population/year), with a rate much lower than osteosarcoma (1.7–4.4 cases per 1 million population/year depending on the age group), Ewing sarcoma (~3 cases per 1 million population/year), and chordrosarcoma (2.9–8.8 cases per 1 million population/year).

Chordomas may present at any age, but most arise between 40 and 60 years of age; less than 5% of cases occur before the age of 20 years and these lesions are usually skull based. Most chordomas (~95%) are intrasosseous tumors involving the axial skeleton, with the base of skull/clivus, vertebral bodies, and sacrococcygeal bones affected in roughly equal proportions. There appears to be a male predominance (2:1) in sacrococcygeal and vertebral body cases, but no sex difference in tumors involving the skull base. Rare cases may involve the...
appendicular skeleton or arise in the soft tissue; the term *chordoma periphericum* is used in this latter situation. These soft tissue chordomas are histologically and immunophenotypically identical to osseous lesions and have a similar metastatic rate.25

Clinical presentation depends on the lesion's anatomic location. Skull-based chordomas often present with headache, neck pain, and cranial nerve palsies, whereas lesions of the mobile spine and sacrum typically result in chronic back pain or urinary/bowel dysfunction due to nerve root compression.9

Computed tomography imaging usually demonstrates a midline, expansile, destructive lobulated mass that invades the adjacent tissues, with lytic bone destruction and soft tissue extension.26 Calcifications within the lesion typically represent entrapped fragments of native bone, not matrix mineralization.27 On T1-weighted magnetic resonance imaging (MRI) chordomas show a predominantly iso-intense signal relative to muscle with focal areas of hyperintensity (Figure 1, A).26,28 High signal intensity is present on T2-weighted MRI due to the lesion’s myxoid matrix, and a lobular appearance may be seen due to septa of low signal intensity (Figure, 1 B).12,27 Chordomas characteristically show moderate to marked gadolinium enhancement with honeycomb appearance,26,29 have isointense or intermediate signal on fluid attenuated inversion recovery (FLAIR) images, and have only limited radioisotope uptake on bone scans.27,30

**PATHOLOGY**

**Notochord Development and Tumor Formation**

Chordomas have notochordal differentiation; therefore, understanding notochord development is helpful in understanding tumor characteristics. Animals from the phylum Chordata possess a notochord during embryologic development.31 The notochord is a rodlike axial structure of mesenchymal origin that serves as the primitive axial skeleton and has an important role in structural support and patterning of ectodermal and mesodermal tissues, including the neural tube and somitic derivatives.32,33 The notochord is composed of notochordal cells, with large intracytoplasmic vacuoles, surrounded by an acellular notochord sheath rich in collagens, laminins, and proteoglycans, which contributes to its mechanical properties.33,34

The mesenchyme around the notochord undergoes segmentation and condensation to form future vertebral bodies.35 The notochord slowly disappears at the levels of vertebral body formation, but notochordal cells are retained within the developing nucleus pulposus. After birth, notochordal cells in the nucleus pulposus are gradually replaced by small cartilage-like nucleus pulposus cells, a process usually complete by early adulthood.34,36,37 Notochordal remnants within the vertebral bodies have been reported in many species, including humans, and it has been suggested that residual dormant notochordal cells may be the source of notochordal rests and tumors.32,37–43 In addition, persistent segments of the notochord have been reported in a few patients.44 Conversely, soft tissue
Chordomas do not arise in regions of notochord formation and notochordal remnants have not been found associated with them, thus questioning whether notochordal remnants are the precursor for notochordal tumor development.25

Gross Pathology

Grossly, chordoma is an expansile, lobulated intraosseous mass that permeates the bony cortex and invades the adjacent tissues (Figure 1, C and D). Lesions are variable in size, ranging from 4 to 22 cm in one study42 and have a gelatinous tan-grey cut surface (Figure 1, D).9

Histopathology

Currently the WHO histologically defines 3 types of chordoma: conventional chordoma, dedifferentiated chordoma, and poorly differentiated chordoma; chordoid chordoma is considered a subtype of conventional chordoma.9

Chordomas exhibit an infiltrative, lobulated low-power appearance, with lobules separated by fibrous bands (Figure 2, A). Within the lobules reside short chords, nests, and single large epithelioid cells with clear to light eosinophilic cytoplasm in an abundant myxoid matrix (Figure 2, B; Figure 3, A and B); in some areas lesional cells may become sheeted. Tumor cell nuclear features are often heterogeneous throughout the neoplasm, with areas containing low-grade–appearing nuclei and other areas with high-grade pleomorphic to spindled nuclei. Nuclear pseudoinclusions may be present and large cells with bubbly clear to eosinophilic cytoplasm (physaliphorous cells) are characteristic (Figure 2, B). Necrosis is often present and may be extensive. In most cases mitotic figures are readily identifiable, particularly in high-grade–appearing areas (see Figure 3, B).9

Chondroid chordoma, a variant of conventional chordoma, contains areas in which the matrix has the appearance of hyaline cartilage. This may be focally identified or diffusely present throughout the lesion. Nearly all cases of chondroid chordoma arise in the base of the skull (Figure 4, A and B).43

Dedifferentiated chordoma is a biphasic neoplasm with 2 distinct components: a conventional chordoma component and a high-grade sarcoma component (Figure 5, A through C). The high-grade sarcomatous component typically has the appearance of a high-grade undifferentiated spindle cell to pleomorphic sarcoma or a high-grade osteosarcoma.9 There is usually an abrupt transition between the 2 components, but they may be intermixed.9 A few studies have found TP53 mutations in the dedifferentiated component, suggesting a role for aberrant p53 inactivation in chordoma dedifferentiation.44 The dedifferentiated component is more commonly diagnosed post radiotherapy and in recurrent chordomas after surgical resection, but de novo cases with dedifferentiated chordoma diagnosed on primary excision have been reported.45,46 Both the conventional chordoma and high-grade sarcomatous components should be present for diagnosis, but some cases with only the sarcomatous component have been reported post radiotherapy at a site of the previously treated conventional chordoma.47

Poorly differentiated chordoma is a rare type of chordoma (~60 cases in the English language literature) that was included as a distinct entity in the most recent (5th) edition of the WHO Classification of Tumours of Soft Tissue and Bone.9 These lesions are seen in children and young adults, with a slight (~2-fold) female predominance, and most commonly involve the skull base (clivus) or cervical spine, with only rare cases reported in the sacrococcygeal region. These
tumors are characterized by loss of SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1/INI) expression, usually due to heterozygous or homozygous deletions involving SMARCB1. Histologically, these tumors contain cohesive sheets or nests of epithelioid cells with eosinophilic cytoplasm and scattered intracytoplasmic vacuoles imparting a signet ring appearance. Nuclei are round to ovoid with mild-moderate atypia and a focal rhabdoid morphology is often seen, typical of tumors with loss of SMARCB1/INI expression. Numerous mitotic figures and geographic necrosis are common. Physaliphorous cells, typical of conventional chordoma, are absent and extracellular myxoid stroma is absent or only focally present. An essential diagnostic criterion is loss of SMARCB1 (INI1) expression. This subtype of chordoma is associated with a poor prognosis, worse than conventional chordoma.

**Immunohistochemistry**

Like the fetal notochord, chordomas express certain keratins (cytokeratin [CK] 8, CK18, and CK19), are often positive for epithelial membrane antigen (EMA) and S100 protein, and negative for CK7 and CK20 (Table 1). Brachyury, a T-box transcription factor encoded by the TBXT gene on chromosome 6, is involved in embryonic notochord development. Brachyury shows nuclear expression in both the fetal notochord and chordomas, but not in many other types of neoplasms including chondroid tumors.

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**Figure 3.** Conventional chordoma, histology. A, Chordoma infiltrates and destroys the native bone. B, Mitoses (see arrow) are often readily apparent (hematoxylin-eosin, original magnifications ×40 [A] and ×400 [B]).

**Figure 4.** Conventional chordoma (chondroid subtype) histology. A and B, This case of chondroid chordoma arose in the clivus. Notice chondroid areas with a hyaline cartilage matrix (hematoxylin-eosin, original magnifications ×200 [A] and ×400 [B]).
and myoepithelial tumors, making it a highly sensitive and specific immunohistochemical marker for chordoma (Table 1). 52

Any or all of these markers may be lost in the sarcomatoid component of a dedifferentiated chordoma (Figure 5, B). 13,52,54 In poorly differentiated chordomas, tumor cells are positive for broad-spectrum CKs and brachyury; they show loss of SMARCB1/INI1 and S100 protein is rarely expressed. 9,14,15,30,35

**Molecular Pathology**

Most chordomas are sporadic, but several familial cases have been identified. 56–58 Somatic duplication of TBXT was identified in 27% of sporadic cases. 16 Germline tandem duplication of TBXT was identified in 3 families with chordoma (in 16 family members) with an autosomal dominant pattern of inheritance. 57 In one study a common genetic variant of TBXT, rs2305089, was observed in all familial cases evaluated and it was associated with an increased risk of developing sporadic chordomas in nonfamilial cases. 57,58 Monosomy of chromosome 1 and gain of chromosome 2, 6, and 7 are frequent cytogenetic abnormalities seen in chordoma. 59,60,61

Comparative genomic hybridization has demonstrated homozygous or heterozygous loss of CDKN2A and CDKN2B in ~70% of cases. 62 Amplification of epidermal growth factor receptor gene (EGFR) is a common finding with 40% of chordomas harboring copy number gains of 7p12, where EGFR is located. 63 In addition, aberrant EGFR expression and signaling have been identified in a high number of chordomas, with increased EGFR protein expression in 69% of tumors and EGFR phosphorylation in 51% of tumors. The EGFR inhibitor tyrphostin has been shown to inhibit growth of a chordoma-derived cell line. 63 A high percentage of chordomas have also been shown to overexpress MET proto-oncogene (MET), another tyrosine kinase. 64

Driver events in PI3K signaling genes, such as activating mutations in PIK3CA and truncating variants of phosphatase and tensin homolog (PTEN), were identified in ~16% of chordomas, providing a rationale for therapeutically targeting the PI3K pathway in these cases. Some promising activity has been observed in patients with chordoma undergoing therapy with imatinib and tacrolimus, the latter targeting the mechanistic target of rapamycin (mTOR) pathway. 16,65 In 17% of the tumors, driver events were also identified in chromatin-remodeling genes, such as ARID1A and PBRM1 (SWI/SNF complex genes) and SETD2. 16 Other epigenetic modifications such as DNA hypomethylation/hypermethylation and microRNA (miRNA) regulation have also been investigated in chordomas. Specifically, 9 hypermethylated/hypomethylated regions were identified: C3, XIST, TACSTD2, FMR1, HIC1, RARB, DLEC1, KL, and RASSF1. 66,67 A separate study 64 showed that the gene copy number of miR-608 and miR-34a is reduced in most chordoma cells and correlates with the downregulated expression levels of miR-608 and miR-34a. These miRNAs inversely correlate with EGFR and MET levels. 64

Thirteen pediatric chordoma cases have been reported in association with tuberous sclerosis complex (TSC). The cases analyzed showed biallelic inactivation of either TSC1 or TSC2 in chordoma cells. Children with TSC appear to be diagnosed with chordomas at an earlier age (including prenatal or neonatal presentations) than children without TSC. The clinical outcome for TSC patients with chordoma appears to be relatively favorable with an estimated 5-year

**Figure 5.** Dedifferentiated chordoma histology. A, This case of a de novo dedifferentiated chordoma contains a conventional chordoma component (left side of image). B, Brachyury immunohistochemical stain is positive in the conventional chordoma component but is lost in the dedifferentiated component. C, Higher-power view of the high-grade spindle cell component (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [C]; original magnification ×100 [B]).
Table 1. Immunohistochemical Findings in Chordoma and Morphologically Similar Lesions

<table>
<thead>
<tr>
<th></th>
<th>Brachyury</th>
<th>Cytokeratin</th>
<th>EMA</th>
<th>S100</th>
<th>Other Positive Stains or Molecular Markers</th>
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<tr>
<td>Chordoma</td>
<td>+ (nuclear)</td>
<td>+ (CK8, CK18, CK19;</td>
<td>+ (± in dediff.)</td>
<td>+ (± in dediff.)</td>
<td>Deletion of SMARCB1 (loss of INI1) in poorly differentiated type</td>
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<tr>
<td></td>
<td></td>
<td>± (CK7, CK20)</td>
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<td></td>
<td></td>
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<tr>
<td>Myoepithelial tumors</td>
<td>–</td>
<td>± (CK8, CK18)</td>
<td></td>
<td>+</td>
<td>EWSR1 rearrangement (50%)</td>
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<tr>
<td></td>
<td></td>
<td>± (CK7, CK20)</td>
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<tr>
<td>Chondrosarcoma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>IDH1 or IDH2 mutations</td>
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<td>Chordoid meningioma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+ (focal)</td>
<td>Somatostatin receptor</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFAP, progesterone receptor CK7</td>
</tr>
<tr>
<td>Chordoid glioma</td>
<td>–</td>
<td>±</td>
<td>±</td>
<td>–</td>
<td>GFAP</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Marker positivity in primary sites, eg: PAX8, TTF1, GATA3</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
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</table>

Abbreviations: CK, cytokeratin; dediff., dedifferentiated; EMA, epithelial membrane antigen; EWSR1, Ewing sarcoma breakpoint region 1; GATA3, GATA binding protein 3; GFAP, glial fibrillary acidic protein; IDH, isocitrate dehydrogenase; PAX8, paired box gene 8; SMARCB1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; TTF1, thyroid transcription factor 1; +, positive; –, negative; ±, either positive or negative.

Survival of 83% (median follow-up of 5 years); however, the study numbers were small. mTOR inhibitors have shown activity against other TSC-associated tumors, but studies are needed to investigate their role as a treatment option for TSC-associated chordoma.68–70

Tissue microarray immunohistochemistry demonstrated absent or reduced protein expression of the tumor suppressor fragile histidine triad (FHIT) in 98% of sacral chordomas and 67% of skull base chordomas.71 Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations are absent in chordomas, aiding in the distinction from chondrosarcoma.72,73

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of chordoma includes various benign and malignant entities. Benign lesions with morphologic similarity include echondrosis physaliphora (EP) and benign notochordal cell tumor (BNCT). EP often presents as a polypoid mass arising on the clivus (echondrosis physaliphora sphenoo-occipitalis), but may be found in the dura anywhere from the skull base to the sacrum. EP is considered a hamartomatous extraskeletal lesion derived from notochordal remnants. BNCT is a benign intraosseous neoplasm with notochordal differentiation. Both EP and BNCT are usually small, asymptomatic lesions incidentally discovered at autopsy.12 In an autopsy study from Japan, foci of BNCT were identified within the axial skeleton in 20% of cadavers.74 On computed tomography studies, BNCT is confined to the bone without cortical permeation (Table 2).75–78 Both EP and BNCT show intermediate to high signal intensity; however, unlike chordomas, they usually lack contrast enhancement and soft tissue extension on imaging studies.9,26,75–78 Both EP and BNCT contain cells with abundant vacuolated clear to eosinophilic cytoplasm and the immunoprofile is identical to chordoma. EP and BNCT have well-delineated borders (BNCT is confined to the bone without cortical permeation) and lack a lobular architecture, necrosis, conspicuous mitoses, and high-grade nuclei. Additionally, BNCT lacks extracellular myxoid matrix.9,12,79 In contrast, chordoma is frankly invasive and often demonstrates necrosis, conspicuous mitoses, and high-grade nuclei (Table 2).9

BNCTs were identified in 7.3% of sacral/coccygeal resections performed for chordoma, suggesting that they may represent a precursor lesion.7 Furthermore, some studies have shown BNCT with areas of atypia and even cases of BNCT recurring as chordoma. Alternatively, based on the distinct separation between the BNCT and chordoma within the same specimen, the possibility that a chordoma developed coincidentally in the vicinity of a BNCT remains a possibility.77

Carter et al80 proposed *atypical notochordal cell tumor (ANCT)* terminology that could be applied to notochordal tumors when the criteria for either BNCT or chordoma are not met. The authors showed that all 4 cases of ANCT investigated had imaging characteristics most consistent with BNCT, except for minimal cortical permeation, mild gadolinium enhancement, and soft tissue extension in 3 cases, with typical BNCT morphology. The fourth case had typical BNCT imaging and histologic features, with the exception of a myxoid matrix (Table 2).80 ANCT is not currently widely used as diagnostic terminology, but such lesions could represent a transitional stage from BNCT to chordoma.9,77,80

Chondrosarcomas may enter the radiographic and microscopic differential diagnosis of chordoma. Both chordoma and chondrosarcoma entrap bony trabeculae as they infiltrate the marrow, which may have a similar radiographic appearance to true peripheral ossification of the lobules of a cartilaginous neoplasm (“ring and arc” pattern).12,81 Chondroid chordomas by definition contain areas in which the matrix has the appearance of hyaline cartilage; however, areas of nonchondroid chordoma are often present pointing to the correct diagnosis. Additionally, chondrosarcomas are negative for epithelial markers (CKs and EMA) and brachyury, and may contain mutations in IDH1 or IDH2 (Table 1). These mutations are not seen in chordoma.9,77,78

Myoepithelial tumors of the soft tissue (and less commonly bone) are usually positive for epithelial markers (CK8, CK18, and EMA) and S100 protein, negative for CK7 and CK20,53 often contain a myxoid matrix, and may have epithelioid cells
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Abbreviations: BNCT, benign notochordal cell tumor; MRI, magnetic resonance imaging.

protein (GFAP), and brachyury (Table 1).83,84

receptor 2A, progesterone receptor, and focal S100 protein, omas, they are positive for CK7, EMA, somatostatin images with strong, mostly homogenous enhancement and often show hypointense to isointense signal on T1-weighted imaging characteristics is difficult, as chordoid meningiomas chordoma (eg, clivus), differentiating these entities on supratentorial. When located at anatomic sites similar to equina, and filum terminale) of young adults. Most cases have a papillary appearance, in which cuboidal to elongated tumor cells radially surround hyalinized to myxoid vascular cores; however, there are cases that lack a papillary architecture, instead containing sheets of polygonal cells with associated myxoid matrix, which may be confused with chordoma. Myxopapillary ependymoma lacks atypia and the

mitotic rate is low. Tumor cells are positive for GFAP, S100, and vimentin and negative for CK and brachyury (Table 1).83 Carcinomas often metastasize to bone and are positive for epithelial markers, potentially mimicking chordoma. Most types of carcinoma are negative for S100 protein and brachyury, and express markers that will aid in the identification of a primary site of carcinoma (eg, paired box gene 8 [PAX8], TTF1, GATA-binding protein 3 [GATA3], caudal type homeobox 2 [CDX2]). Morphology, immunohistochemical analysis, and correlation with chest, abdomen, and pelvic imaging usually point to a primary site.

TREATMENT

Currently, the mainstay of chordoma treatment is en bloc resection, but the axial location of most cases often makes it difficult to completely resect the tumor. Most unresectable cases receive radiation therapy, while adjuvant radiation may be added in some cases. High-dose photon/proton radiation therapy performed on unresectable chordomas yields a 5-year local control rate of ~85%, with ~89% disease-specific survival and ~20% rate of distant failure.85 Chordomas are highly resistant to conventional chemotherapy, but clinical trials are currently underway that aim to treat chordoma with targeted therapy.

Cyclin-dependent kinase inhibitor 2A (CDKN2A; p16INK4A) deletion in chordoma cells results in increased cyclin-dependant kinase 4 (CDK4) activity. In one study, CDK4 expression was assessed via Western blot in chordoma cell lines and 10 freshly isolated primary chordoma specimens; 7 of the 10 primary chordoma specimens demonstrated high CDK4 expression levels and none of the 10 patient samples showed p16INK4A expression. This study also found that high CDK4 levels were associated with metastasis and recurrence, and treatment with palbociclib, a small-molecule CDK4/6 inhibitor, decreased cell growth and proliferation.13 There is currently an open phase II clinical trial (ClinicalTrials.gov Identifier: NCT03110744) evaluating the efficacy of palbociclib in cases of locally advanced/metastatic chordoma in patients who are not candidates for standard therapy.86

Another open phase II clinical trial assessing the safety and efficacy of tazemetostat, a small-molecule inhibitor of

<table>
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<tr>
<th>Histology</th>
<th>Imaging</th>
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<tr>
<td><strong>Chordoma</strong></td>
<td>Lobules containing short chords or nests of large epithelioid cells with clear to light eosinophilic and vacuolated cytoplasm</td>
</tr>
<tr>
<td></td>
<td>Abundant myxoid matrix</td>
</tr>
<tr>
<td></td>
<td>Variable atypia</td>
</tr>
<tr>
<td></td>
<td>Necrosis and mitoses are common</td>
</tr>
<tr>
<td><strong>Ecchordosis physaliphora</strong></td>
<td>Cells with abundant vacuolated clear to eosinophilic cytoplasm</td>
</tr>
<tr>
<td></td>
<td>No necrosis, mitoses, or atypia</td>
</tr>
<tr>
<td></td>
<td>Myxoid matrix</td>
</tr>
<tr>
<td><strong>BNCT</strong></td>
<td>Cells with abundant vacuolated clear to eosinophilic cytoplasm</td>
</tr>
<tr>
<td></td>
<td>No necrosis, mitoses, or atypia</td>
</tr>
<tr>
<td></td>
<td>No myxoid matrix or lobular architecture</td>
</tr>
<tr>
<td><strong>Atypical notochordal cell tumor</strong></td>
<td>Usually the same as BNCT (rarely myxoid matrix)</td>
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</table>

Abbreviations: BNCT, benign notochordal cell tumor; MRI, magnetic resonance imaging.
enhancer of zeste homolog 2 (EZH2), an enzyme involved in chromatin remodeling, is being conducted in solid tumors with INI1 loss, including INI1-negative chordomas, as determined by immunohistochemistry or molecular testing (ClinicalTrials.gov Identifier: NCT02601950).87

Although EGFR gene mutation is almost never present in chordomas, as previously mentioned, EGFR protein is often overexpressed. Sensitivity to the tyrosine kinase inhibitor afatinib in chordoma cell lines has been reported as well as its efficacy in mouse models.88 It was found that afatinib had the ability to promote degradation of EGFR and brachyury. An open phase II European study is currently assessing the efficacy of afatinib in cases of inoperable, recurrent, or metastatic chordoma.89

In one study, increased PDGFRB expression was seen in all 18 analyzed chordomas. Six patients with advanced disease were treated with imatinib mesylate, which demonstrated antitumor activity.67,90 Efficacy of imatinib was evaluated in a phase II trial (ClinicalTrials.gov Identifier: NCT00150072) with 32.4% of patients showing some clinical benefit; however, the tumor objective response rate was 0%.91 A related treatment, pilotinib, is currently under investigation in combination with radiation therapy in a phase I study (ClinicalTrials.gov Identifier: NCT01407198).67,92

Studies assessing immune regulation have shown that chordoma cell lines and tissue specimens express high levels of programmed cell death ligand-1 (PD-L1) and the expression of PD-L1 is correlated with tumor-infiltrating lymphocytes.93 There is currently a phase II study assessing the benefit of combining the monoclonal antibodies nivolumab (anti–programmed cell death-1 [PD-1]) and relatlimab (anti–lymphocyte activation gene-3 [LAG-3]) in patients with advanced chordomas.94 Additionally, there is a separate phase I study assessing the safety of nivolumab alone or in combination with stereotactic radiotherapy in recurrent or metastatic chordoma.95

Two phase II trials are currently investigating the use of brachyury therapeutic vaccines (Yeast-Brachyury Vaccine, ClinicalTrials.gov Identifier: NCT02383498 or MVA-BN/FPV-Brachyury, ClinicalTrials.gov Identifier: NCT03595228) in combination with radiotherapy.66,96

PROGNOSIS

The prognosis of chordoma depends on tumor location (which correlates with resectability), the presence of absence of metastases, patient age, and the presence or absence of dedifferentiation. A study using data from 357 spinal chordomas in the Surveillance, Epidemiology, and End Results registry found 3-, 5-, and 10-year overall survival rates of 80.5%, 68.4%, and 39.2%, respectively. The 3-, 5-, and 10-year disease-specific survival rates were 89.0%, 80.9%, and 60.1%. Overall survival was decreased in the setting of nonsurgical therapy, distant metastasis, and age 60 years or older.22 The median survival time for patients with all types of chordomas is 6.3 years.18 In contrast, overall survival in dedifferentiated chordoma of the spine is only ~16 months.89

Poorly differentiated chordoma type with SMARCB1/INI1 loss has a worse prognosis than conventional chordoma.9 Poor expression of brachyury and copy number gain of the T gene, gain of chromosome arm 2p, and lack of irradiation were significantly associated with shorter progression-free survival.99 Increased expression of PDGFRB has been associated with increased dural invasion in clival chordomas and worse prognosis.87,100

Tauziede-Espariat et al11 assessed 108 cases of chordoma and proposed a histopathologic and immunohistochemical grading system that correlates with patient progression-free survival (PFS) and overall survival (OS). A point was awarded for the presence of each of the following parameters: (1) Ki-67 labeling index of 6% or greater, (2) p53 labeling index of 25% or greater, (3) a poorly differentiated component (defined as containing sarcoma-tous cells or epithelioid cells arranged in a solid pattern), (4) necrosis, (5) prominent nucleoli, (6) apoptosis, or (7) or more mitoses per 10 high-power fields. Based on cumulative score, tumors were considered low-grade (scores <4) or high-grade (scores ≥4). Tumor grade significantly correlated with PFS and OS (median PFS = 75.0 months for low-grade tumors and 26.0 months for high-grade; median OS = 146.5 months for low-grade and 11.2 months for high-grade). While this grading system is not widely used in clinical practice, it is mentioned owing to the significant number of chordoma cases analyzed in the study.11

CONCLUSIONS

Chordomas are malignant neoplasms with notochordal differentiation that primarily involve the axial skeleton, often making complete surgical resection difficult or impossible. Most cases have the classic morphology of conventional chordoma, but a subset of cases have undergone dedifferentiation or lost INI1, resulting in more biologically aggressive neoplasms. Treatment of chordoma has largely been predicated on surgical excision, which is often incomplete, thus yielding poor results; however, several fairly recently identified molecular alterations have led to ongoing clinical trials using targeted therapy.

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