De Novo Dedifferentiated Chordoma of the Sacrum: A Case Report and Review of the Literature

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Dedifferentiated chordoma is a rare primary malignant bone cancer. Most cases of dedifferentiated chordoma (DC) are transformed from recurrent chordoma after surgical resection or radiation. The prognosis of DC is extremely poor because of the aggressive nature of the tumor and the potential distant metastases. We report a case of *de novo* DC of the sacrum in a patient without prior surgical procedure or radiation treatment. A complete review of reported cases sourced from reports published in English literature is discussed and expanded upon and conclusions on the treatment of DC are presented. *(Chang Gung Med J 2009;32:330-5)*

Key words: chordoma, dedifferentiated chordoma, sacrum

A chordoma is a tumor arising from the remnant of neuroaxia. It usually occurs in the sacrum, skull base (mainly the clivus), and the vertebral column.[1,2] A chordoma is a malignant, slow-growing tumor; most clinical symptoms are related to the mass effect of the tumor. Surgical excision is the primary treatment for chordomas; however, local recurrence is frequent due to the difficulty in achieving complete excision.[1,3,4] Dedifferentiated chordoma (DC) has been reported as the result of malignant transformation of recurrent chordomas or post-irradiation changes. The clinical course of DC is distinguished from chordomas by the rapidity of tumor growth and the potential for distant metastases. In this paper, we report a rare case of *de novo* DC of the sacrum in a 63-year-old female without prior surgical procedure or sacral irradiation.

CASE REPORT

In September 2000, a 63-year-old female presented for evaluation with an eight-to-ten month history of a sacral mass and intermittent lower abdominal dull pain. The patient had no complaints of urinary incontinence, stool retention, tenesmus, sciatic pain, or paresis of the lower extremities. The patient's medical, surgical, and family history were unremarkable. On physical examination, a large, palpable mass was noted over the lower sacrum area, approximately 10 x 13 cm in size. The tumor was blue in color and fragile. A pelvic plain film revealed a destructive lesion over the sacrum (Fig. 1A). A pelvic computed tomography (CT) revealed a 15 x 17 x 17 cm osteolytic, expansible mass involving the sacrum (Fig. 1B). Pelvic magnetic resonance imaging (MRI) showed a 15 x 17 cm mass in the sacrococcygeal area with peripheral bony destruction (Fig. 1C). Laboratory studies, including a hemogram and biochemistry examination, were unremarkable. The patient underwent a debulking excision. Microscopic examination revealed a dedifferentiated chordoma (Fig. 2). Neither post-operative radiotherapy nor

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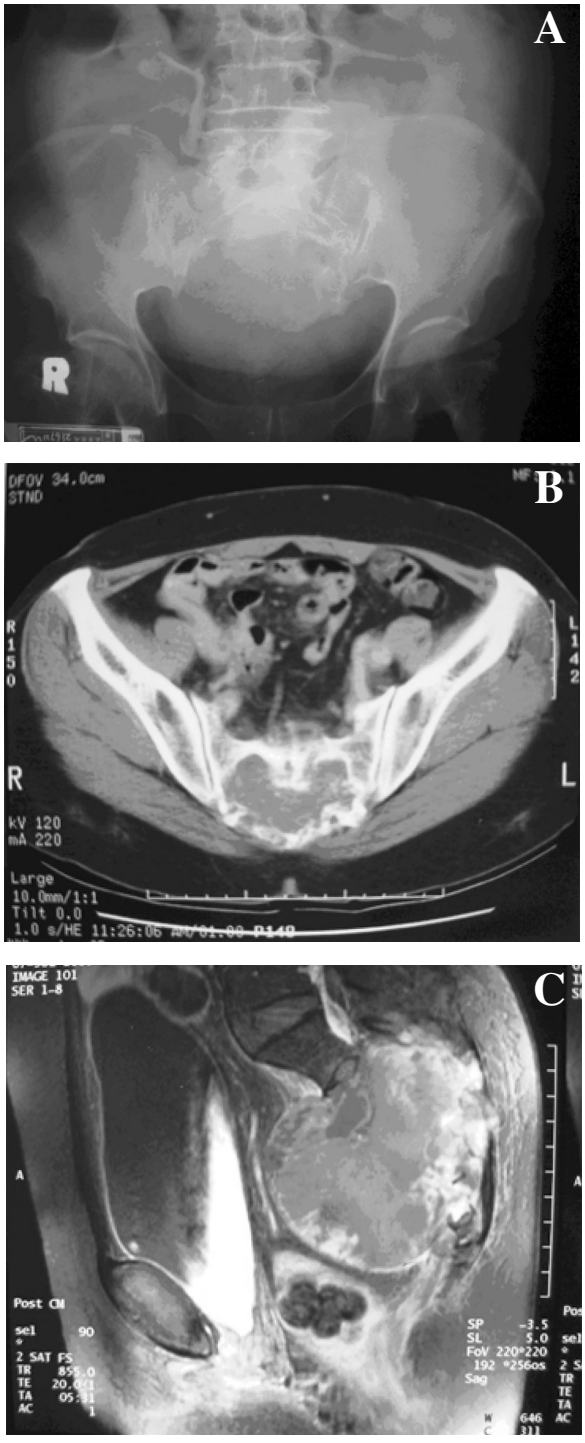

Fig. 1 (A) Pelvic plain film showing extensive destruction of the sacrum. (B) CT scan of the pelvis showing the sacro-coccygeal mass with bone destruction. (C) Post-contrast T-1 weighted MRI showing sacro-coccygeal mass with heterogeneous enhancement.

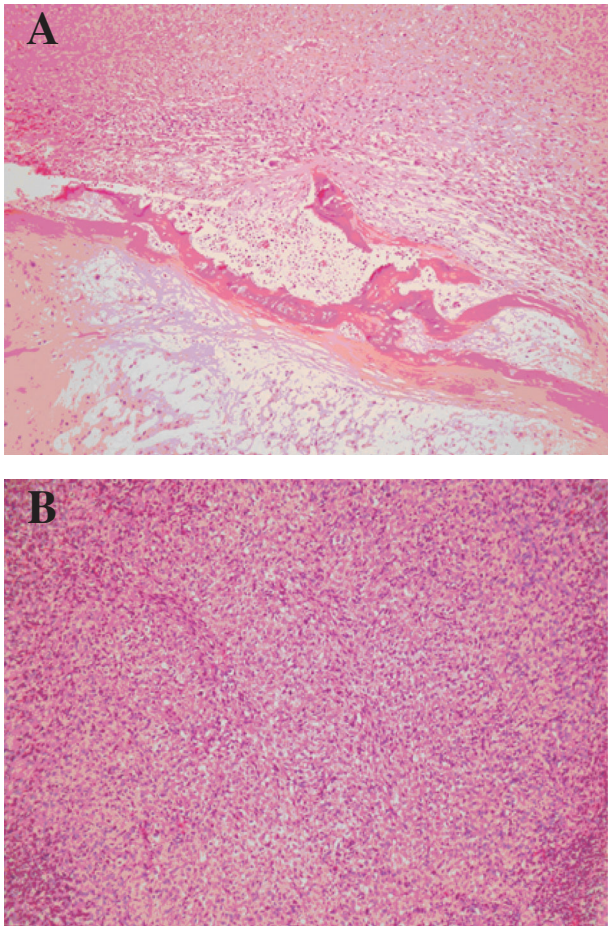

Fig. 2 (A) The tumor had two components. The lower field shows a conventional chordoma with vacuolated physaliferous cells; the upper field shows a sarcomatous component of the dedifferentiated chordoma. No transitional features were noted between the two components (H&E). (B) The area involving the sarcomatous component showed bizarre and multinucleated cells (H&E).

chemotherapy was recommended. The tumor recurred locally two months post-operatively. The recurrent tumor was complicated by bleeding and infection in the wound. The patient had received one course palliative chemotherapy regimen consisting of cisplatin (50 mg/m^2), epirubicin (30 mg/m^2), and ifosfamide (1.4 mg/m^2/daily) x 2 days for one cycle. Neutropenic fever (the absolute neutrophil count was 100/cmm) occurred on the 7th day after chemotherapy. The sacral mass progressed rapidly after chemotherapy. The patient died due to wound infection and sepsis one month after chemotherapy.

DISCUSSION

DC, first defined by Meis et al.,[5] was characterized as a sharp demarcation of a conventional chordoma with a high-grade sarcomatous component. It was distinguished from the term "chordoma with sarcomatous transformation" because of a lack of transitional features between the two components. The differential diagnosis between DC and chordoma is important because of the distinctions in clinical prognosis. Conventional chordoma is a slow-growing tumor with a benign behavior and an indolent clinical course. In contrast, a DC is characterized by the potential for distant metastases and rapid progression.

One cannot distinguish chordoma from DC based on imaging studies unless distant metastases exist. Typical findings on a plain film of chordomas include osteolytic lesions of the bone with sclerotic bone reaction.[6] CT scan or MRI studies are indicated to evaluate the extent of the tumor and to identify the tissues that the tumor has infiltrated.[7-9] An expanding, destructive, lytic lesion with an associated soft tissue mass is characteristic of serial CT scans. MRI has a better resolution of the soft-tissue component than a CT scan. Chordomas show hyperintensity in T2 and hypointensity in T1-weighted images on MRI.

There have been 15 reported cases of DC since 1970 (Table 1).[5,10-20] The median age of patients at the time of diagnosis of DC is 63 years (range, 24-73 years). The male-to-female ratio is nearly 2: 1. Of the 15 cases 9 were derived from pre-existing chordomas and another 6 case presented as *de novo* disease. The median transformation interval between chordoma and DC in the 9 patients was 6.6 years (range, 2-26 years). Of the 9 patients 7 received local radiation therapy. Of the 16 patients 9 (including the patient reported herein) had distal metastatic lesions, in addition, lung metastases presented in all of the patients. Other metastatic sites include the pleura, inguinal and para-aortic lymph nodes, bone marrow, heart, and spine.

The treatment of choice for DC is surgical resection. Of the 16 patients 6 had undergone surgical resection alone for DC; a disease-free status for more than 5 months was achieved in 3 of the patients; the other 3 patients had recurrent disease post-operatively. Of the 6 patients 2 expired at 3 and 8 months post-operatively as a result of the recurrent disease. Of the 16 patients 4, all of whom had recurrent or metastatic disease, underwent surgical resection followed by local radiotherapy to the sacrum. The poor outcomes in these patients may have been due to the difficulty in resection of locally advanced disease, which in turn may have led physicians to boost local radiotherapy as adjuvant treatment post-operatively. There were 4 patients with unresectable tumors or who were intolerant to systemic treatment and received local radiotherapy alone to the sacrum or lung metastases. The survival was between 3 weeks and 8 months in these patients; all these patients had progressive disease with new metastatic lesions during or after the course of radiation. Radiation therapy is particularly limited as a primary treatment modality for DC.

Of the 16 patients 7 received chemotherapeutic agents as systemic treatment. Felming et al.[15] reported the use of a 6-drug regimen including etoposide, cisplatin, vincristine, dacarbazine, cyclophosphamide, and doxorubicin for 2 patients with DC who presented with multiple lung metatases. In one patient, complete response was achieved without recurrence for a 24 month follow up period. In the other a partial response to the 6-drug regimen was achieved, and following salvage therapy with ifosphamide, a complete response followed from the therapy. The patient died with recurrent disease 28 months after DC was diagnosed. Both patients received aggressive lung metastatectomy after chemotherapy, which was complicated with neutropenic fever during the 6-drug regimen treatment and required a reduction in dose during the next treatment cycle. Meis et al.[5] reported the use of a dororubicin-based regimen in 2 DC patients with lung metastases. In one patient partial response was achieved after treatment with doxorubicin, DTIC, and cyclophosphamide combination chemotherapy. The other presented with lung tumor regression, but the sacral mass progressed after treatment with doxorubicin and cisplatin. The patient in our case report received ifosfamide, epirubicin, and cisplatin combination therapy. Grade IV myelosuppression (i.e., an absolute neutrophil count of 100/mm^3) with a febrile episode was noted on the 7th day after chemotherapy. The sacral tumor progressed rapidly after chemotherapy and our patient died of wound infection and

Table 1. Reported Cases of Dedifferentiated Chordoma of the Sacrum

	Reference	Age/ Gender	Previous radiation*	Transformation interval†	Metastatic sites	Treatment§	Palliative chemotherapy	Chermotherapy regimen	Response to chemotherapy	Outcome‡
De Novo Group										
Case 1	5	66/M	Nil	Nil	Lung, bone marrow, and heart	OP, RT	Yes	CYC, ADR, DTIC	Partial response	6 months
Case 2	5	44/M	Nil	Nil	Lung	No	Yes	ADR, CDDP	Mixed response‖	5.5 months
Case 3	15	34/F	Nil	Nil	Lung	OP, RT	Yes	VP16, CDDP, VIN, DTIC, CYC, ADR	Complete response	AWD > 2 years
Case 4	15	34/F	Nil	Nil	Lung	OP, RT	Yes	VP16, CDDP, VIN, DTIC, CYC, ADR	Partial response	28 months
Case 5	18	39/F	Nil	Nil	Lung	OP	Yes	NA	NA	NA
Case 6	19	24/M	Nil	Nil	Lung and T-L spine	RT	Nil	–	–	3 weeks
Case 7	Present case	63/F	Nil	Nil	Nil	OP	Yes	CDDP, EPI, IFO	Progressive disease	3 months
Transformation Group										
Case 1	10	53/M	Yes	2 year	Lung, pleura, and inguinal	RT	Nil	–	–	6 months
Case 2	11	67/M	Nil	15 years	Lung	OP, RT	Nil	–	–	4 years
Case 3	12	57/F	Yes	7.5 years	Nil	OP	Nil	–	–	8 months
Case 4	13	64/M	Yes	2 years	Lung	Nil	Yes	NA	NA	> 12 months
Case 5	14	71/M	Yes	26 years	Nil	OP	Nil	–	–	AWD, 6 months
Case 6	15	65/M	Yes	6.6 years	Lung	RT	Nil	–	–	8 months
Case 7	16	73/M	Yes	10 years	Lung	RT	Nil	–	–	1 month
Case 8	17	50/M	Nil	3 years	Nil	OP	Nil	–	–	AWD, 5 months
Case 9	20	41/M	Yes	5 years	Nil	OP	Nil	–	–	AWD, NA

Abbreviations: M: male; F: female; DN: *de novo*; AWD: alive without disease; NA: not available; OP: surgical resection; RT: radiation; CYC: cyclophosphamide; ADR: adriamycin; DTIC: dacarbazin; CDDP: cisplatin; VP16: etoposide; VIN: vincristine; EPI: epirubicin; IFO: ifosfamide; NA: not available; *: Previous radiation for conventional chordoma; †: Transformtion interval: interval from conventional chordoma to de-differentiated change; ‡: Outcome: duration between recognition of de-differentiated chordoma and death; §: Treatment modality for sacral de-differentiated chordoma; II: Sacral mass progression, but metastatic lung nodule regression.

uncontrolled sepsis one month later. Indeed, the role of chemotherapy and the chemotherapeutic agents used in the treatment of metastatic DC is uncertain. For some patients the combination of chemotherapy with a doxorubicin, cisplatin, and cyclophosphamide-based regimen appears to be optimal. Physicians, however, should effectively manage associated complications to treatment, specifically myelosuppresion.

Conclusion

DC is a rare and highly aggressive tumor. The prognosis is poor due to the difficulty achieving resection of the tumor, in addition, existing chemotherapeutic regimens do not consistently achieve or complete responses after treatment. Most patients die soon after surgery mainly due to the mass effect of a large local tumor or multiple distant metastases.

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薦骨的原生性去分化脊索瘤：病例報告及歷史文獻回顧

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去分化脊索瘤是一種非常罕見的原發性惡性骨瘤，絕大多數的去分化脊索瘤病例是由脊索瘤經手術切除或放射線治療後再復發而產生。因爲去分化脊索瘤具高度侵犯性及容易遠處轉移，此類病患的預後非常不佳。我們報告一個以原發性去分化脊索瘤爲初始表現的個案，個案之前未曾接受任何手術或化學治療；同時回顧及整理有關於去分化脊索瘤的歷史文獻報告。(長庚醫誌 2009;32:330-5)

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