Dedifferentiated chordoma

A REPORT OF FOUR CASES ARISING 'DE NOVO'

S. A. Hanna,
R. Tirabosco,
A. Amin,
R. C. Pollock,
J. A. Skinner,
S. R. Cannon,
A. Saifuddin,
T. W. R. Briggs

From the Royal
National
Orthopaedic
Hospital, Stanmore,
England

■ S. A. Hanna, MRCS, Research Registrar
■ A. Amin, MRCS, Specialist Registrar
■ R. C. Pollock, FRCS, Consultant Orthopaedic Surgeon
■ J. A. Skinner, FRCS, Consultant Orthopaedic Surgeon
■ S. R. Cannon, MCh(Orth), FRCS, Consultant Orthopaedic Surgeon
■ T. W. R. Briggs, MCh(Orth), FRCS, Consultant Orthopaedic Surgeon
Department of Orthopaedic Oncology
■ R. Tirabosco, MD, Consultant Histopathologist
Department of Histology
■ A. Saifuddin, MRCP, FRCR, Consultant Radiologist
Department of Radiology
Royal National Orthopaedic Hospital, Stanmore, Middlesex HA7 4LP, UK.

Correspondence should be sent to Mr S. A. Hanna; e-mail: sammyhanna@hotmail.com

©2008 British Editorial Society of Bone and Joint Surgery
doi:10.1302/0301-620X.90B5.20365 \$2.00

J Bone Joint Surg [Br]
2008;90-B:652-6.

Received 22 October 2007;
Accepted after revision 9 January 2008

Dedifferentiated chordoma is a rare and aggressive variant of the conventional tumour in which an area undergoes transformation to a high-grade lesion, typically fibrous histiocytoma, fibrosarcoma, and rarely, osteosarcoma or rhabdomyosarcoma. The dedifferentiated component dictates overall survival, with smaller areas of dedifferentiation carrying a more favourable prognosis. Although it is more commonly diagnosed in recurrences and following radiotherapy, there have been a few reports of spontaneous development. We describe four such cases, which were diagnosed *de novo* following primary excision, and discuss the associated clinical and radiological features.

Chordomas are tumours arising from embryonic notochordal remnants accounting for 17.5% of primary malignant bone tumours of the axial skeleton, with a reported incidence of 0.5 to 0.8 per 1 000 000 population.^{1,2} Lesions arise from the sacrococcygeal region (50%), the base of the skull (35%) and the vertebral column (15%), with sacrococcygeal tumours typically presenting in the sixth to seventh decades of life.¹⁻³ Chordomas grow slowly and metastasise late in 20% to 40% of cases to the lungs, liver, bone and soft tissues. The survival rates at five to ten years range between 30% and 55%.⁴⁻⁷ *En bloc* excision is a prerequisite for prolonged survival. Adjuvant radiotherapy is often used, but although it appears to reduce the incidence of local recurrence, it has little influence on overall survival.⁸ The coexistence of sarcomatous areas, most commonly malignant fibrous histiocytoma,⁹⁻¹⁷ fibrosarcoma,¹⁸ osteosarcoma,^{17,19} or rarely rhabdomyosarcoma²⁰ within a conventional chordoma is rare, but prognostically significant. Sharp demarcation of the sarcomatous elements indicates a dedifferentiated chordoma, whereas the presence of a transitional feature suggests the diagnosis of sarcomatoid chordoma.⁹ The prognosis for both subtypes of tumour is dismal, with patients pursuing a fulminant clinical course, similar to dedifferentiation associated with chondrosarcoma and liposarcoma.^{19,21} Metastasis and/or death occur in the majority of patients from tumour-related complications within one year of diagnosis.^{9,11,12,16,17,19,20}

Patients and Methods

We performed a retrospective review of 29 patients with histologically-verified sacrococcygeal chordoma who had been referred to our orthopaedic oncology unit between 1997 and 2007. These cases were identified using the histopathology database of the department. Of the 29 patients, four had a dedifferentiated chordoma, which was diagnosed '*de novo*' following primary excision. There were no cases of dedifferentiation arising in recurrences or after radiation treatment. We obtained data from the case notes, hospital databases, imaging studies and clinic reviews.

Results

Case 1. In 2000, a 57-year-old man presented with a history of acute-on-chronic urinary retention for four weeks and of lower back pain and rectal tenesmus for six months. Rectal examination revealed a large mass overlying the sacrum.

A radiograph of the lower sacrum showed erosion and destruction, with areas of patchy sclerosis (Fig. 1). MRI revealed a large tumour arising from the S3 segment and extending anteriorly to fill the whole width of the pelvis, with a large posterolateral extension into the left buttock. A pre-operative needle biopsy revealed moderately pleomorphic spindle cells in a collagenous matrix. Vimentin was uniformly positive, and S100 was positive in scattered tumour cells. These findings were suggestive of a primary spindle-cell tumour. The patient underwent a partial sacrectomy combined with an abdominoperineal resec-

Fig. 1

Radiograph of a chordoma causing destruction of the lower sacrum in case 1.

Fig. 2

The high-grade pleomorphic sarcomatous component (right) is abruptly juxtaposed to a conventional chordoma component (left) in case 1 (haematoxylin & eosin stain, 4 × magnification).

tion. Histopathological examination revealed a lobulated, necrotic tumour consistent with the diagnosis of chordoma, with multiple areas of high-grade dedifferentiation (Fig. 2). The margins of excision were incomplete. The patient was treated with single agent, doxorubicin, but within ten weeks developed extensive local recurrence in the scar and in the pelvis, in addition to mediastinal and pulmonary metastases. He died seven months after initial presentation.

Case 2. In 2002, a 61-year-old man presented with a six-month history of a progressively enlarging mass in his lower back. It did not cause pain, but he was aware of it when sitting for long periods or when driving. Clinical examination revealed a large soft-tissue lump over the sacrum and coccyx in the midline, firm in consistency and

Fig. 3

An axial T₂-weighted MR image in case 2. Note the presence of hyperintense (arrowhead) conventional and low signal (arrows) dedifferentiated areas.

fixed to the underlying tissues. MRI showed a large mass, 14 cm in diameter, arising from the coccyx and displacing the rectum anteriorly, with both anterior and posterior extraosseous components. On MRI the T₂-weighted images showed two different areas within the lesion in terms of signal characteristics, a hyperintense component and a reduced signal component (Fig. 3). He underwent partial sacrectomy, and histopathological examination confirmed the diagnosis of chordoma containing a small area of high-grade spindle-cell dedifferentiation. The margins of excision were incomplete. After operation radiotherapy was instituted, with fractions of 55 Gy over six weeks. After this, he was in remission for three years. In 2005 he developed an enlarging mass in the ninth left rib. A needle biopsy confirmed that this was a metastasis but did not show areas of dedifferentiation. The rib was completely excised. Histopathological examination showed a high-grade spindle cell component, which the needle biopsy had failed to detect. As the surgical margins were clear, no further treatment was deemed necessary. In early 2007 he began to experience shooting pains in his lower back. Clinical examination revealed an ataxic gait, brisk reflexes and bilateral extensor plantar responses. There was patchy sensory loss and reduced power in both limbs. MRI showed a 5 cm soft-tissue mass arising from T9 and compressing the thoracic cord (Fig. 4). An urgent surgical decompression with complete excision of the mass was successfully performed, with instrumented stabilisation from T7 to T11. Histology showed a metastatic dedifferentiated chordoma with clear margins of excision. He remains well 63 months after the initial treatment, and no further treatment is planned.

Fig. 4

An axial T₂-weighted MR image of T9 in case 2. Metastatic chordoma (arrow) encroaching on the canal, causing compression of the cord. The inset shows the level of the MRI slice (T9).

Fig. 5

High-power view of the dedifferentiated component in case 3. This is composed of severely atypical cells with pleomorphic nuclei and numerous mitoses (haematoxylin & eosin stain, 20× magnification).

Case 3. A 57-year-old man was referred in 2003 with severe coccygeal pain, worse at night, with difficulty in defecation. He had been diagnosed with prostatic carcinoma two years earlier and this was responding to simple hormone treatment. His prostatic specific antigen level had fallen from 2800 ng/ml to 0.3 ng/ml. Rectal examination revealed a significant mass displacing the rectum anteriorly. MRI showed a large mass extending distally from the level of the S2-3

disc to involve the majority of the distal sacrum. It was associated with a huge extraosseous component with well-defined margins. The tumour had two small satellite lesions in contact with the main mass. An abdominoperineal resection and subtotal sacrectomy were performed and histological analysis confirmed that the lesion was a chordoma. There was extensive necrosis within the tumour, and a significant number of focal high-grade dedifferentiated areas where the cells were spindle-shaped with pleomorphic hyperchromatic nuclei, in keeping with a high-grade spindle-cell sarcoma (Fig. 5). The margins of excision were clear. The posterior wound broke down partially, leaving a small sinus that healed uneventfully. This delayed the commencement of radiotherapy. The patient died of lung metastases nine months after operation.

Case 4. In 2006, an 81-year-old woman presented with a history of pain in the buttock for seven months without any bowel or urinary symptoms. Examination revealed a large, smooth, firm mass lying in the midline behind the rectum and extending to the tip of the coccyx. MRI revealed a spherical, lobulated mass, 9 cm in diameter, arising from the S3 level and displacing the rectum anteriorly. The T₂-weighted images demonstrated two different components within the lesion, one with a hyperintense signal and the other with a low signal intensity (Fig. 6). Further imaging did not detect any secondary lesions. A partial sacrectomy was performed. Histological examination revealed a biphasic tumour displaying two patterns. One component had the appearance of a classic chordoma, whereas the other showed high-grade cellular spindle-cell dedifferentiation. The margins of excision were incomplete. After operation, radiotherapy was instituted in the form of 25 fractions of 50 Gy over five weeks. The patient is alive and free from tumour one year later.

Discussion

Dedifferentiation within a chordoma heralds an ominous prognosis with an aggressive clinical course culminating in metastases and rapid demise. The metastases commonly contain the dedifferentiated component.^{4,21} The clinical features of patients presenting with conventional chordoma are similar to those of the four cases in this series. Dedifferentiated tumours arising *de novo* are rare.^{19,22} Sarcomatous change following radiation has been observed more frequently, but a causal relationship is difficult to prove.^{9,11-13,17,23} Although the prognosis is almost universally dismal, this may not always hold true. One patient reported by Meis et al¹⁹ was found to have only a small focus of dedifferentiation with the appearances of osteosarcoma. This patient survived for 76 months, eventually succumbing to metastatic disease. Of note was that the metastases did not contain the dedifferentiated elements. Case 2 in our series, who also had only a small focus of dedifferentiation showing a malignant fibrous histiocytoma, is alive 63 months after initial treatment. In contrast, cases 1 and 3 had multiple significant foci of sarcomatous changes and both died of their disease after

Fig. 6

A T₂-weighted MR image in case 4. Hyperintense (arrowheads) conventional and low signal (arrow) dedifferentiated areas are present within the tumour mass.

seven and nine months, respectively. This suggests that the size of the dedifferentiated component is a significant predictor of survival. MRI features suggesting sarcomatous change within conventional chordoma have not been previously reported. Typically, conventional lesions are hyperintense on the T₂-weighted images, with intralesional septation a common feature.²⁴ Pre-operative T₂-weighted MR images in three of our cases clearly identified areas of low-signal intensity, indicating dedifferentiation, in a predominantly hyperintense, conventional component. Pre-operative identification of sarcomatous change has potential advantages, including increasing the accuracy of the definitive diagnosis, which enables earlier institution of adjuvant treatment, such as chemotherapy. The identification of areas of dedifferentiation with respect to chondrosarcoma using MRI has been described,²¹ with obvious implications for preferential targeting of pre-operative biopsies.²⁵ It has also been shown that infiltration of tumour into the surrounding musculature, namely the glutei and piriformis, is an important predictor of local recurrence, and more aggressive resection has been advocated.²⁶ Thus, accurate assessment of the sacrococcygeal region by MRI is vital when planning surgery in these cases.

Cases 2 and 4 in this series received conventional photon radiotherapy following primary excision, which was mar-

ginal in both patients. It was given with the aim of achieving better local control, thereby improving survival. The local control of chordomas irradiated with doses of up to 40 Gy to 60 Gy of conventional photon beams at five years range between 20% and 40%.^{27,28} A few authors have advocated the use of hadrons, such as high-dose protons or charged particles carbon or helium, either alone or in combination with photons to improve the radiobiological effect, mainly in lesions at the base of the skull.²⁹⁻³¹ The physical and ballistic properties of hadrons allow the delivery of higher doses to the target volume, while sparing organs at risk.³² The rates of local control at five years range between 50% and 60%.²⁹⁻³² However, there are few published prospective studies to demonstrate the superiority of proton beam therapy in managing sacral chordoma.³³

Fleming et al³⁴ analysed the role of chemotherapy in metastatic disease, achieving complete remission in two cases. Given the poor prognosis, they suggested that primary adjuvant chemotherapy be considered prior to radiotherapy in newly diagnosed patients. Earlier identification of the sarcomatous elements would allow appropriate treatment. Chemotherapy was used in the second case in our series following primary diagnosis, but without success, highlighting the unpredictable and poor prognosis associated with dedifferentiation.

Imatinib mesylate, which is a tyrosine kinase inhibitor targeting platelet-derived growth factor receptor- β , has been shown to have an anti-tumour effect.³⁵ In this study, clinical and radiological improvement was seen in six patients with advanced chordoma treated with 800 mg daily of imatinib for one year.

Primary dedifferentiated chordoma is an extremely rare and distinct entity with a more aggressive clinical course than conventional chordoma. Careful assessment of the MRI studies, especially the T₂-weighted images, should always be carried out to identify any areas of low signal intensity, which might indicate the presence of dedifferentiation and should be the preferred site of biopsy. Further studies are required to evaluate the role of radio- and chemotherapy in this disease.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. McMaster ML, Goldstein AM, Bromley CM, Ishibe N, Parry DM. Chordoma: incidence and survival patterns in the United States, 1973-1995. *Cancer Causes Control* 2001;12:1-11.
2. Eriksson B, Gunterberg B, Kindblom LG. Chordoma: a clinicopathologic and prognostic study of a Swedish national series. *Acta Orthop Scand* 1981;52:49-58.
3. Chetiawardana AD. Chordoma: results of treatment. *Clin Radiol* 1984;35:159-61.
4. Volpe R, Mazabraud A. A clinicopathologic review of 25 cases of chordoma (a pleomorphic and metastasizing neoplasm). *Am J Surg Pathol* 1983;7:161-70.
5. Hulen CA, Temple HT, Fox WP, et al. Oncological and functional outcome following sacrectomy for sacral chordoma. *J Bone Joint Surg [Am]* 2006;88-A:1532-9.
6. Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH. Operative management of sacral chordoma. *J Bone Joint Surg [Am]* 2005;87-A:2211-16.
7. Soo MY. Chordoma: review of clinicoradiological features and factors affecting survival. *Australas Radiol* 2001;45:427-34.

8. Cheng EY, Ozerdemoglu RA, Transfeldt EE, Thompson RC Jr. Lumbosacral chordoma: prognostic factors and treatment. *Spine* 1999;24:1639-45.
9. Morimitsu Y, Aoki T, Yokoyama K, Hashimoto H. Sarcomatoid chordoma: chordoma with a massive spindle cell component. *Skeletal Radiol* 2000;29:721-5.
10. Belza MG, Ulrich H. Chordoma and malignant fibrous histiocytoma: evidence for transformation. *Cancer* 1986;58:1082-7.
11. Hruban RH, May M, Marcove RC, Huvos AG. Lumbo-sacral chordoma with high-grade malignant cartilaginous and spindle cell components. *Am J Surg Pathol* 1990;14:384-9.
12. Halpern J, Kopolovic J, Catane R. Malignant fibrous histiocytoma developing in irradiated sacral chordoma. *Cancer* 1984;53:2661-2.
13. Makek M, Leu HJ. Malignant fibrous histiocytoma arising in a recurrent chordoma: case report and electron microscopic findings. *Virchows Arch A Pathol Anat Histol* 1982;397:241-50.
14. Miettinen M, Lehto VP, Virtanen I. Malignant fibrous histiocytoma within a recurrent chordoma: a light microscopic, and immunohistochemical study. *Am J Clin Pathol* 1984;82:738-43.
15. Knechtges TC. Sacrococcygeal chordoma with sarcomatous features (spindle cell metaplasia). *Am J Clin Pathol* 1970;53:612-16.
16. Choi YJ, Kim TS. Malignant fibrous histiocytoma in chordoma: immunohistological evidence of transformation from chordoma to malignant fibrous histiocytoma. *Yonsei Med J* 1994;35:239-43.
17. Fukuda T, Aihara T, Ban S, Nakajima T, Machinami R. Sacrococcygeal chordoma with malignant spindle cell component: a report of two autopsy cases with a review of the literature. *Acta Pathol Jpn* 1992;42:448-53.
18. Kishikawa H, Tanaka K. Chordoma: report of an autopsy case with fibrosarcoma. *Acta Pathol Jpn* 1974;24:299-308.
19. Meis JM, Raymond AK, Evans HL, Charles RE, Giraldo AA. "Dedifferentiated" chordoma: a clinicopathologic and immunohistochemical study of three cases. *Am J Surg Pathol* 1987;11:516-25.
20. Bisceglia M, D'Angelo VA, Guglielmi G, Dor DB, Pasguinelli. Dedifferentiated chordoma of the thoracic spine with rhabdomyosarcomatous differentiations: report of a case and review of the literature. *Ann Diagn Pathol* 2007;11:262-73.
21. MacSweeney F, Darby A, Saifuddin A. Dedifferentiated chondrosarcoma of the appendicular skeleton: MRI-pathological correlation. *Skeletal Radiol* 2003;32:671-8.
22. Saito A, Hasegawa T, Shimoda T, et al. Dedifferentiated chordoma: a case report. *Jpn J Clin Oncol* 1998;28:766-71.
23. Ikeda H, Honjo J, Sakurai H, et al. Dedifferentiated chordoma arising in irradiated sacral chordoma. *Radiat Med* 1997;15:109-11.
24. Sung MS, Lee GK, Kang HS, et al. Sacrococcygeal chordoma: MR imaging in 30 patients. *Skeletal Radiol* 2005;34:87-94.
25. Saifuddin A, Mann BS, Mahroof S, et al. Dedifferentiated chondrosarcoma: use of MRI to guide needle biopsy. *Clin Radiol* 2004;59:268-72.
26. Ishii K, Chiba K, Watanabe M, et al. Local recurrence after S2-3 sacrectomy in sacral chordoma: report of four cases. *J Neurospine Spine* 2002;97:98-101.
27. Cummings BJ, Hodson DJ, Bush RS. Chordoma: the result of megavoltage radiation therapy. *Int J Radiat Oncol Biol Phys* 1983;9:633-42.
28. Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. *Radiother Oncol* 1996;41:67-72.
29. Munzenrider JE, Liebsch NJ. Proton therapy for tumours of the skull base. *Strahlenther Onkol* 1999;175(Suppl 2):57-63.
30. Hug EB, Loredi L, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999;91:432-9.
31. Noël G, Feuvret L, Calugaru V, et al. Chordomas of the base of skull and upper cervical spine: one hundred patients irradiated by a 3D conformal technique combining photon and protons beams. *Acta Oncol* 2005;44:700-8.
32. Casali PG, Stacchiotti S, Sangalli C, Oli P, Gronchi A. Chordoma. *Curr Opin Oncol* 2007;19:367-70.
33. Brada M, Pilks-Johannesma, De Ruyscher D. Proton therapy in clinical practice: current clinical evidence. *J Clin Oncol* 2007;25:965-70.
34. Fleming GF, Heimann PS, Stephens JK, et al. Dedifferentiated chordoma: response to aggressive chemotherapy in two cases. *Cancer* 1993;72:714-18.
35. Casali PG, Messina A, Stacchiotti S, et al. Imatinib mesylate in chordoma. *Cancer* 2004;101:2086-97.