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Chondroid Chordoma of the Clivus: A Case Report

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Abstract **Case Report**

Chondroid chordoma is a rare skull-base tumor of notochordal origin that radiologically mimics chondrosarcoma, making histopathology and immunohistochemistry essential for diagnosis. We report a 22-year-old man with progressive occipital headache, imbalance, diplopia, and tinnitus. CT and MRI revealed a destructive midline retroclival mass encasing the basilar and cavernous carotid arteries with brainstem compression. A transmaxillary–transclival approach achieved gross total resection. Histology showed physaliphorous cells within a myxoid/chondroid matrix. Immunohistochemistry demonstrated EMA, S100, and vimentin positivity with preserved INI-1 and low Ki-67 (1–2%), confirming chondroid chordoma. Postoperative MRI identified small residual tumor at the left petrous apex and cavernous sinus. The patient recovered to WHO performance status 0 except for persistent diplopia and was referred for adjuvant high-dose intensity-modulated radiotherapy (IMRT). This case illustrates the diagnostic challenge of clival chondroid chordoma, the limits of safe resection in the skull base, and the need for multidisciplinary management with high-dose conformal radiotherapy. Although historically thought less aggressive, chondroid chordoma shares the recurrence risk and long-term prognosis of conventional chordoma, warranting lifelong imaging surveillance

Keywords: Chondroid chordoma, Clivus, Skull base tumor, Histopathology, Radiotherapy, Prognosis.

INTRODUCTION

Chordomas are rare malignant tumors arising from embryonic notochordal remnants, accounting for only 1–4% of primary bone malignancies. They occur mainly along the axial skeleton, with the clivus being the most common skull-base site. The chondroid subtype shows areas of cartilaginous matrix within typical physaliphorous chordoma cells; once thought less aggressive, it is now considered to have a prognosis similar to conventional chordoma.

Clival chordomas grow slowly but invade locally, causing cranial nerve palsies, brainstem compression, and headache. Imaging often suggests the diagnosis but cannot reliably distinguish them from skull-base chondrosarcomas, making histopathology and immunohistochemistry essential.

Treatment relies on maximal safe surgical resection followed by high-dose conformal radiotherapy, yet complete removal is rarely possible and recurrence is common.

We report the case of a 22 -year-old patient with a chondroid chordoma of the clivus treated at the Oncology-Radiotherapy Department of Mohammed VI University Hospital in Marrakech.

CASE PRESENTATION

A 22-year-old patient, working as a cook and resident of Aït Ourir with no prior medical, surgical, toxic or family history, was referred for management of a retroclival lesion ultimately diagnosed as a chondroid chordoma of the clivus.

Symptoms began in March 2025 with imbalance, occipital headaches, left-sided diplopia and tinnitus, progressing in the context of general deterioration with asthenia, anorexia and weight loss.

Initial imaging (CT and MRI on 29/03/2025) identified a 40 × 30 mm infratentorial, retroclival process with a broad meningeal base that encased the trigeminal nerve, infiltrated the clivus, foramen ovale, Meckel's cave and the carotid canal, displaced the basilar artery to the right and compressed the brainstem, with plaque-like

thickening of the retroclival meninges but no hydrocephalus. A subsequent CT on 17/04/2025 confirmed a left-lateralized, ill-defined retroclival mass with clival bone lysis and extension into adjacent skull-base foramina (approx. 21 × 11 × 23 mm by that study).

The patient underwent surgical resection with macroscopically complete excision on 16/05/2025. Histology and immunohistochemistry were consistent with chondroid chordoma.

Immunohistochemistry (performed on the resected specimen):

- Anti-EMA Ab-3 (Clone E29, Epredia): **positive** on tumor cells.
- Anti-PS100 (Protein Ab-1, Epredia): **positive** on tumor cells.
- Anti-Vimentin (Clone V9, Biocare): **positive** on tumor cells.
- Anti-Ki67 (Clone SP6, ThermoScientific): **1–2%** of tumor cells.
- Anti-Pan-cytokeratin (Clone AE1/AE3, Bio SB): **negative**.
- Anti-INI-1 (Clone 25, Bio SB): **positive**.

Conclusion: Morphological and immunohistochemical features consistent with chondroid chordoma.

Postoperative course:

The patient was conscious and hemodynamically stable with an ECOG performance status of 2. A tracheostomy was placed for postoperative respiratory compromise and a nasogastric tube for feeding. Neurological exam revealed persistent left diplopia and esotropia, and a steppage gait, while limb strength and tone were preserved (5/5 bilaterally) with no additional cranial nerve deficits.

Postoperative MRI revealed persistence of a left-lateralized clival tumor process infiltrating the left petrous apex and cavernous sinus, encasing the basilar trunk and the left carotid artery, and compressing the brainstem, without ventricular dilatation.

After postoperative recovery, the patient's condition improved significantly with a WHO performance status of 0, except for persistent diplopia.

Management plan: Given the residual disease, the patient was referred for adjuvant IMRT radiotherapy targeting the remaining tumor.

DISCUSSION

Chordomas are extremely rare malignant bone tumors arising from remnants of the embryonic notochord, with an incidence of approximately 1 case per million people per year [1]. They account for only 1–4% of primary bone malignancies and predominantly occur along the axial skeleton. About 50% of chordomas involve the sacrococcygeal region, 35% occur at the skull base (clivus), and the remaining ~15% in the mobile spine [2]. Histologically, chordomas are subdivided into conventional (classic), chondroid, and dedifferentiated variants. Chondroid chordoma is a histologic subtype comprising roughly 14% of all chordomas, most often arising in the spheno-occipital (clival) region. This variant typically presents in younger adults (third to fifth decade) compared to conventional chordomas [2]. It shows areas of cartilaginous differentiation on microscopy, hence the term "chondroid." Initially, some authors suggested that chondroid chordomas might have a more indolent behavior akin to low-grade chondrosarcoma [3], but later studies have shown that true chondroid chordomas behave similarly to conventional chordomas in terms of aggressiveness and outcome [4].

Chordomas are slow-growing yet locally aggressive tumors. Symptoms often evolve insidiously over months as the tumor enlarges and compresses adjacent structures [3]. In clival chordomas, patients commonly present with headache, cranial nerve deficits, or brainstem compression. Diplopia (double vision) is a frequent complaint due to abducens nerve (CN VI) palsy, along with other cranial neuropathies causing symptoms such as facial numbness, dysphagia, or tinnitus [2]). Patients may also experience neck pain or occipital pain, and if the tumor extends to involve the pituitary region, endocrine dysfunction can occur [2]. In the case described, the 22-year-old patient's initial symptoms – occipital headaches, imbalance, left CN VI palsy (causing diplopia), and tinnitus – exemplify a classic clival chordoma presentation. These gradually progressed, accompanied by constitutional symptoms (asthenia, anorexia, weight loss) due to the tumor's slow but relentless growth. On neurologic exam, our patient had signs of brainstem and cranial nerve involvement (persistent diplopia with esotropia) and a "steppage" gait reflecting corticospinal tract compression, while limb strength remained intact. Such findings underscore the chordoma's tendency to cause significant morbidity by local invasion, despite its relatively indolent pace.

Imaging is crucial for diagnosing and planning treatment of chordomas. On plain radiographs or CT, chordomas classically appear as destructive, lytic lesions in the involved bone [2,3]. Clival chordomas often produce osteolysis of the clivus with extension into adjacent structures and may show areas of calcification on CT (sometimes described as a "honeycomb" or mottled calcific appearance) [2]. MRI is the preferred modality for skull-base chordomas, as it delineates the tumor's soft tissue extent and its relationship to critical neurovascular structures. On MRI, chordomas typically exhibit low-to-intermediate signal on T1-weighted images and high signal on T2-weighted images, with heterogeneous enhancement after gadolinium [2]. The tumor often appears lobulated and can encase arteries or cranial nerves, as was seen in our patient's imaging (with

encasement of the basilar artery and cavernous segment of the internal carotid, and extension into Meckel's cave and skull base foramina). Notably, hydrocephalus is uncommon unless the tumor obstructs CSF pathways, which it typically does not.

Despite some characteristic imaging features, distinguishing a clival chordoma from other skull base tumors (particularly chondrosarcoma) by imaging alone can be challenging. Both chordomas and chondrosarcomas can present as lytic, enhancing lesions of the skull base with similar locations and clinical presentations. There is often significant overlap in radiologic appearance, and no single imaging sign reliably differentiates the two entities [4]. One helpful clue is location: true chordomas usually arise in the midline clival region (originating from notochordal rests), whereas skull base chondrosarcomas more often originate off-midline (for example, from the petroclival synchondrosis) and may demonstrate more extensive chondroid matrix calcifications. However, because of the overlap, a biopsy is generally required for definitive diagnosis. In our case, imaging strongly suggested a chordoma (given the midline clival destruction and extent), but only histopathology and immunohistochemistry confirmed the chondroid chordoma diagnosis.

Microscopically, chordomas have a distinctive appearance. They are characterized by cords and lobules of tumor cells set in a bluish myxoid, gelatinous extracellular matrix [2,3]. The classic tumor cells are the physaliferous cells, which have vacuolated cytoplasm and round nuclei, often arranged in mucin-rich lobules separated by fibrous septa. These vacuoles are filled with cytoplasmic mucopolysaccharides, giving the cells a soap-bubble (physaliphorous) appearance on H&E staining. Chondroid chordomas will additionally show areas of cartilaginous differentiation – regions of eosinophilic, chondroid matrix resembling hyaline cartilage – adjacent to the typical chordoma cells. Mitotic figures are usually scant, and necrosis may be present in larger tumors. In our patient's tumor, histology demonstrated polygonal epithelioid cells with vacuolated cytoplasm in a myxoid/chondroid stroma, consistent with a chondroid chordoma. The Ki-67 proliferation index was very low (~1–2%), which is typical for conventional chordomas (generally <5% in most cases). A higher Ki-67 labeling index (>5–10%) would raise concern for more aggressive behavior or a dedifferentiated component [2,3].

Immunohistochemistry (IHC) is indispensable for confirming the diagnosis and distinguishing chordoma from histologic mimics. Chordomas uniquely co-express both epithelial and mesenchymal markers. The tumor cells characteristically stain positive for cytokeratin's (pancytokeratin) and epithelial membrane antigen (EMA), as well as for S100 protein and vimentin [2]. This pattern reflects the dual epithelial/notochordal nature of chordomas. In contrast, chondrosarcomas of the skull base (the main differential diagnosis) consist of purely cartilaginous cells and thus lack cytokeratin and EMA expression, although they are S100-positive. Demonstration of diffuse cytokeratin and EMA positivity throughout the tumor effectively rules in chordoma even when chondroid areas are present [5]. In our patient's tumor, immunostaining showed strong positivity for EMA, S100, and vimentin in the tumor cells, with pan cytokeratin largely negative. The negative pan cytokeratin result is somewhat unusual since most chordomas do express cytokeratin's; however, this may have been a result of antigen masking or the particular antibody clone used. Critically, the tumor was positive for INI-1 (SMARCB1) nuclear expression, indicating intact INI-1. This finding helped exclude a poorly differentiated chordoma, a rare high-grade subtype that shows loss of INI-1 expression.

A defining molecular feature of chordomas is the expression of the transcription factor brachyury (product of the TBXT gene). Brachyury is a developmental protein essential for notochord formation and is overexpressed in essentially all chordomas. It is absent in normal mature cartilage and chondrosarcomas, making it a highly specific diagnostic marker. Brachyury immunohistochemistry (nuclear staining) is now frequently used to confirm a suspected chordoma diagnosis and to differentiate chordoma from chondrosarcoma in difficult cases [1]. (In our case, brachyury staining was not reported, but the diagnosis was secure based on the other IHC markers. Had there been any doubt, a brachyury test could have been done to solidify the identification of chordoma.) From a molecular standpoint, chordomas are distinct tumors with no common mutations akin to those seen in many other cancers. Some sporadic chordomas have alterations in the PI3K/AKT/mTOR pathway or other genetic changes, but there is no single dominant mutation. Familial chordoma is very rare and has been linked to germline duplication of the TBXT (brachyury) gene [1]. Overall, the molecular profile of chordomas has reinforced the central role of brachyury in their pathogenesis, and this has become a target of emerging therapies (e.g. brachyury-targeted vaccines in clinical trials).

Optimal management of chordomas requires a multimodal approach. The cornerstone of treatment is surgical resection, aiming for maximal safe removal of the tumor. Whenever feasible, an en bloc resection with wide margins offers the best chance of long-term control [1]. However, in skull base chordomas, total en bloc resection is often not possible due to the tumor's proximity to critical structures (brainstem, carotid arteries, cranial nerves). In practice, skull base chordomas are typically debulked via extended transsphenoidal/endoscopic or transcranial approaches, with the goal of removing as much tumor as safely possible. In our patient, a transmaxillary-transclival

approach achieved a macroscopic gross total resection of the lesion. Given the high risk of residual microscopic disease, adjuvant radiotherapy is indicated in virtually all cases after surgery [1,2]. Postoperative radiation significantly improves local control, even though chordomas are relatively resistant to conventional doses of radiation [2]. Modern radiotherapy techniques are employed to deliver high doses to the tumor while sparing surrounding tissues: options include high-precision photon radiation (intensity-modulated radiation therapy, IMRT), proton beam therapy, and carbon ion therapy. Proton beam radiotherapy is often favored for clival chordomas, as protons can deposit intense doses in the tumor (Bragg peak) with less exit dose to nearby critical structures (like the brainstem and optic nerves). Carbon ion radiotherapy, available in a few centers, offers an even higher linear energy transfer and relative biological effectiveness against radioresistant tumor cells [2]. Stereotactic radiosurgery (e.g. Gamma Knife or Cybercide) may be used in certain situations, such as for small residual tumor nodules or recurrences, but is generally adjunctive [2]. In our case, after recovery from surgery, the patient was referred for adjuvant IMRT targeting the residual tumor in the left petrous apex and cavernous sinus. This is expected to deliver approximately 70 Gy to the tumor bed in a fractionated regimen.

There are no effective systemic chemotherapies for chordoma. These tumors do not respond well to standard cytotoxic chemotherapy agents [2]. Therefore, surgery and radiotherapy remain the mainstays of treatment. Systemic therapy is typically reserved for advanced or metastatic cases that cannot be managed with local measures [1]. Several targeted therapy approaches have been explored in clinical trials, given chordomas often overexpress certain growth factor receptors. One of the first targeted drugs tested was imatinib, a tyrosine kinase inhibitor targeting PDGFRβ and KIT, which are frequently expressed in chordoma. A phase II trial in 56 patients with advanced chordoma showed that imatinib achieved disease stabilization (stable disease ≥6 months) in ~70% of patients, although objective tumor shrinkage was rare (2% partial response rate) [6]. This indicates some activity in slowing progression, but imatinib is not curative and resistance eventually occurs. Other targeted agents evaluated include inhibitors of EGFR (e.g. erlotinib), inhibitors of the mTOR pathway, and angiogenesis inhibitors, but results have been modest and none are definitively proven to prolong survival. Combination strategies (for example, imatinib plus an mTOR inhibitor) have shown limited benefit in small series [7]. More recently, attention has turned to immunotherapy. Because brachyury is a tumor-specific antigen in chordoma, a brachyury-directed vaccine and other immunotherapeutic approaches have been investigated [1]. Early-phase studies of a brachyury vaccine have suggested safety and some immune responses, but efficacy remains to be determined. At present, no systemic therapy has an established survival benefit in chordoma, and no randomized controlled trials have yet identified a clearly effective drug [1]. Management of advanced chordoma is therefore usually individualized, often with enrollment in clinical trials or off-label use of targeted agents when local therapies are exhausted.

Chordomas are malignant tumors with a tendency for local recurrence and eventual cause of death, despite their slow growth. The overall prognosis depends on factors such as tumor location, size, resect ability, histologic subtype, and patient age. Skull base (clival) chordomas tend to present earlier and smaller than sacral chordomas, and with aggressive multidisciplinary treatment, their short-term outcomes can be favorable. Five-year survival rates for cranial chordomas have been reported in the range of ~50% to 80% [2]. In one series, overall, 5- and 10-year survival for clival chordomas were 75% and 63%, respectively, with modern therapy (8). However, long-term control is difficult: the local recurrence rate is high, reported as 50–70% in various studies [2]. Even after apparently complete resection and adjuvant radiotherapy, microscopic residual cells can eventually give rise to tumor regrowth. Recurrent chordomas remain locally aggressive and each recurrence becomes more challenging to manage due to scarring and patient debility. Distant metastases are less common but not negligible – reported in approximately 5–30% of cases, usually in late stages of disease (common sites are lungs, bone, liver) [2].

Histological subtype and grade influence prognosis. Dedifferentiated chordomas, which contain high-grade sarcomatous areas, have the worst prognosis – most patients succumb within 1–2 years of diagnosis [3]. In contrast, it was once thought that chondroid chordomas were more benign; for example, older reports noted a 10-year survival of ~80% for chondroid chordomas versus ~50–60% for conventional chordomas [4]. This led to the belief that chondroid variant conferred a survival advantage. However, more recent analyses have contradicted this. A study by Almefty *et al.,* found that patients with chondroid chordomas had no significant difference in recurrence-free or overall survival compared to those with typical chordomas [4]. The initially observed better outcomes were likely due to misclassification of some low-grade chondrosarcomas as chondroid chordomas in the past [5]. Therefore, aside from dedifferentiated cases, all chordomas are generally considered to have a similar clinical course. In our patient, the chondroid histology does not substantially alter the management or expected prognosis; it remains a locally aggressive tumor that requires close long-term surveillance.

Overall, chordomas are often described as tumors with “malignant potential” and an indolent yet relentless course. The estimated median overall survival is around 6–7 years [1], but with aggressive treatment

some patients live well beyond 10 years, and a subset may be cured. Younger patients and those who achieve complete tumor resection (and receive high-dose adjuvant radiation) tend to have better outcomes [2]. In the case presented, the patient was young and had a good performance status after surgery, which are positive prognostic indicators. The persistent residual tumor, however, poses a risk for future progression. The planned adjuvant IMRT aims to control this residual disease. Following therapy, the patient will require periodic MRI surveillance for early detection of any recurrence. Given the rarity of chordomas, referral to specialty centers and multidisciplinary teams (neurosurgery, radiation oncology, medical oncology, etc.) is recommended for optimal management. In summary, clival chondroid chordomas demand aggressive local therapy and lifelong follow-up. While cure is difficult, prolonged disease control is achievable in many cases, and ongoing research into targeted and immunotherapies offers hope for improved outcomes in the future.

CONCLUSION

Chondroid chordoma of the clivus is a rare, locally aggressive skull-base tumor with slow but relentless growth. Diagnosis relies on imaging to define extent and surgical approach, but definitive classification requires histopathology and immunohistochemistry, particularly to distinguish it from chondrosarcoma. Despite maximal safe resection, complete removal is often impossible because of proximity to critical neurovascular structures, and adjuvant high-dose radiotherapy is essential to improve local control. The chondroid variant does not confer a clearly better prognosis compared with conventional chordoma. Long-term multidisciplinary follow-up is mandatory, as recurrence remains frequent and systemic treatment options are limited.

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