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CASE REPORT

Intra-articular extra-axial chordoma of the wrist: a case report with review of the current literature

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Abstract

Chordomas are rare bone malignancies that are thought to arise from remnants of the notochord and usually are located in the axial skeleton. Immunophenotypical matching neoplasms primarily found in appendicular locations, referred to as extra-axial chordoma, are rarely encountered by radiologists, surgeons, and pathologists. Only a few of these cases have been described in the literature with only one intra-articular case with involvement of the knee joint. We present the first case of an intra-articular extra-axial chordoma of the wrist. Diagnostic imaging patterns were initially ambiguous and histopathological reprocessing was crucial in order to determine the diagnosis of an intra-articular neoplasm with co-expression of cytokeratins, S-100 protein, and brachyury.

Keywords Extra-axial chordoma · Intra-articular · Wrist · Brachyury · Notochord

Introduction

Chordomas are a rare neoplasm accounting for only 1–4% of all malignant bone tumors [1]. With a slightly higher occurrence in males, chordomas can affect all age groups, but the majority of lesions are diagnosed in the fifth to seventh decades of life. The tumor genesis is connected to undifferentiated notochordal cell remnants and thus most chordomas occur in the spine (32.8%), skull base (32%), and sacrococcygeal bones (29.2%). Additionally, a small number of chordoma-like neoplasms are found in the extra-axial skeleton and soft tissues [2]. If primarily located in appendicular locations, these chordoma-like neoplasms are referred to as chordoma peripheriсum, parachordoma, or extra-axial chordoma. Due to their rarity, these tumors pose a diagnostic challenge for clinicians and radiologists. In addition to a complete radiological workup, immunohistochemical analysis is crucial to identify the expedient histological characteristics. Aside from conventional HE staining, which shows a characteristic appearance including physaliferous tumor cells embedded in a myxoid matrix, immunohistochemical analysis reveals the co-expression of keratins and S-100 and a diagnostic distinct nuclear positivity for brachyury [3].

To the best our knowledge, we present the first reported case of an intra-articularly located extra-axial chordoma of the wrist.

Case report

A 40-year-old male patient was referred to our institution for evaluation of a growing mass located at his right wrist. Recurrent periods of pain were noted, connected to certain movements or when applying pressure to trigger points along the wrist. A history of previous surgery or trauma involving the wrist was denied. Examination showed a well-visible swelling of the wrist and upon palpation, a deeply located tender-to-elastic, fixed mass was noted. Motility of the wrist was severely impaired. Circulation, sensation, and motor function distal to the wrist were normal.

Radiographs of the right wrist showed multiple erosions of the carpal bones as well as the bases of the metacarpal bones (Fig. 1), which appeared relatively well

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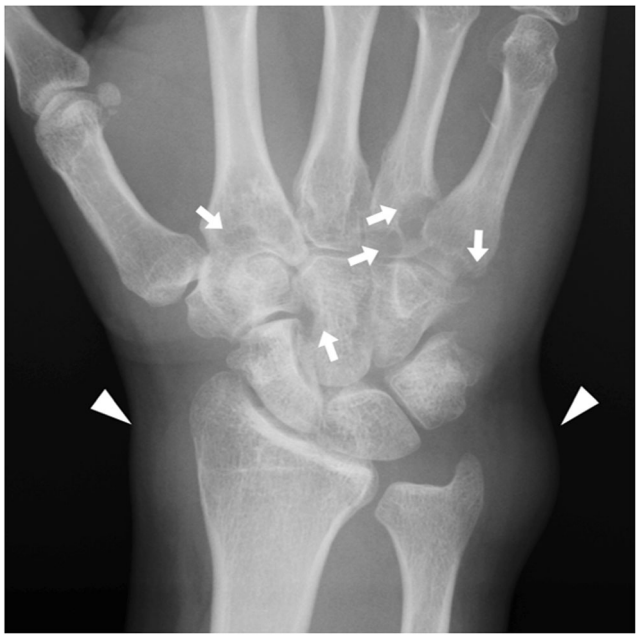

Fig. 1 AP radiograph of the right wrist showing multiple carpal and metacarpal bone erosions with non-sclerotic margins (*white arrows*) as well as a dense soft tissue mass (*white arrowheads*)

defined with non-sclerotic margins. MR imaging revealed an intra-articular carpal mass with intermediate signal intensity on T1- (Fig. 2a), and high signal intensity with hypointense septations on T2-weighted images (Fig. 2b, c). Predominantly peripheral enhancement was seen on contrast-enhanced MR images (Fig. 2d, e). The lesion involved all carpal joint compartments including the distal radioulnar joint and caused multiple bone erosions without evidence of bone marrow edema. Considering the patient's clinical findings and MR imaging features, showing a lobulated intraarticular mass with marked T2 hyperintensity and peripheral contrast enhancement, synovial osteochondromatosis was suggested as the most likely diagnosis. Similar to radiography however, unenhanced computerized tomography (CT) also did not show any calcifications of tumor tissue, and several bone erosions showed irregular and indistinct margins (Fig. 3a, b). Therefore, the diagnosis of synovial chondromatosis was doubted and incisional biopsy for histopathological evaluation was indicated.

Following preoperative medical assessment, surgical incision was performed along the base of the fourth metacarpal bone. The operative site revealed a soft, multi-chambered cyst-like mass with ill-defined margins. Further inspection revealed tumor infiltration of more deeply located tendons, capsules and bone. A 0.5-cm-large, partly synovial and soft tissue section from the dorsal side of the wrist and a 0.3-cm-large, partly synovial and soft tissue section from the base of the fourth metacarpal bone were obtained. Following primary closing of the wrist under draining via Redon catheter, the post-surgical evaluation did not show any complications.

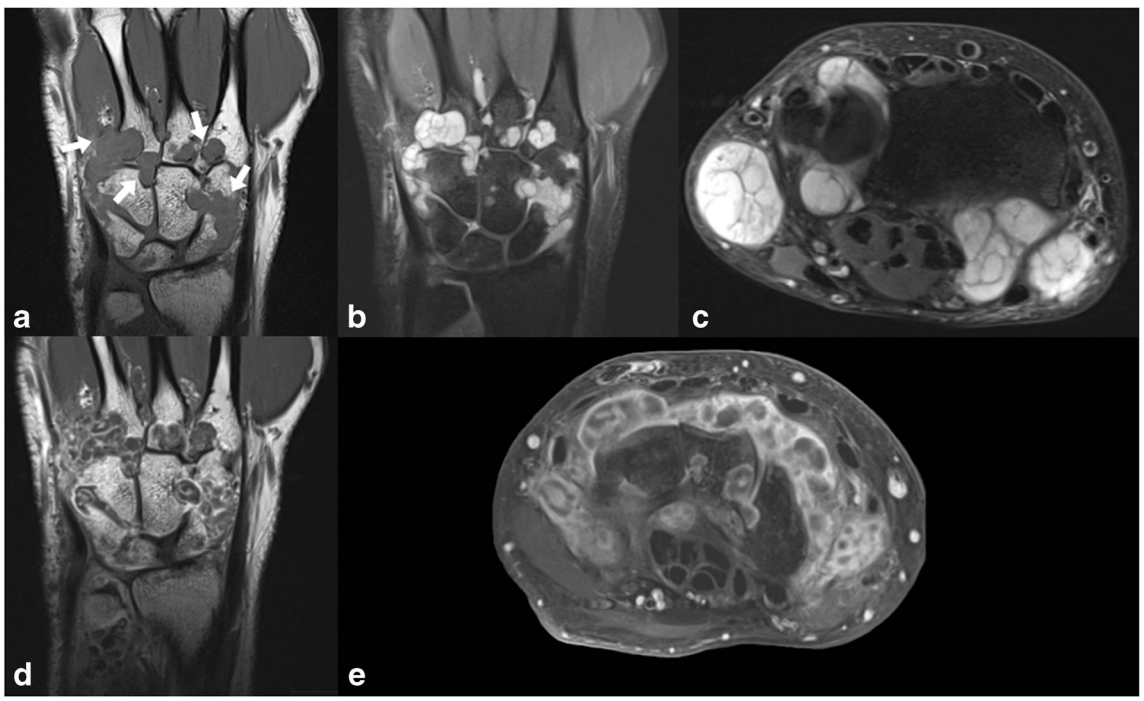

Fig. 2 MR imaging of the right wrist. **a** Coronal T1-weighted TSE images shows a large intraarticular mass (*white arrows*) of intermediate signal intensity with multiple bone erosions. On coronal and axial T2-weighted images with fat-suppression, the well-defined lobulated lesion reveals hyperintense signal intensity with fine separations (**b**, **c**). Coronal and axial contrast-enhanced images shows peripheral and septal enhancement (**d**, **e**)

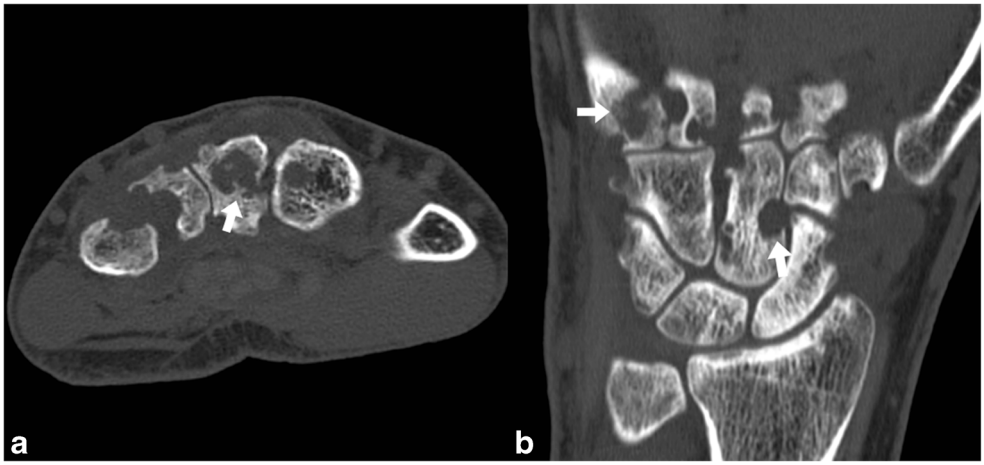

Fig. 3 Axial and coronal CT reformation images show erosions involving the metacarpal bones as well as several carpal bones (**a**, **b**). The lesions lack a sclerotic margin and appear partially ill defined. (**a**, **b**, *white arrows*). Note absence of calcifications within the soft tissue mass

On histological analysis, performed with conventional hematoxylin and eosin staining, all tumor nodules showed features suggestive of a chordoma.

Further immunohistochemical work-up to confirm the diagnosis and exclude differential diagnosis revealed a co-expression of CKpan MNF116, EMA, p63, and (weak nuclear and cytoplasmatic) S-100 protein. There was no immunoreactivity for p16 and INI1 expression was retained. CDK6 showed nuclear positivity whereas CDK4 was negative. Furthermore, Rb and phospho-RB were expressed in tumor cells. In an immunoreactivity test with the monoclonal antibody MIB-1, the proliferation index was 20–30%. This immunohistochemical expression profile led to the differential diagnosis of a myoepithelial proliferation versus an (extra-axial) chordoma not otherwise specified (NOS). An immunohistologic staining against brachyury was performed, revealing a nuclear expression of brachyury in all tumor cells. Based on morphology and expression profile, the diagnosis of an (extra-axial) chordoma was made, pointing out that the metastasis of an axial chordoma should be ruled out (Fig. 4). In addition, a fluorescence in situ hybridization (FISH) to detect potential CDKN2A deletions, which are found in 80% of axial chordomas, was performed and revealed a disomy of the CDKNA gene locus.

Following the pathological report and in order to rule out a primary lesion in the axial skeleton, the patient underwent additional MR imaging of the entire spine and skull. The examinations revealed no evidence of an axial chordoma. Due to

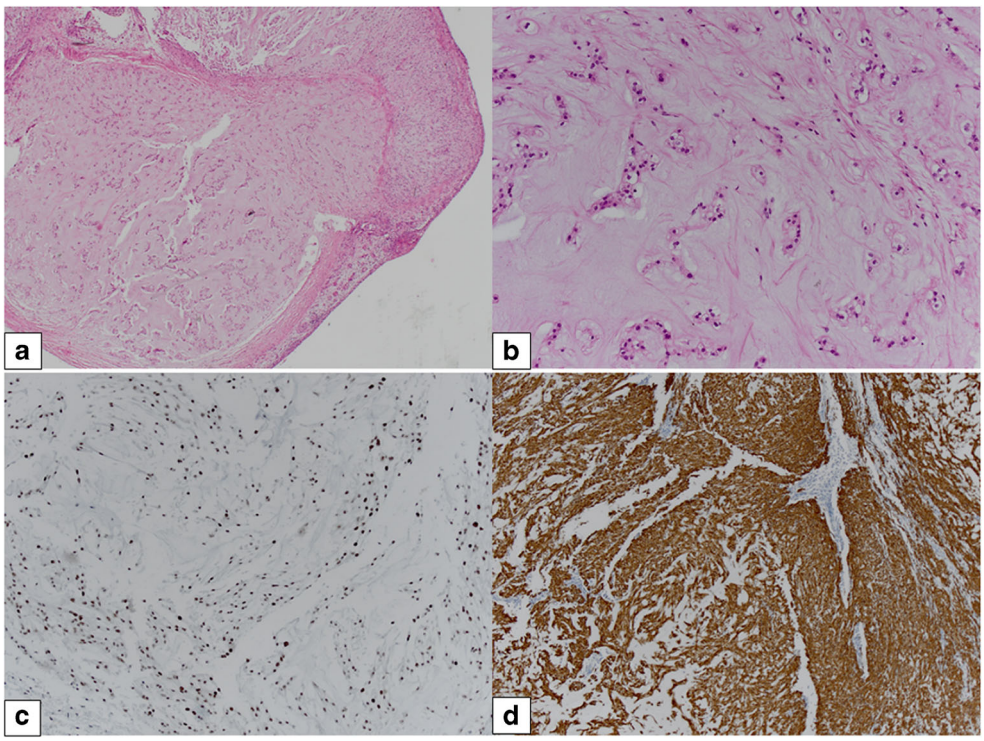

Fig. 4 Representative stainings of the extra-axial chordoma. **a**, **b**) H&E stain, showing characteristic epithelioid, partially physaliphorous tumor cells arranged in cords embedded in a myxoid matrix. **c** Nuclear brachyury expression in tumor cells. **d** Cytokeratin panMNF 116 stain revealing positive staining result

the already advanced local progression of the tumor, involving all carpal joint compartments including the distal radioulnar joint with multiple bone erosions, local excision was not feasible and the only curative option would have been an amputation. This option however was declined by the patient. The patient was then transferred to a Center for Proton Therapy to undergo a proton beam therapy of his wrist. It was reported to us, that after the first treatment session the mass did not decrease in seize but also did not grow any further (stable disease). Distant metastases have still not been reported yet.

Discussion

The radiologic appearance of chordomas in axial locations is rather specific. They commonly present as a large, lobulated midline lesions of high T2-weighted signal intensity compared to subcutaneous fat with T2-hypointense septations and low to intermediate signal intensity compared to skeletal muscle on T1-weighted images. Contrast enhancement detected with T1-weighted images with or without fat saturation is usually moderate and heterogeneous and frequently shows a honeycomb pattern.

Whereas modern immunocytochemistry allows distinguishing chordomas and extra-axial chordomas from parachordomas [2, 3] (in earlier studies from some authors also referred to as chordoma peripheric um [4]), the solely radiological characteristics of extra-axial located chordoma-like lesions do not significantly deviate from those of axial chordomas [3, 5–14]. Moreover, the imaging findings of extra-axial chordomas resemble those of well-differentiated cartilage tumors, which are by far more common [15], making the diagnosis of e.g., a synovial osteochondromatosis much more likely.

The imaging similarities between chordomas and cartilage tumors might be explained by their common embryogenetic pattern, since both malignancies originate from the embryonic notochord. The notochordal origin of the axial chordoma plays a critical role in embryonic tissue pattern. Additionally, notochord progenitors consist of embryonic tissue from which bone or other skeletal tissues such as cartilaginous tissue arises [16]. In this context, it has been shown previously that the notochordal expression profile of certain malignancies is similar to the profile of other neoplasms, and that the differentiation of chordomas from other neoplasms (e.g., cartilaginous tumors) therefore is challenging [3, 16].

Particularly in soft-tissue locations, some investigators have questioned the existence of chordomas since, due to the embryonic patterns, the definition of these malignancies has not been quite clear. For a long time chordomas were thought to be indistinguishable from particularly myoepithelial proliferations, which also co-express cytokeratins and S-100 protein [17]. In an early study by Salisbury et al., the authors were able to show that immunohistochemical staining with antibodies against epithelial antigens can be used to distinguish chordomas from cartilaginous tumors, since they found the same cytokeratins and oligosaccharide sequence in chordomas as in the human fetal notochord but not in cartilaginous proliferations [18]. Folpe et al. were already able to show that parachordomas have a very similar histomorphologic, physaliferous-like appearance in conventional stainings, but are distinct from axial chordomas in their cytokeratin expression profile and cytogenetics [19], furthermore, Tirabosco et al. demonstrated that parachordomas could also be distinguished from extra-axial chordomas, based on their (nuclear brachyury) immunoreactivity [3].

Only recently Henderson et al. reported a high level of expression of the transcription factor brachyury in chordomas [20], which is known to be involved in notochordal development. Vujovic et al. demonstrated its utility as a specific diagnostic marker [21] for notochord and notochord derived tumors. Therefore the transcription factor brachyury is a highly characteristic diagnostic finding of chordomas.

As shown, the T-box brachyury transcription factor is required for the specification of mesodermal identity, regulating the notochord formation and is specifically linked to the embryogenic structure of this neoplasm [21]. The diagnostic advantage of this novel and compelling marker has already been used in more recently published studies in appendicular chordoma-like lesions. These lesions were found to be positive for brachyury by immunohistochemistry, which defines these cases as (extra-axial) chordomas. Based on these studies, the pathological diagnosis of an extra-axial chordoma should be limited to malignancies/neoplasms that share the characteristic appearance and the specific immunohistochemical expression profile (co-expression of cytokeratin and S-100 protein and nuclear expression of brachyury) of axial chordomas.

Our literature search (English language) for cases with diagnosis of an extra-axial chordoma revealed 11 publications with a total of 20 malignancies that were reported to be brachyury-positive and were identified as extra-axial chordomas [3, 5–14]. Similarly, our case had the typical histomorphological appearance and revealed a positive immunohistochemical profile for brachyury and co-expression of cytokeratin and S-100 protein. This indicates that the presented lesion is in line with the diagnosis of an extra-axially located chordoma.

Only one previously published case described an intra-articular location at the knee, whereas the majority of the other cases was located either intramedullary or intracortically. Additionally, a few cases with soft tissue extra-axial chordomas were reported previously [3]. To the best of our knowledge, this is the first case reporting an intra-articularly located extra-axial chordoma of the wrist.

Our immunohistochemical work-up was positive for epithelial membrane antigen (EMA), cytokeratin, p63, S100, and brachyury, combining the typical immunohistochemical features of notochordal neoplasms [21]. Surprisingly, the FISH analysis for the cyclin-dependent kinase inhibitor 2A (CDKN2A) protein

yielded a disome signal, indicating that the tumor did not show loss of the CDKN2A loci (in 9p21), which is lost in 80% of chordomas [22, 23]. Interestingly, despite disomy upon FISH, p16 immunohistochemistry was negative indicating a yet unknown mechanism of p16 inactivation. Potential mechanisms of p16 inactivation, which can not detected by CDKN2A FISH analysis, might be point mutations, promotor hypermethylation or splicing errors [24, 25]. The CDK4/6 pathway, as indicated by expression of Phospho-Rb and Rb, was also activated. None of the previously published cases of a brachyury-positive extra-axial chordoma provided information on the deletion of the CDKN2A gene nor the activation of the downstream pathways. Although not tumor specific, further investigation of inactivation of the CDKN2A gene in an extra-axial chordoma would be of great interest to promote our understanding of why chordoma-like lesions occur in appendicular locations.

In conclusion, our presented case of an extra-axial chordoma coincides with that of previously reported cases, but with an unique intra-articular location. Despite the image appearance of a chordoma-like lesion, this is a very rare diagnosis. Due to certain imaging features the diagnosis synovial osteochondromatosis was considered first. Yet, certain missing features such as absent calcifications made this diagnosis doubtful and biopsy was performed. Together with the imaging features, immunohistochemical analysis supported the view of a notochordal differentiation as seen in axial chordomas. However, the none-deleted CDKN2A loci/gen showed a certain difference to those of typical axial chordomas, raising the question of whether or not this presented malignancy is to be considered an extra-axial chordoma or a unique entity with very similar immunohistochemical patterns to the classic chordoma.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Walcott BP, Nahed BV, Mohyeldin A, Coumans J-V, Kahle KT, Ferreira MJ. Chordoma: current concepts, management, and future directions. Lancet Oncol. 2012;13:e69–76. https://doi.org/10.1016/S1470-2045(11)70337-0.
2. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO classification of tumours of soft tissue and bone. Lyon: IARC Press; 2013. p. 328–9.
3. Tirabosco R, Mangham DC, Rosenberg AE, et al. Brachyury expression in extra-axial skeletal and soft tissue chordomas: a marker that distinguishes chordoma from mixed tumor/myoepithelioma/parachordoma in soft tissue. Am J Surg Pathol. 2008;32:572–80. https://doi.org/10.1097/PAS.0b013e31815b693a.
4. Laskowski J. Pathology of tumors. In: Kolodziejska H, editor. Zarys onkologii. Warsaw: PZWL; 1955. p. 91–9.
5. Kurzawa P, Fundowicz M, Dopierała M, Larque AB, Nielsen GP. Primary extra-axial, para-articular chordoma of the knee. A case report and the review of literature. Histopathology. 2018;72:883–5. https://doi.org/10.1111/his.13440.
6. Righi A, Sbaraglia M, Gambarotti M, et al. Extra-axial chordoma: a clinicopathologic analysis of six cases. Virchows Arch. 2018;472:1015–20. https://doi.org/10.1007/s00428-018-2334-0.
7. Bitzer A, McCarthy EF, Morris CD. Extra-axial chordoma of the hand. J Hand Surg. 2017;42:933.e1–5. https://doi.org/10.1016/j.jhsa.2017.05.033.
8. Tsukamoto S, Vanel D, Righi A, Donati DM, Errani C. Parosteal extra-axial chordoma of the second metacarpal bone: a case report with literature review. Skelet Radiol. 2018;47:579–85. https://doi.org/10.1007/s00256-017-2818-z.
9. Huang J, Bhojwani N, Oakley FD, Jordanov MI. Proximal tibial extra-axial chordoma masquerading as renal cell carcinoma metastasis. Skelet Radiol. 2017;46:1567–73. https://doi.org/10.1007/s00256-017-2711-9.
10. Rekhi B. Primary, large extra-axial chordoma in proximal tibia: a rare case report with literature review and diagnostic implications. APMIS. 2016;124:238–42. https://doi.org/10.1111/apm.12468.
11. Lantos JE, Agaram NP, Healey JH, Hwang S. Recurrent skeletal extra-axial chordoma confirmed with brachyury: IMAGING features and review of the literature. Skelet Radiol. 2013;42:1451–9. https://doi.org/10.1007/s00256-013-1615-6.
12. Suzuki H, Yamashiro K, Takeda H, Nojima T, Usui M. Extra-axial soft tissue chordoma of wrist. Pathol Res Pract. 2011;207:327–31. https://doi.org/10.1016/j.prp.2011.02.001.
13. DeComas AM, Penfornis P, Harris MR, Meyer MS, Pochampally RR. Derivation and characterization of an extra-axial chordoma cell line (EACH-1) from a scapular tumor. J Bone Joint Surg Am. 2010;92:1231–40. https://doi.org/10.2106/JBJS.I.00594.
14. O'Donnell P, Tirabosco R, Vujovic S, et al. Diagnosing an extra-axial chordoma of the proximal tibia with the help of brachyury, a molecule required for notochordal differentiation. Skelet Radiol. 2007;36:59–65. https://doi.org/10.1007/s00256-006-0167-4.
15. Almefty K, Pravdenkova S, Colli BO, Al-Mefty O, Gokden M. Chordoma and chondrosarcoma: similar, but quite different, skull base tumors. Cancer. 2007;110:2457–67. https://doi.org/10.1002/cncr.23073.
16. Stemple DL. Structure and function of the notochord: an essential organ for chordate development. Development (Cambridge, England). 2005;132:2503–12. https://doi.org/10.1242/dev.01812.
17. Scolyer RA, Bonar SF, Palmer AA, et al. Parachordoma is not distinguishable from axial chordoma using immunohistochemistry. Pathol Int. 2004;54:364–70. https://doi.org/10.1111/j.1440-1827.2004.01633.x.
18. Salisbury JR, Isaacson PG. Demonstration of cytokeratins and an epithelial membrane antigen in chordomas and human fetal notochord. Am J Surg Pathol. 1985;9:791–7.
19. Folpe AL, Agoff SN, Willis J, Weiss SW. Parachordoma is immunohistochemically and cytogenetically distinct from axial chordoma and extraskeletal myxoid chondrosarcoma. Am J Surg Pathol. 1999;23:1059–67.
20. Henderson SR, Guiliano D, Presneau N, et al. A molecular map of mesenchymal tumors. Genome Biol. 2005;6:R76. https://doi.org/10.1186/gb-2005-6-9-r76.
21. Vujovic S, Henderson S, Presneau N, et al. Brachyury, a crucial regulator of notochordal development, is a novel biomarker for chordomas. J Pathol. 2006;209:157–65. https://doi.org/10.1002/path.1969.
22. Hallor KH, Staaf J, Jönsson G, et al. Frequent deletion of the CDKN2A locus in chordoma: analysis of chromosomal imbalances using array comparative genomic hybridisation. Br J Cancer. 2008;98:434–42. https://doi.org/10.1038/sj.bjc.6604130.

23. von Witzleben A, Goerttler LT, Marienfeld R, et al. Preclinical characterization of novel chordoma cell systems and their targeting by pharmocological inhibitors of the CDK4/6 cell-cycle pathway. Cancer Res. 2015;75:3823–31. https://doi.org/10.1158/0008-5472.CAN-14-3270.
24. Inoue K, Fry EA. Aberrant expression of p16INK4a in human cancers—a new biomarker? Cancer Rep Rev. 2018;2. https://doi.org/10.15761/CRR.1000145.
25. Witkiewicz AK, Knudsen KE, Dicker AP, Knudsen ES. The meaning of p16(ink4a) expression in tumors: functional significance, clinical associations and future developments. Cell Cycle (Georgetown, Texas). 2011;10:2497–503. https://doi.org/10.4161/cc.10.15.16776.