Clinical and immunohistochemical characteristics of benign giant cell tumour of bone with pulmonary metastases: case series

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ABSTRACT

Purpose. Giant cell tumour of bone with pulmonary metastases is rare. However, some patients die of pulmonary metastases, and histological examination cannot distinguish between benign tumour and malignant metastases. In this study, we present clinical and immunohistochemical findings associated with giant cell tumour of bone with pulmonary metastases.

Methods. Five patients with benign giant cell tumour of bone with pulmonary metastases (one man and 4 women) were studied. Patients’ ages ranged between 20 and 23 years (mean age, 21.8 years). Tumours were in the distal femur in 2 cases, and in the proximal tibia, distal tibia, and lumbar spine in one case each. The tissue specimens from primary tumours, recurrent tumours, and pulmonary metastases were studied using immunohistochemical techniques.

Results. Three of the 5 primary tumours were of the spontaneous regression or growth cessation type, or the continuously slow-growing type, showing 4.2% to 6.2% of positive cells for Ki-67 after immunohistochemical staining. However, 2 patients with the rapid-growing type of disease died of pulmonary metastases; their primary, recurrent, and metastatic tumour specimens contained 9.0% to 11.5% of positive cells for Ki-67.

Conclusion. Three of the 5 primary tumours had a benign clinical pattern and immunohistochemistry. Two of the 5 patients died of pulmonary metastases, which had an aggressive clinical pattern and a high prevalence of positive cells in Ki-67. Examination of Ki-67 should be carried out for aggressive type of giant cell tumour.

Key words: bone neoplasms; giant cell tumor of bone; immunohistochemistry; lung neoplasms

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INTRODUCTION

Giant cell tumour (GCT) of bone is usually a benign bone tumour, but the rate of recurrence is high. Campanacci et al.1 classified this type of tumour as grade I, II, and III according to radiographic findings; grade II or III tumours have a higher rate of recurrence than grade I tumours. GCT of bone rarely metastasises to the lungs: the reported rate ranges between 2% and 6%.1–9 Pulmonary metastasis is divided into 3 types—namely, the spontaneous regression or growth cessation type, the continuously slow-growing type, and the rapid-growing type.6

Approximately 20% of patients with pulmonary metastases of the continuously slow-growing type and the rapid-growing type die of the disease.2–4,7–10 Survival of the remaining 80% of patients suggests that GCT of bone with pulmonary metastases has a relatively good prognosis, even in advanced cases.1,4,7,8,11–15 Histological findings frequently show fields rich in giant cells, bizarre stromal cells, mitotic cells, and osteoid cells. Furthermore, GCT of bone resembles malignant GCT, giant cell–rich osteosarcoma, and malignant fibrous histiocytoma of bone.9,16,17 Clinicohistological1–4,8,13 and immunohistochemical18–20 studies of tissue specimens of primary tumours, recurrent tumours, and pulmonary metastases have been performed to evaluate the biological behaviour of GCT of bone and to select the treatment for GCT with pulmonary metastases. However, reports of the clinical and immunohistochemical characteristics of benign GCT of bone with pulmonary metastases among Japanese patients are rare. In this study, we describe the clinical and immunohistochemical findings of 5 cases of benign GCT of bone with pulmonary metastases that were encountered at two hospitals in Japan.

MATERIALS AND METHODS

During the study period, we encountered 5 patients with benign GCT of bone. Three of the 5 patients presented to the Nihon University School of Medicine and 2 presented to another hospital. The age of the patients (one man and 4 women) at presentation ranged from 20 to 23 years, with a mean of 21.8 years. Among the tumours, 2 were located in the distal femur and one each in the proximal tibia, distal tibia, and lumbar spine. According to Campanacci’s radiographic classification system,1 3 tumours were grade II (cases 1, 2, and 3) and 2 were grade III (cases 4 and 5). Patients’ information is shown in Table 1.

We analysed tissue specimens from primary tumours, recurrent tumours, and pulmonary metastases using histological and immunohistochemical techniques. In one case (case 1), we could not obtain a specimen from the primary tumour, because the initial excision was performed in another hospital.

Primary tumours were diagnosed histologically as benign GCT of bone in all patients. Treatment for the primary tumours included intralesional or marginal excision, bone grafting, and arthrodesis using standard techniques. All patients experienced local recurrence, as detected by histological examination of excisional tissue (cases 1, 2, and 4) or biopsy (case 5). In case 3, computed tomography, magnetic resonance imaging, and radio-isotope studies were used to detect spine and pulmonary metastases; hence we did not obtain a sample of the recurrent tumour in this case. Recurrent tumours were surgically treated in 3 cases: marginal excision in 2 cases and amputation in one case. Pulmonary metastases were excised in cases 1 to 3, identified at biopsy in case 4, and identified at autopsy in case 5. Two cases (cases 3 and 4) showed early pulmonary metastases after primary local recurrence, and chemotherapy and radiotherapy were performed.

Tissue obtained from the primary, recurrent, and metastatic tumours were fixed in 10% buffered formalin solution, processed according to standard histological methods, and embedded in paraffin. Slides of tissue sections were examined by light microscopy after dewaxing and immunohistochemical staining using the streptavidin-biotin method and antibodies to alpha–smooth muscle actin (α-SMA), MIC-2, p53, cyclin D1, tc-erb-B2, and Ki-67. The staining intensities for α-SMA, MIC-2, p53, cyclin D1, tc-erb-B2 were classified according to the proportions of cells within the tumour samples that showed staining: negative staining (−), up to 25% of positive cells (+), 26% to 50% of positive cells (++), 51% to 75% of positive cells (+++), and 76% to 100% of positive cells (++++). To evaluate the staining intensity for the Ki-67 antigen, which is an indicator of nuclear proliferation, positive cells were counted among randomly selected 100 tumour cells.

RESULTS

The interval between initial surgery and recurrence ranged from 6 to 17 months (mean, 9.8 months), and the interval between initial surgery and metastasis ranged from 7 to 43 months (mean, 21.2 months). Three patients were still alive at the time of writing this report; of whom, 2 (cases 1 and 2) had
no evidence of recurrence and one (case 3) had developed a persistently slow-growing pulmonary tumour following local radiotherapy (Figs 1 to 5). Two patients (cases 4 and 5) died of GCT with no malignant transformation in either the primary and recurrent tumours or in the pulmonary metastases (Table 1).

From the level of Ki-67 staining in tissue samples, we identified 3 cases of pulmonary metastasis of either the spontaneous regression or growth cessation type, or the continuously slow-growing type (cases 1 to 3): in these cases, all primary, recurrent, and pulmonary metastatic tumour samples showed a low proportion (4.2%–6.2%) of positive cells for Ki-67. In the remaining 2 cases, the tumours were the rapid-growing types: the primary tumours had 9.2% to 9.4% of positive cells for Ki-67, recurrent tumours 10.8% to 11.5%, and pulmonary metastatic tumours 9.0% to 9.8%. However, staining for α-SMA, MIC-2, p53, cyclin D1, and tc-erb-B2 showed no specific differences among the 5 cases (Table 2).

Figure 1  Case 3: (a and b) Radiographs showing that the third lumbar spine had a destructive lesion and a pathological compression fracture. (c) Computed tomogram showing a tumour in the extraskeletal area.
Figure 2  Case 3: (a and b) Postoperative radiographs: the primary tumour was excised intralesionally, and the defect was reconstructed with an autologous bone graft and anterior instrumentation. Local recurrence happened at 6 months and pulmonary metastases at 7 months after the primary surgery. We carried out chemotherapy (cyclophosphamide) and radiotherapy for the primary lesion. (c and d) Radiographs at 33 months showing that the vertebrae compressed and the instrumentation broke.
Figure 3  Case 3: Pulmonary metastases were excised with surgery. (a) Preoperative radiograph. (b) Postoperative radiograph.

Figure 4  Case 3: Multiple recurrent pulmonary metastases were shown in the (a) radiograph, and (b and c) computed tomograms. We performed local radiation therapy (50 Gy) for bilateral pulmonary metastatic nodules (arrows).
DISCUSSION

Benign GCT of bone with pulmonary metastases is rare, and few reports exist in the literature. Rock et al. reported that 26 of 407 patients in a case series had secondary malignant GCT of bone; 19 of the 26 patients had radiation-induced sarcoma. Malignant GCT of bone was seen in only 5 patients. Recently, 29 cases of malignant GCT have been reported; 12 were due to malignant transformation of initially benign tumours. Giant cell–rich osteosarcoma of standard osteosarcoma was found in 13% of cases, and cases of malignant fibrous histiocytoma were difficult to differentiate by histopathological evaluation. Benign GCT of bone with pulmonary metastasis occurs most frequently in recurrent cases; these recurrent tumours have the potential to develop malignant biological behaviour. In our series, 2 of the 5 patients with GCT of bone succumbed to the disease. The histopathological grade in GCT of bone is not indicative of prognosis. However, radiographic grading using Campanacci’s classification system is useful to assess the prognosis.

Grade I tumours are usually treated by curettage, bone grafting, or cementation. For disease of grade II and III, we selected resection and arthrodesis or prosthetic joint replacement. Immunohistochemical studies using antibodies to α-SMA, MIC-2, p53, cyclin D1, tc-erb-B2, and Ki-67 were performed in primary, recurrent, and metastatic tumours. We, like other researchers, showed that primary and recurrent tumours of the rapid-growing type displayed high proportions of positive cells for Ki-67. Studies of GCT of bone with pulmonary metastases following the continuously slow-growing or the rapid growing type of tumour have assessed the effects of surgery and chemotherapy. However, approximately 20% of patients with metastases die of the disease. Following malignant transformation, cells become positive for p53 and a high proportion of cells become positive for Ki-67. Radiotherapy has been used in a few cases of primary lesion and pulmonary metastasis, although it sometimes induces malignant tumours. In our series, growing pulmonary metastatic tumours were reduced using localised radiotherapy (case 3). Prevention of pulmonary metastases may depend on adequate surgical treatment of the primary tumour in cases of grade II and III tumour.

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### Table 1
Clinical data of patients with benign giant cell tumour of bone with pulmonary metastases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Location of primary tumour</th>
<th>Initial surgery</th>
<th>Treatment for recurrence</th>
<th>Initial surgery to recurrence/metastases (months)</th>
<th>Treatment for pulmonary metastases</th>
<th>Follow-up status/time after metastases (years+months)</th>
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<tbody>
<tr>
<td>1</td>
<td>20/F</td>
<td>Distal femur</td>
<td>Curettage; bone graft</td>
<td>Excision; arthrodesis</td>
<td>12/36</td>
<td>Excision</td>
<td>NED /30+</td>
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<tr>
<td>2</td>
<td>22/F</td>
<td>Distal tibia</td>
<td>Curettage; bone graft</td>
<td>Excision; arthrodesis</td>
<td>17/43</td>
<td>Excision</td>
<td>NED/12+8</td>
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<tr>
<td>3</td>
<td>23/F</td>
<td>3rd lumbar spine</td>
<td>Curettage; bone graft</td>
<td>Radiotherapy</td>
<td>6/7</td>
<td>Excision + radiotherapy (each tumour area 40 Gy) + chemotherapy (CP)</td>
<td>AWD /17+10</td>
</tr>
<tr>
<td>4</td>
<td>22/M</td>
<td>Distal femur</td>
<td>Curettage; bone graft</td>
<td>Amputation</td>
<td>6/10</td>
<td>Biopsy (inoperable) + radiotherapy (30 Gy) + chemotherapy (ADR, CDDP)</td>
<td>Died/1+2</td>
</tr>
<tr>
<td>5</td>
<td>22/F</td>
<td>Proximal tibia</td>
<td>Intralosional excision; arthrodesis</td>
<td>Biopsy; chemotherpay (VCR)</td>
<td>8/10</td>
<td>Chemotherapy (VCR)</td>
<td>Died/2+2 (autopsy)</td>
</tr>
</tbody>
</table>

* Clinical features of cases 1, 3, 4, and 5 are based on those reported in reference 6
† NED no evidence of disease
‡ CP cyclosphamide
§ AWD alive with disease
|| ADR, CDDP adriacin, cisplatinum
¶ VCR vincristine

### Table 2
Immunohistochemical results for giant cell tumour with pulmonary metastases

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<tr>
<th>Case No.</th>
<th>Tumour</th>
<th>α-SMA</th>
<th>MIC-2</th>
<th>p53</th>
<th>cyclin D1</th>
<th>tc-erb B2</th>
<th>Ki-67 (%)</th>
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<tr>
<td></td>
<td>Recurrent</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Pulmonary metastasis</td>
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<td></td>
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<tr>
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<td>+</td>
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* Negative staining (-), up to 25% of positive cells (+), 26% to 50% of positive cells (±), 51% to 75% of positive cells (++), 76% to 100% of positive cells (+++)
REFERENCES