Case Report

Dedifferentiated chordoma: A rare tumor with diagnostic challenge

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ABSTRACT

Chordomas are rare locally invasive malignant bone tumors arising from remnants of embryonic notochord. Dedifferentiated chordoma (DC), a rare subtype, is characterized by the presence of a sarcomatous component in conventional chordoma (CC) which may arise *de novo* or as a malignant transformation of previously treated chordoma. The presence of dedifferentiation warrants a poor prognosis due to distant metastasis and recurrences. *De novo* DCs pose a diagnostic challenge especially in small biopsies and at metastatic sites. Here, we report the case of a 45-year-old female presenting with a long history of backache and constipation, finally diagnosed as DC. Radiological as well as histomorphological pictures of the tumor posed diagnostic challenges because they can mimic other tumors occurring in a similar location. We found this case worth reporting as *de novo* DC is rarely reported in the literature and it has the potential to pose diagnostic as well as therapeutic challenges.

Key words: Chordoma, *De novo* dedifferentiated chordoma, Dedifferentiated chordoma, Immunohistochemistry

Chordomas are rare locally invasive malignant bone tumors arising from remnants of embryonic notochord [1,2]. They account for 1–4% of all bone tumors, with an annual incidence of 0.088 chordomas per 100,000 persons documented in the United States, commonly involving cranial followed by sacral and spinal location [3]. Histologically, chordomas are classified into four subtypes, classical, chondroid, dedifferentiated, and recently proposed poorly differentiated type [4,5]. At present, the World Health Organization histologically defines three types of chordoma: Conventional, dedifferentiated, and poorly differentiated chordoma; chondroid chordoma is now considered a subtype of conventional chordoma (CC) [6]. Dedifferentiated chordoma (DC) is characterized by the presence of a sarcomatous component in CC which may arise *de novo* or as a malignant transformation of previously treated chordoma. The sarcomatous component may be fibrous (malignant fibrous histiocytoma and fibrosarcoma) and non-fibrous (rhabdomyosarcoma, osteosarcoma, and others) [6,7]. Being one of the rare subtypes, DC comprises < 1% of all chordomas [8] and only a handful of case reports and case series are available to date. In a pooled data analysis by Liu *et al*., total 96 cases of DC including 67 *de novo* cases from literature research have been analyzed [5].

The presence of dedifferentiation warrants a poor prognosis due to distant metastasis and recurrences. *De novo* DC poses a diagnostic challenge especially in small biopsies and at metastatic sites. Here, we report a case of *de novo* DC because of its rarity, interesting histomorphology and therapeutic challenges.

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CASE REPORT

A 45-year-old female patient presented to the neurosurgery outpatient department with a history of chronic backache radiating to both legs for the past 8–10 years. The patient also complained of chronic constipation for the past 3–4 years. For these complaints, the patient was given conservative treatment in the form of analgesic medication and stool softeners. However, in the past 3 months, her condition deteriorated and the severity of her pain increased to an extent causing significant limitations in daily routine activities.

The patient was evaluated clinically and radiologically. General examination findings were normal and local examination revealed no palpable mass lesion or neurological deficit.

Magnetic resonance imaging lumbosacral spine revealed a well-circumscribed lobulated midline mass arising from the sacrum. The mass was displacing the rectum anteriorly and the intervening fat plane was maintained, the features were suggestive of chordoma or plasmacytoma.

A trucut biopsy of the lesion was performed elsewhere and was reported as moderately differentiated chondrosarcoma. On further investigation, computed tomography pelvis of the sacrum

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and lower lumbar vertebra with 3D reconstruction revealed a large well-defined smoothly marginated heterogeneous density mass measuring 114 mm transverse and 121 mm anterioposterior and 121 mm craniocaudal arising from the sacrum and first coccygeal segment projecting anteriorly with mass effect on the rectum, sigmoid colon, and pelvic organs and also extending to the bilateral sacroiliac joints. Small curvilinear foci of calcification were also seen within the mass suggestive of destroyed sacral bone. No osseous or chondroid matrix was seen within the mass.

Subsequently, surgery was performed on the patient and the sacral mass was excised as much as possible and sent for histopathological examination. Grossly, the mass comprised of the sacrum and soft-tissue components together measuring 12 × 9 × 9 cm (Fig. 1a and b). It was partly encapsulated grey-brown mass, attached to muscle and bone. The mass had a variegated appearance; predominantly grey-brown to tan-colored, partly friable, and partly firm in consistency.

On microscopic examination, a biphasic tumor with heterogeneous morphology was seen (Fig. 2a). One component comprised of predominantly medium to large sized, oval to polygonal cells with abundant eosinophilic, multivacuolated bubbly cytoplasm (physaliphorous cells) arranged as lobules separated by fibrous septa (Fig. 2b). Within the lobules, tumor cells were arranged in sheets. The nuclei were oval and vesicular with mild anisonucleosis, focally large nuclei and multinucleation were seen. Within the lobules myxoid matrix was present. Mitotic activity was not appreciated in lobulated areas. Interspersed areas showed extensive hemorrhage and ischemic necrosis. Foci of epithelioid cells in solid nests and sheets were also seen (Fig. 2c). Spindle cell component comprising of spindle-shaped cells arranged in intersecting fascicles, showing nuclear atypia and mitotic activity up to 8–10 mf/10 hpf with atypical forms seen at places (Fig. 2d). Focally variably mineralized osteoid was also seen. Bone was involved in the tumor. No lymphovascular or perineural invasion was seen. The resected margin was involved by tumor at places. Differential diagnosis of chordoma with dedifferentiation having epithelioid, chondroid, sarcomatoid, and osteoid components and dedifferentiated chondrosarcoma was made.

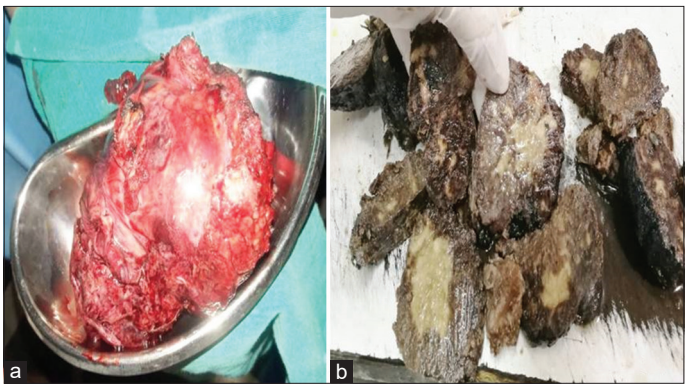

Figure 1: Gross picture of the specimen. (a) Partly encapsulated specimen. (b) Cut surfaces

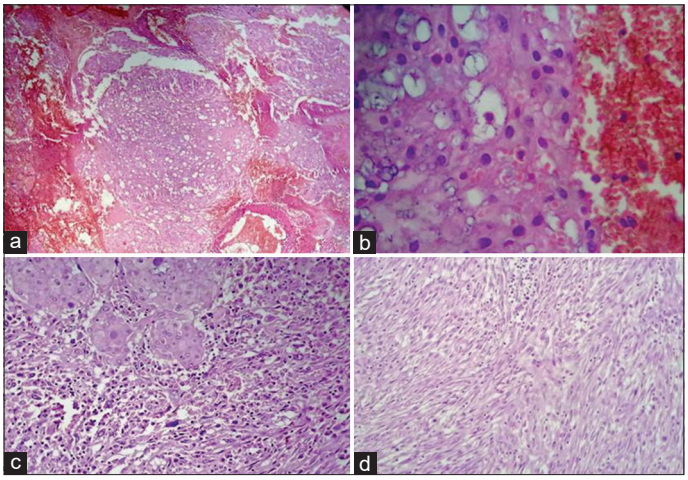

Figure 2: Microscopic picture: (a) Heterogeneous morphology showing tumor with hemorrhage and necrosis (Hematoxylin and Eosin, 10×), (b) Lobules with physaliphorous cells (H and E, 40×), (c) Lobules of epithelioid cells, (H and E, 40×), and (d) Spindle cell component, (H and E, 40×)

Immunohistochemistry was done for confirmation of the tumor type. Chordoid and epithelioid tumor cells in lobules showed strong diffuse positivity for pan CK, CD 56, CK8/18, CK19, HBME1 (Fig. 3a-c); and moderate positivity for EMA. S100 and D2-40 were negative. Ki 67 (Proliferation index) was 6% in the epithelioid component and 30% in the spindle cell component (Fig. 3d). The final diagnosis of DC with sarcomatous and osteosarcomatous component was hence made.

The patient was given a standard dose of radiotherapy (RT) but after 4 months, she developed a recurrence. She refused further therapy in our hospital and took RT in another hospital. During telephonic interaction with her relative, she was found to be alive with the disease after 3 years of diagnosis.

DISCUSSION

DC is a clinically and genetically distinct entity from CC. They have an overall poorer prognosis compared with CC s due to their highly aggressive behavior and high metastatic potential. In our case, it appears to be a spontaneous transformation of a long-standing chordoma to this highly aggressive and treatment

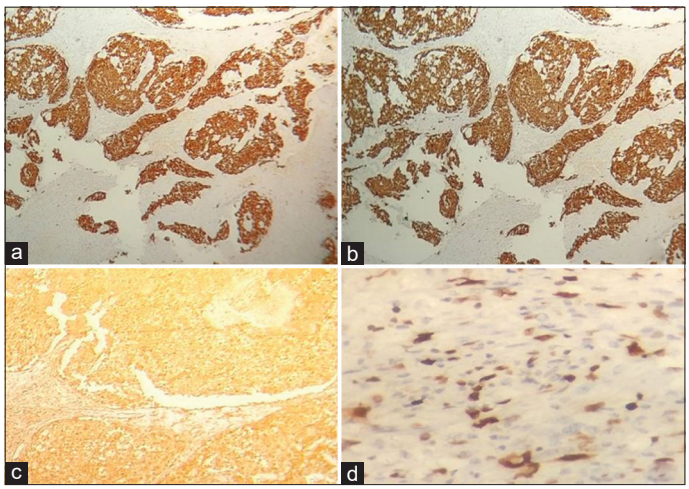

Figure 3: Immunohistochemistry (a) Pan CK, (b) CK 8/18, (c) HBME 1, and (d) Ki 67 in spindle cell components

resistance tumor as the patient had symptoms for several years before diagnosis.

Most of the chordomas are of classical and chondroid subtypes. Rarely, poorly differentiated chordoma and DC are encountered, which pose diagnostic challenges for histopathologists. In our case, the tumor had varied morphology such as epithelioid, sarcomatoid, chondroid, and osteoid along with classical chordoid areas [9]. The presence of myxoid component and vacuolated cells and the location of the tumor lead to the two main differentials. Besides these two tumors, other tumors with cells having clear or vacuolated cytoplasm and mucinous or myxoid stroma, for example, liposarcoma, renal cell carcinoma, mucinous carcinoma, and myoepithelial carcinoma, come into differential diagnosis, especially in small biopsies. The diagnostic problem mostly occurs in small biopsies where only the sarcomatoid component is sampled in primary or metastatic sites, especially in *de novo* cases. Therefore, in the evaluation of metastatic deposits having epithelioid or biphasic morphology with myxoid/mucinous stroma, we should keep the possibility of DC in mind.

Immunohistochemistry with a panel of selected markers helps to establish the diagnosis of chordoma and to rule out all other possibilities. Before the introduction of the Brachyury, many markers were used for this purpose, out of which commonly used markers were pan CK, EMA, D2-40, HBME1, and GFAP [10]. Brachyury, the notochordal transcription factor, a relatively new marker, is fairly sensitive and specific for chordoma and is not expressed in chondrosarcoma and other sarcomas, with few exceptions. Inconsistence expression of Brachyury in dedifferentiated sarcomatoid component has been reported by authors in various studies, which may lead to more challenges, especially in small biopsies or metastatic sites [8,11].

Brachyury was not available so a panel of multiple antibodies was needed in our case. HBME 1 shows positivity in chordoma and chondrosarcoma, but not in colorectal and renal cell carcinomas. Expression of HBME 1 along with pan CK, EMA, CK8/18, CK 19, and lack of D2-40 expression, (a true chondroid marker) ruled out chondrosarcoma and confirmed the diagnosis of chordoma in our case.

Chordoma continues to present a considerable treatment challenge due to a number of factors, including indolent growth rate and resultant tendency to present late in the disease course, propensity for invading through tissue planes, encapsulating critical nearby anatomy and seeding after resection, and its relative insensitivity to conventional RT and chemotherapy. DC carries a poor prognosis with rapid local progression, distant metastasis, and treatment resistance. Surgery followed by adjuvant RT is considered to be the treatment that was done in our case. In a study of 11 patients of DC, sacral location, absence of metastatic disease, and *en bloc* resection with negative margins at the time of upfront surgery are found to be favorable factors for comparatively longer survival [12]. Our patient did not develop metastasis at the time of presentation but developed early recurrence and a protracted course which is remarkable. Radiation therapy has been used as an upfront treatment in case of diffuse metastatic disease. Local recurrence is very common and depends upon the completeness of resection. In a study of 11 patients of DC, it had been observed that although the local failure rate is similar in both CC and DC, the time of local failure is significantly shorter along with a significantly lower median survival rate [12].

CONCLUSION

DC is a rare disease due to low prevalence and continues to be a diagnostic and therapeutic challenge. For diagnosis of *de novo* DC on biopsy specimens, a high index of suspicion and a panel of immunohistochemical markers are required. With the available treatment options, distant metastasis and incomplete excision usually lead to treatment failure and short survival. An early diagnosis is required to enable complete resection which may improve survival with conventional therapies; however, for aggressive cases with distant metastasis, there is a need for more effective systemic therapeutic approach that cannot be overemphasized.

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