Bone sarcomas arising in patients with neurofibromatosis type 1

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We identified eight patients of 2900 with a primary malignant bone tumour who had coexisting neurofibromatosis type 1. This was a much higher incidence than would be expected by chance. The patients had a mean age of 22.4 years (9 to 54): five were male. Two patients subsequently developed a second bone sarcoma, one of which was radiation induced. Four of the primary tumours were osteosarcomas, four were spindle-cell sarcomas and one a Ewing’s sarcoma. All the patients were treated with chemotherapy and surgery: six of the eight appear to be cured.

This study suggests a possible relationship between neurofibromatosis type 1 and the development of a bone sarcoma, the increased risk being estimated at eight times that of the normal population. We recommend that further research into this possible link should be considered.

Neurofibromatosis or von Recklinghausen’s disease is an inherited autosomal dominant disorder that affects the skeletal system, skin and cerebral function. The disease mainly involves ectodermal tissue arising from the neural crest, and has two main forms: neurofibromatosis 1 (NF1) and 2 (NF2). The former is the more common, with an incidence of one in 3000 births, regardless of race, gender or ethnic background. It is diagnosed by the presence of two or more of the following features: six or more café-au-lait spots, two or more cutaneous neurofibromas, axillary or groin freckling, optic pathway glioma, two or more Lisch nodules, a characteristic bone dysplasia or a first-degree relative with NF1.

There is an increased incidence of soft-tissue sarcomas such as malignant tumours of the peripheral nerve sheath in patients with NF1, with an estimated lifetime risk of 8% to 13%. These tend to be very aggressive and have a high propensity to spread to distant organs. They have a poor prognosis, which is worse when they arise in patients without NF1. Occasionally they can form other malignant tumours as a result of focal divergent differentiation to mesenchymal malignant tissue, resulting in osteosarcomas or rhabdomyosarcomas of soft tissue, but this is exceedingly rare. A systematic search of the literature has shown that there are only a handful of case reports of patients with neurofibromatosis who go on to develop primary bone tumours. There is no published information that shows any way to predict which patients with NF1 will develop a bone tumour, or whether there is a causal relationship between the two.

The aim of this paper is to describe a series of patients with NF1 who developed primary malignant bone tumours, to outline their management and to discuss a possible causal relationship.

Materials and Methods
We conducted a retrospective search of a prospective tumour database to identify all patients who had NF1 associated with a primary malignant bone tumour. Patients who were not ultimately treated at our centre or who had bone tumours that were metastases from another primary tumour were excluded from the study.

The diagnosis of NF1 was based on the standard clinical criteria but was not confirmed by genetic studies. The diagnosis of a primary malignant bone tumour was confirmed by biopsy, and subsequent treatment was based on the standard protocols for that particular tumour in use at the time of diagnosis.

A search of our database, which holds prospectively gathered data on over 20,000 patients including over 8000 malignancies, of which 2900 are primary bone sarcomas and 2600 soft-tissue sarcomas, found 97 cases of NF1, of which 40 had a coexisting soft-tissue sarcoma, and nine primary sarcomas of bone in eight patients.
patients. All had been diagnosed between 1978 and 2006. There were five men (62.5%) and three women (37.5%), with a mean age of 22.1 years (8 to 39) at the time of diagnosis (Table I).

**Results**

All patients had a positive biopsy for a primary malignant bone tumour (Table I). One (case 4) had an Ewing’s sarcoma treated with chemo- and radiotherapy when aged nine, and 21 years later developed a radiation-induced osteosarcoma. We have discounted this case from our results as radiotherapy is a well-documented predisposing factor for the development of primary bone tumours.17 A second patient (case 6) had a spindle-cell sarcoma of the tibia treated by through-knee amputation at the age of eight and 17 years later developed an osteosarcoma in the amputation stump. The histology was different from that of the primary tumour, and it was felt that this was a new primary tumour rather than a recurrence. There were therefore nine primary tumours in eight patients.

There was no suggestion that any of these tumours arose from a pre-existing abnormality of bone or from a neurofibroma (Figs 1 and 2). The most commonly affected site was the femur (four patients, 50%), then the tibia (two patients, 25%) and the humerus (two patients, 25%). Of the nine primary tumours four were osteosarcomas, four spindle-cell sarcomas and one a Ewing’s sarcoma. None of the tumours had the histological appearance of a malignant tumour of peripheral nerve sheath.

All patients received appropriate chemotherapy, and all apart from the patient with an Ewing’s sarcoma underwent surgery. Two patients were treated by amputation, and six had limb salvage surgery with endoprosthetic replacement. In those patients who had neoadjuvant chemotherapy, the percentage of necrosis in the resected tumour ranged from nil to over 95%. Using the accepted figure of > 90% as indicating a good response, three of the seven patients (43%) for whom data was available had a good response to chemotherapy.

Two patients (cases 2 and 7) developed both bone and lung metastases at 21 and 29 months, respectively. The latter died within five months, but the other remains alive 21 months after developing metastatic disease. One patient (case 5) developed a local recurrence after undergoing limb salvage surgery for a distal femoral tumour and underwent an above-knee amputation. She remains alive and free of disease after 6.5 years. The other five patients remain alive and disease free at a mean of 18 years (8 to 29) from diagnosis, despite the fact that one patient had two tumours in the same limb and another had a radiation-induced sarcoma following radiotherapy for an Ewing’s sarcoma 29 years ago.

### Table I. Details of the patients, their tumours and the outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Site</th>
<th>Diagnosis</th>
<th>Chemotherapy/ radiotherapy*</th>
<th>Surgery</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>39</td>
<td>Distal humerus</td>
<td>Spindle-cell sarcoma</td>
<td>Adria/cisplat (no necrosis)</td>
<td>EPR† distal humerus</td>
<td>Disease free 19 years</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>37</td>
<td>Distal femur</td>
<td>Osteosarcoma</td>
<td>Adria/cisplat/MTX (&gt; 95% necrosis)</td>
<td>EPR distal femur</td>
<td>Lung and bone metastases 29 months. Died 34 months Disease free 8 years</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9</td>
<td>Distal femur</td>
<td>Spindle-cell sarcoma</td>
<td>Adria/cisplat (&gt; 95% necrosis)</td>
<td>EPR distal femur</td>
<td>Disease free 8 years</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>9</td>
<td>Distal tibia</td>
<td>Ewing’s</td>
<td>Chemo- and radiotherapy</td>
<td>None</td>
<td>Disease free 29 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>Proximal tibia</td>
<td>Radiation-induced osteosarcoma</td>
<td></td>
<td>Above-knee amputation</td>
<td>Disease free 8 years</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>20</td>
<td>Distal femur</td>
<td>Spindle-cell sarcoma</td>
<td>Adria/cisplat (20% necrosis). Post-operative radiotherapy</td>
<td>EPR distal femur</td>
<td>Local recurrence 6 months, above-knee amputation, alive 6.5 years later</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>8</td>
<td>Mid-tibia</td>
<td>Spindle cell sarcoma</td>
<td>Cyclophosphamide/ vincris/adria Ifos/MTX/etop (20% necrosis)</td>
<td>Through-knee amputation</td>
<td>Alive 26 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>Distal femur (amputation stump)</td>
<td>Osteosarcoma</td>
<td></td>
<td>High above-knee amputation</td>
<td>Disease free 10 years</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>21</td>
<td>Proximal humerus</td>
<td>Osteosarcoma</td>
<td>Adria/cisplat/MTX (50% necrosis). Post-operative radiotherapy</td>
<td>EPR proximal humerus</td>
<td>Metastases to lung and bone 21 months. Alive 42 months</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>34</td>
<td>Proximal tibia</td>
<td>Osteosarcoma</td>
<td>Adria/cisplat (100% necrosis)</td>
<td>EPR proximal tibia</td>
<td>Alive 20 years</td>
</tr>
</tbody>
</table>

* Adria, adriamycin; cisplat, cisplatin; vincris, vincristine; Ifos, ifosfamide; MTX, methotrexate; etop, etoposide
† EPR, endoprosthesis
‡ discounted from results
Discussion

The aim of this study was to use a large database of patients with orthopaedic oncology to consider the possibility of an identifiable link between NF1 and primary bone tumours. Of a total of 2900 patients with a primary bone sarcoma collected over 30 years we found eight with NF1 who had a primary bone sarcoma. The oft-quoted incidence of one in 3000 for NF1 would suggest that we should have seen just one in this time. However, we saw eight times that number (p = 0.01, comparison of two independent proportions). We have no reason to believe that there is an especially high incidence of NF1 in our catchment population, and none of the patients with bone tumours in NF1 was referred from outside our catchment area.

We saw an equal number of cases of osteosarcoma and spindle-cell sarcoma, and no cases of associated malignant peripheral nerve sheath tumour or chondrosarcoma. Three of our patients received radiotherapy, but only one subsequently developed an osteosarcoma and we discounted this case from our results.

It is well known that patients with NF1 are at an increased risk of developing soft-tissue sarcomas, with a lifetime risk of 8% to 13%, but there is no convincing evidence that they are at an increased risk of developing a bone sarcoma. Most of the available literature is based on case reports, and describe the tumours found as being composite lesions, of which only one element is osteosarcoma. Sakaguchi et al described a 48-year-old man who developed a malignant peripheral nerve sheath tumour and a phaeochromocytoma, a well-described relationship where the nerve sheath tumour showed a varied histological appearance with a suggestion of the presence of osteosarcoma. Miyoshi et al reported a rare case of primary jejunal malignant mixed tumour that contained various sarcomatous components, including osteosarcoma.

Ferreira et al described one case of osteosarcoma of a long bone in association with NF1. Hatori et al described a 23-year-old patient who underwent excision of a malignant peripheral nerve sheath tumour in association with NF1 and six years later developed a second tumour, found to be an osteosarcoma, arising at the same site. It was thought that this represented the spread of a malignant peripheral nerve sheath tumour into the medullary cavity of the adjacent femur. This was not a composite tumour. Papagelopoulos et al found an example of a malignant fibrous histiocytoma growing in the femur of a 38-year-old man with NF1, with no evidence of any other previous tumour or irradiation. They identified one other example of malignant fibrous histiocytoma in the literature, which had occurred in a patient who had received radiotherapy for a neurofibromatous bone lesion.

The incidence of bone tumours is nine per million population per year. Our database has data on 2900 primary malignant bone tumours, suggesting that this represents...
322 million population-years. If 1 in 3000 has NF1, then the population of patients with NF1 would be 107 407 patient-years. This population resulted in eight patients with a primary malignant bone tumour, an incidence of one per 13 425 population per year with NF1. This converts to an incidence of 74 bone tumours per million population per year of patients with NF1: an eightfold increase compared to the normal population.

No other centre has reported as many malignant bone tumours associated with NF1. This leads us to question whether our findings were coincidental or whether there is indeed an increased risk of bone malignancy in NF1. A review of other large series of patients with primary bone tumours or from registries of patients with neurofibromatosis may help clarify this.

It is well recognised that patients who develop soft-tissue sarcomas in association with NF1 tend to have a worse prognosis than those without NF1. The same poor outlook does not appear to be the case in those with bone tumours. The overall cure rate of non-NF1 patients with bone sarcomas throughout the period of this study was between 50% and 60%, yet six of the eight patients (75%) with bone sarcomas in association with NF1 tend to have a worse prognosis than those without NF1. The association is sufficiently strong to warrant further investigation. We suggest that a multi-institutional study may go some way to answering this question.

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