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CASE REPORT

Spinal chordomas dedifferentiated to osteosarcoma: a report of two cases and a literature review

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Abstract
Purpose Chordoma is a rare, locally aggressive neoplasm of the bone that arises from embryonic notochordal remnants. In less than 5 % of cases, chordomas contain a highly malignant sarcomatous component. Because of the rarity of such tumors, little is known about their clinical features and optimal treatment options. Herein, we report two chordoma cases with malignant sarcomatoid areas, consistent with high-grade osteosarcoma in the primary spine lesions, and discuss the presentation and characteristics of this disease.
Methods and results In both patients, the diagnosis on the first computed tomography (CT)-guided trocar biopsy of the tumor was a conventional chordoma. The two cases represent dedifferentiated chordomas with a sharp demarcation between the conventional chordoma and the high-grade sarcomatous component, which was identified on T2-weighted magnetic resonance imaging (MRI). One patient experienced a symptomatic tumor recurrence 4 months after carbon-ion radiotherapy, and underwent en bloc wide resection of the tumor following chemotherapy. The patient remained well 36 months after surgery without tumor recurrence. The other patient underwent a gross total excision as the second surgery followed by carbon-ion radiotherapy. At the 39-month follow-up, there was no evidence of active disease.
Conclusions Accurate analyses of MRI and positron emission tomography scans should suggest the most representative section for histological assessment. Unlike the treatment of conventional chordomas, the treatment of this disease should include chemotherapy first, followed by en bloc resection and/or carbon-ion radiation.

Keywords Dedifferentiated chordoma · Osteosarcoma · Spine

Introduction

Chordoma is a rare, slowly growing, locally aggressive neoplasm of the bone that arises from embryonic notochordal remnants. It accounts for 17.5 % of primary malignant tumors of the axial skeleton, with a reported incidence of 0.5–0.8 per 1,000,000 people [1, 2]. Lesions arise from the sacrococcygeal region (50 %), the base of the skull (35 %) and the vertebral column (15 %) [3]. Metastases occur in 20–40 % of the cases to the lungs, liver, bone, and soft tissues. The overall median survival time of patients with chordoma has been estimated to be approximately 6 years, with a survival rate of 70 % at 5 years, dropping to 40 % at 10 years [3]. Chordoma is resistant to most non-surgical treatments, and resection with negative oncological margins is currently the mainstay of treatment [4, 5].

In less than 5 % of cases, chordomas contain a highly malignant sarcomatous component [3]. The prognosis of these tumors tends to be poor because of their aggressive nature and potential for distant metastases [6–10]. Because of the rarity of such tumors, little is known about their clinical features and optimal treatment options. We

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recently encountered two chordoma cases that contained malignant sarcomatoid areas, consistent with high-grade osteosarcoma in the primary spine lesions. Herein, we report the clinical and pathological features of these two cases and discuss the presentation and characteristics of spinal chordomas dedifferentiated to osteosarcoma.

Patients and methods

A retrospective review of a single institution prospectively collected database was performed. Two patients diagnosed with chordomas that had dedifferentiated to osteosarcoma were identified. Both patients were submitted to exhaustive laboratory and imaging analyses, and computed tomography (CT)-guided trocar biopsies were performed. The treatment options were determined based on the location of the tumor, the characteristics of the tumor, and patient-informed decisions. Clinical and radiological information for each patient was recorded until the latest follow-up. As part of the pathological analysis, we performed immunohistochemical examinations of tumor tissues for cytokeratin, epithelial membrane antigen, brachyury, and SATB2.

Results

Case 1

A 54-year-old man presented with a 5-year history of pain in the buttocks. He did not present with any symptoms of bladder or bowel dysfunction, or neurologic deficit of the lower extremities. A rectal examination revealed a large mass overlying the lower sacrum. A radiograph of the lower sacrum showed an expansive lytic lesion with cortical disruption. Magnetic resonance imaging (MRI) showed a large mass, 78 cm in width and 89 cm in height, arising from the distal sacrum and the coccyx. The T2-weighted MRI image showed two distinct signal intensities, indicating two different areas within the lesion in terms of signal characteristics, a reduced signal component, and a hyperintense component with an irregular border, most likely indicating necrosis (Fig. 1). CT scans of the lungs showed non-specific lung nodules. Conventional chordoma was diagnosed by CT-guided trocar biopsy of the sacrum. The patient underwent carbon-ion radiotherapy and experienced pain relief.

After 4 months of recovery, the patient was referred to our institution again, because of increasing pain in the buttocks without any neurological symptoms. Positron emission tomography (PET) scans showed increased uptake of SUV 13.2 by the tumor mass. Another CT-guided trocar biopsy showed a high-grade sarcoma with malignant

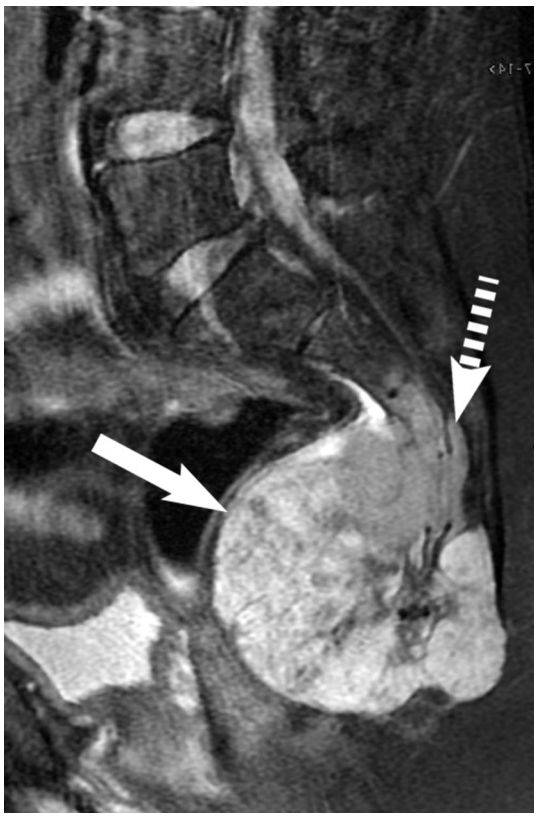

Fig. 1 Sagittal T2-weighed magnetic resonance imaging of the sacrum showing conventional chordoma appearing hyperintense (*solid arrow*), and dedifferentiated chordoma appearing hypointense (*dashed arrow*)

osteoid formation, consistent with high-grade malignant osteosarcoma. A 2-drug chemotherapy regimen including cisplatin (100 mg/m^2) and doxorubicin (60 mg/m^2) was administered for 5 days. Two cycles were repeated at 3-week intervals. En bloc resection of the tumor was performed following chemotherapy 2 months after the second diagnosis. To achieve a wide margin, the rectum was resected together with the sacral tumor, as a post-radiation scar was connecting the tumor with the rectum. A histological evaluation of the resected tumor revealed a dedifferentiated chordoma with high-grade osteosarcoma, with clear margins of excision (Fig. 2). The patient had a complete loss of bladder-bowel function and required a permanent stoma after surgery. However, he could walk with a cane and mostly maintain his performance of activities of daily living without assistance 36 months after surgery without recurrence of the sacral chordoma (Fig. 3) or progression of the lung nodules.

Case 2

A 75-year-old woman received a laminectomy and open biopsy in another hospital for a lytic lesion eroding the

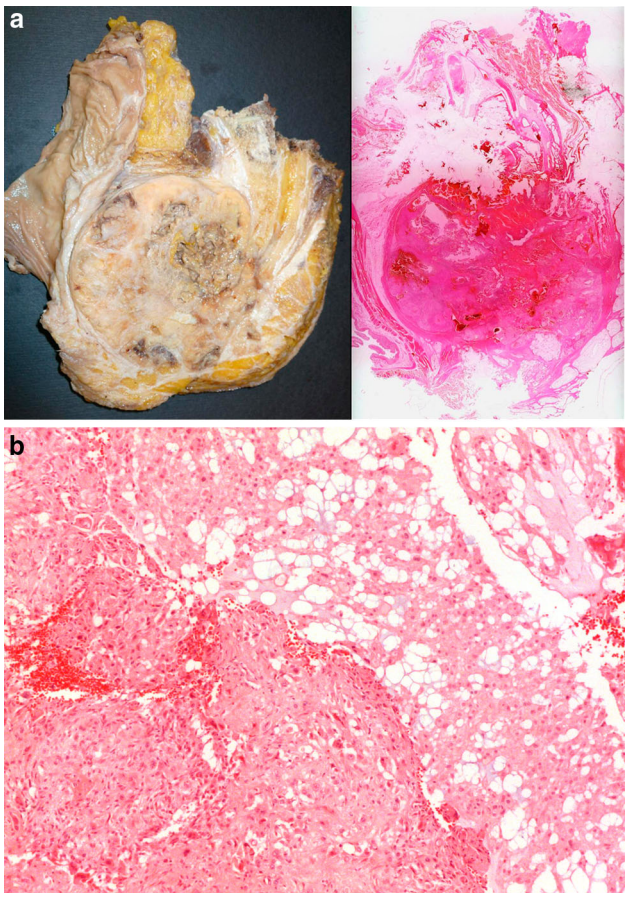

Fig. 2 **a** Gross section of the sacrum demonstrating the big lesion with soft tissue involvement: the image on the *left* shows the colon, which is not infiltrated by the tumor, and the image on the *right* shows a histological macrosection of the resected specimen. **b** Abrupt passage between a typical chordoma (*right side*) with bubble-like physaliphorous cells set in a myxoid matrix and a high-grade sarcoma (*left side*) (hematoxylin–eosin, ×10)

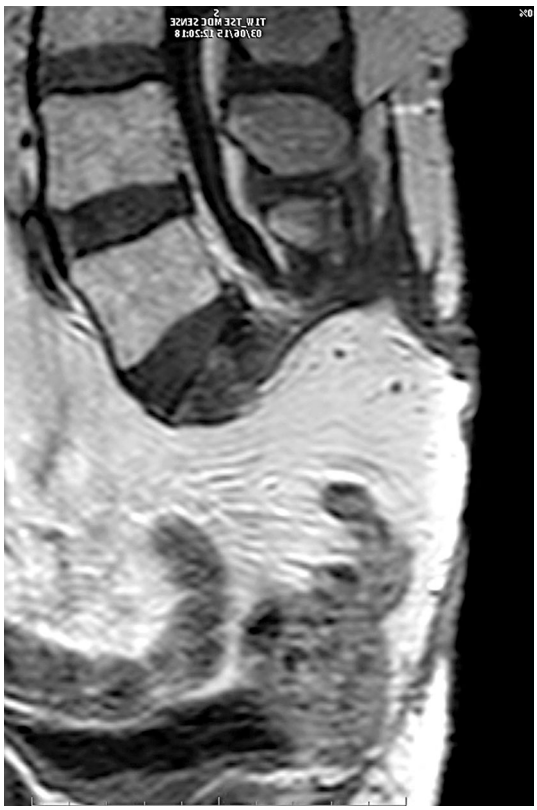

Fig. 3 Postoperative sagittal T1-weighed magnetic resonance imaging showing no evidence of sacral chordoma recurrence

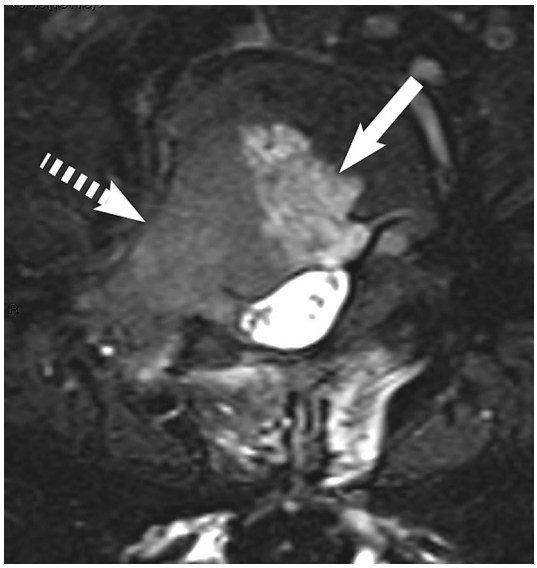

Fig. 4 Axial T2-weighed magnetic resonance imaging of the L4 showing conventional chordoma appearing hyperintense (*solid arrow*) and dedifferentiated chordoma appearing hypointense (*dashed arrow*)

right half of L4 vertebral body and encroaching into the spinal canal. No histologic diagnosis was obtained at that time. The patient experienced relief from back pain and limping after surgery, and further diagnostic examinations or treatments were not considered. Four months after surgery, she was referred to our institution for increased back pain, lower limb weakness, and an increased soft tissue mass detected by MRI. The T2-weighted image revealed a tumor involving the L3 and L4 vertebrae exhibiting two distinct signal intensities indicating two different areas within the lesion in terms of signal characteristics, a hyperintense component, and a reduced signal component (Fig. 4). The patient was diagnosed with conventional chordoma using CT-guided trocar biopsy at the L4 vertebral body. Because of the patient's history of cardiovascular surgery for the aneurysm of aortic bifurcation that required endovascular stent graft, and the patient's current condition consisting of a large spinal tumor involving L3 and L4, we performed gross total excision and stabilization using carbon fiber hardware to avoid interference with carbon-ion therapy that was planned 6 months after the

surgery. The final histological diagnosis of the specimen obtained from the second surgery was chordoma dedifferentiated to osteosarcoma (Fig. 5). The patient was referred to a center of carbon-ion radiotherapy. At the 39-month follow-up after surgery, the patients could walk normally without any neurological deficits or evidence of active disease (Fig. 6).

Discussion

Several cases of chordoma with a highly malignant sarcomatous component have been reported in the literature [6–16]. In most of the reported cases, the sarcomatous component was a pleomorphic sarcoma resembling an undifferentiated pleomorphic sarcoma or undifferentiated spindle cell sarcoma. Dedifferentiated chordoma was distinguished from "chordoma with sarcomatous transformation" by a sharp demarcation of the sarcomatous elements

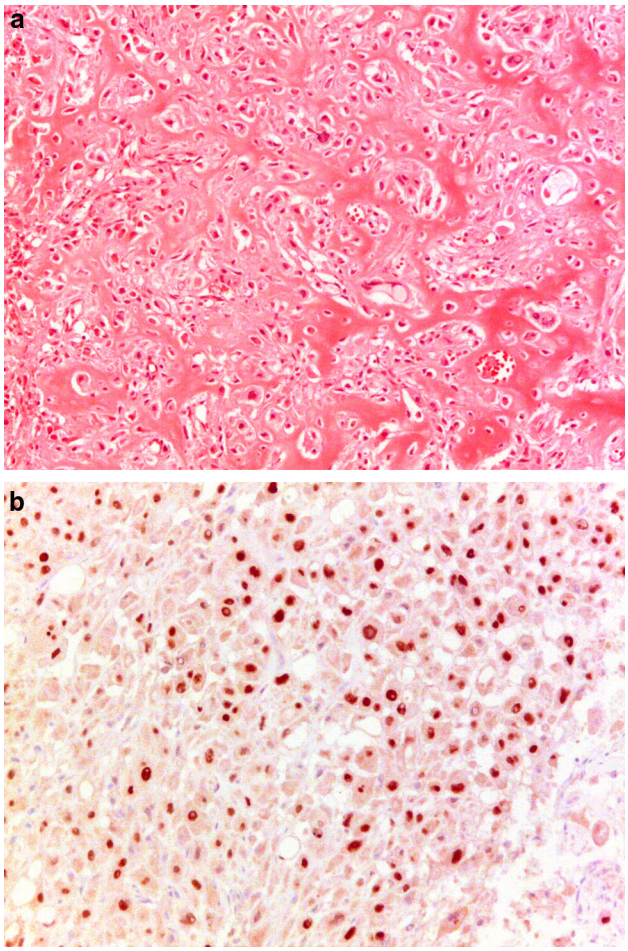

Fig. 5 **a** Malignant osteoid formation in the high-grade sarcomatous component, consistent with the diagnosis of high-grade osteosarcoma (hematoxylin–eosin, ×20). **b** Immunohistochemical positivity for brachyury in both components (×20)

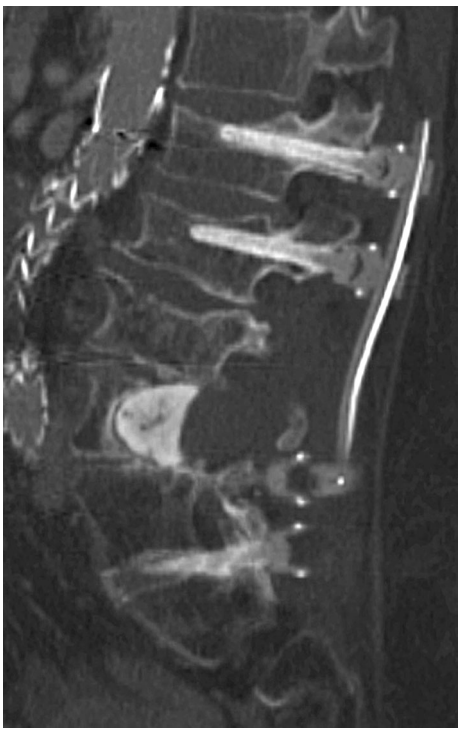

Fig. 6 Postoperative sagittal computed tomography image showing no evidence of active disease

and a lack of transitional features between the conventional chordoma and the high-grade sarcomatous component [6, 11]. The two cases presented here represent dedifferentiated chordomas with a sharp demarcation between the conventional chordoma and the high-grade sarcomatous component. A literature review found only two reported cases of chordomas dedifferentiated to osteosarcoma [6, 12]. One of these cases reported by Meis et al. was a dedifferentiated chordoma in the sacrum without any history of prior radiation. The patient died of a tumor-related complication 76 months after the primary diagnosis (approximately 9 years after the emergence of initial symptoms). In this case, no osteosarcoma was identified in any of the local recurrences or metastases, which were composed exclusively of conventional chordoma [6]. The other reported case of chordoma dedifferentiated to osteosarcoma was in the sacrum of a patient who was treated with surgical resection and irradiation. The patient died of pulmonary failure approximately 9 years after the emergence of initial symptoms. At autopsy, some areas of the pulmonary and brain metastases showed the histological appearance of osteosarcoma, while the primary sacral tumor was diagnosed as conventional chordoma [12]. Typically, dedifferentiation within a chordoma indicates poor prognosis with an aggressive clinical course, culminating in metastases and rapid demise. However, the two reported cases of chordoma dedifferentiated to

osteosarcoma [6, 12] displayed clinical features similar to conventional chordoma with distant metastases. This finding indicates that local control of primary tumors is important for patient survival and prevention of metastases in chordomas dedifferentiated to osteosarcoma, as well as in conventional chordomas. Although resection with negative oncological margins is the mainstay of treatment for chordomas [4], new technique of radiation has recently become a promising method of treatment and palliation of unresectable chordomas or chordoma recurrences [17–19]. By contrast, chordomas dedifferentiated to osteosarcoma might be resistant to modern radiation therapy compared to conventional chordomas, as demonstrated by case 1 presented herein, which showed tumor recurrence only 4 months after carbon-ion radiotherapy. Similarly, Kayani et al. reported local tumor recurrence in 6 out of 7 patients (85.7 %) treated with adjuvant radiotherapy (20–70 Gy) in a case series of 10 dedifferentiated sacral chordomas [10].

The clinical management of lesions suspected of malignancy relies not only on the accurate diagnosis of benign versus malignant entities, but also on tumor grading, immunohistochemical findings, and genetic information. Pathological analysis remains the gold standard for definitive diagnoses. An accurate pathological diagnosis is imperative to determine an appropriate treatment strategy for dedifferentiated chordoma, and therefore should be made before the initiation of treatment. Success of biopsy and accurate diagnosis depends on the availability of an adequate tissue from the correct location. Rimondi et al. [20] reviewed the results of 2027 CT-guided core needle biopsies of the musculoskeletal system and reported that the accuracy rate of the first biopsy was 77.3 %. T2-weighted MRI imaging is useful for locating a biopsy site because it enables distinction between dedifferentiated disease, which appears hypointense, and conventional disease, which appears hyperintense with commonly visible intralesional separation [10, 11]. PET/CT-guided biopsy can be a good option for obtaining adequate tissue and making an accurate diagnosis. Fluorodeoxyglucose-PET is used not only to detect malignancies but also to help locate the most active areas within the malignancy [21]. PET/CT biopsy can pinpoint the most active tissue within a large mass and reduces the need for biopsy repetition. Cerci et al. reported that PET/CT-guided biopsy is feasible and may optimize the diagnostic yield of image-guided interventions [22]. If the histological diagnosis after percutaneous needle biopsy is still doubtful, or the biopsy result is not consistent with the suspected diagnosis by clinical features and/or imaging, the percutaneous needle biopsy should be repeated [20].

Owing to the rarity of dedifferentiated chordomas and their poor prognoses, neither tumor response to chemotherapy nor optimal treatment regimens have been fully investigated. Fleming et al. [7] analyzed the role of chemotherapy in dedifferentiated chordomas with metastatic disease, achieving complete remission in two cases. Given the poor prognosis of dedifferentiated chordomas, they suggested that primary adjuvant chemotherapy should be considered before radiotherapy in newly diagnosed patients. Earlier identification of the sarcomatous elements would enable the more effective treatment of the disease. Chemotherapy was used in case 1 of our series before the en bloc resection of tumor. No local recurrence or progression of the lung nodules was detected at the last follow-up 36 months after surgery.

Conclusion

Two rare cases of spinal chordomas dedifferentiated to osteosarcoma are reported. In both cases, the first biopsies were not accurately diagnosed. Accurate analyses of MRI and PET scans should suggest the most appropriate representative area to submit to the pathologist for histological assessment. CT scan trocar biopsy should be repeated if the diagnosis is not consistent with imaging evidence or disease evolution. Unlike conventional chordomas, chordomas dedifferentiated to osteosarcoma must be first treated with chemotherapy, followed by en bloc resection and/or carbon-ion treatment. Further studies are needed to evaluate the relative results and morbidity of surgery, carbon-ion treatment, or a combination of both.

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Conflict of interest None of the authors declare any potential conflict of interest.

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