Report of Four Cases with High-Grade Surface Osteosarcoma

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High-grade surface osteosarcoma is the rarest of the three types of surface osteosarcoma. Four cases with high-grade surface osteosarcoma arising from the distal femur and tibia are reported in this study. One patient was previously diagnosed with Turner’s syndrome. Radiologically, three cases presented characteristic appearances suggesting high-grade bone-forming sarcoma arising from the bone surface; however, one case was similar to other juxtacortical lesions such as periosteal and parosteal osteosarcoma, which typically have a better prognosis than high-grade surface osteosarcoma. Therefore, all cases underwent biopsy to determine a definitive diagnosis. Our strategy of treatment for high-grade surface osteosarcoma was a combination of wide resection and pre-/post-operative chemotherapy, equivalent to the treatment for conventional intramedullary osteosarcoma. At the last follow-up, two cases were still undergoing chemotherapy, one case was continuously disease free during the follow-up period of 81 months, and one patient was living with no evidence of disease 60 months after surgery. The aim of this study is to report the clinical information, oncological outcome and appropriate treatment for high-grade surface osteosarcoma.

Key words: high-grade surface osteosarcoma – wide resection – chemotherapy – Turner’s syndrome

INTRODUCTION

Osteosarcoma is a primary malignant bone tumor in which neoplastic cells produce osteoid. Most osteosarcomas arise intramedullarily in the long bones and present a specific radiological appearance and a typical clinical course. But some osteosarcomas arise extramedullarily on the outer surface of the underlying bones, when they are called ‘surface osteosarcomas’ (1). The growth pattern of a surface osteosarcoma is quite different from that of a conventional osteosarcoma. Surface osteosarcomas can be classified into three types according to the nature of the tumor: parosteal, periosteal and high-grade surface osteosarcoma. High-grade surface osteosarcoma is a high-grade bone-forming malignancy which arises from the surface of the bone without medullary involvement (2). This disorder is the rarest of the three types of surface osteosarcoma, and its incidence has been reported to be <1% of all osteosarcomas (3). Because of the rarity of high-grade surface osteosarcoma, few reports are available concerning the clinical features, treatments and prognosis. We present clinical information on four cases and the oncological outcome and suggest appropriate management.

CASE REPORT

Among 249 osteosarcomas which were treated with surgery at our institution between April 1978 and June 2005, only four cases were diagnosed as high-grade surface osteosarcoma (1.6%). All four patients and/or their families were informed that data from their cases would be submitted for publication, and we received their consent. Clinical information concerning age, sex, location of tumor, past history of the patient, chief complaint and radiological findings is summarized in Table 1, and some information concerning treatment and prognosis is summarized in Table 2.

Two out of four patients were males. The age of the four patients at diagnosis ranged from 15 to 29 years (mean, 22.5 years). The involved bone sites were distal femurs in three of four cases and the distal tibia in one case. One case was previously diagnosed as Turner’s syndrome.

Radiologically, all four cases arose from the surface of the underlying cortical bone. The patterns of ossification and calcification and periosteal reaction were assessed. Medullary involvement was also analyzed using computed tomography (CT) and magnetic resonance imaging (MRI). The amount of ossification and calcification varied from mild to severe. Two cases exhibited severe mineralization and two mild (Fig. 1a, b, and c). Severe periosteal reaction was associated with only one case. Minimum medullary involvement was seen
in only one case (Case 3); the remaining three cases displayed no medullary involvement (Fig. 1d). Radiologically, images of three of our cases were consistent with high-grade bone-forming sarcoma, but Case 4 revealed a relatively dense, well-demarcated ossified mass at a juxtacortical lesion of the distal femur, which indicated a low- or intermediate-grade bone-forming tumor.

After definitive diagnosis by biopsy, systemic pre-operative chemotherapy was administered to all four patients. Three cases of four (Cases 1, 3 and 4) received systemic chemotherapy at our institution and one case (Case 2) received chemotherapy at a previous institution. At our institution, pre-operative chemotherapy was carried out according to our chemotherapy protocol for conventional high-grade osteosarcoma, which is based on the Rosen T12 chemotherapy protocol and consists of cisplatin, adriamycin, methotrexate, ifosfamide and BCD (combination of bleomycin, cyclophosphamide and dactinomycin) (4,5). Each chemotherapy is summarized in Table 2. We evaluated the chemotherapeutic effect on radiological findings on a weekly basis with plain film and/or CT, and repeated the effective systemic chemotherapy for each case pre-operatively and/or post-operatively.

In terms of surgical procedure, two cases (Cases 2, 3 and 4) underwent wide resection of the tumors and reconstruction with tumor prostheses; in addition, Case 3 underwent free vascularized fibula grafting. Only one case (Case 1), who was operated on in 1991, had above-the-knee amputation.

The surgical margins of the resected specimens were evaluated according to the evaluation system of the Japanese Orthopedic Association (JOA) (6,7). A curative wide margin was obtained in Case 1, an adequate wide margin in Cases 2 and 4, and an inadequate wide margin in Case 3.

Pathologically, two cases were classified as the osteoblastic type, one as the chondroblastic type, and one as the fibroblastic type (Fig. 2a). Radiologically, in Case 4, a low- or intermediate-grade bone-forming tumor, similar to parosteal osteosarcoma or periosteal osteosarcoma, had to be excluded for the differential diagnosis. This tumor was confirmed to be the same as conventional osteoblastic osteosarcoma (Grade 3), differing from parosteal and periosteal osteosarcoma (Fig. 2b). In addition, the possibility of dedifferentiation of parosteal osteosarcoma was excluded after extensive investigation of the overall cut surface. The histological response for our pre-operative treatment of chemotherapy and/or radiation therapy was evaluated on at least two dimensions of the maximum cut surface of the resected specimen, according to the General Rules for Clinical and Pathological Studies on Malignant Bone Tumor of the JOA Committee of Tumors. Three cases were considered as Grade 0 and one as Grade 1.

### Table 1. Clinical information and radiological findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Past history</th>
<th>Chief complaint</th>
<th>Ossification</th>
<th>Periosteal reaction</th>
<th>Medullary involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>F</td>
<td>Distal femur</td>
<td>None</td>
<td>Swelling</td>
<td>Mild</td>
<td>Severe, fluffy</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>M</td>
<td>Distal femur</td>
<td>None</td>
<td>Swelling</td>
<td>Severe</td>
<td>Moderate, fluffy</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>F</td>
<td>Distal tibia</td>
<td>Turner’s syndrome</td>
<td>Pain</td>
<td>Mild</td>
<td>Mild</td>
<td>Minimum</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>Distal femur</td>
<td>None</td>
<td>Limited range of motion</td>
<td>Severe (well-demarcated)</td>
<td>Minimum</td>
<td>None</td>
</tr>
</tbody>
</table>

### Table 2. Treatment and oncological outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Pre-operative Chemotherapy</th>
<th>Post-operative Chemotherapy</th>
<th>Pre-operative Radiation</th>
<th>Surgical procedure</th>
<th>Surgical margin</th>
<th>Pathological findings</th>
<th>Radiological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTX</td>
<td>CDDP</td>
<td>MTX × 2</td>
<td>Wide resection</td>
<td>W(3)</td>
<td>Osteoblastic grade 3</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>ADR</td>
<td>ADR + IFM</td>
<td>30 Gy/10 fraction</td>
<td>Tumor prosthesis</td>
<td></td>
<td></td>
<td>CDF (81 months)</td>
</tr>
<tr>
<td>2</td>
<td>(IFM + VP-16) × 2</td>
<td>(ADR + CDDP) × 2</td>
<td>None</td>
<td>Wide resection</td>
<td>W(4)</td>
<td>Osteoblastic grade 3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ADR</td>
<td>BCD × 1</td>
<td>MTX × 2</td>
<td>Tumor prosthesis</td>
<td></td>
<td></td>
<td>CDF (3 months)</td>
</tr>
<tr>
<td>3</td>
<td>CDDP</td>
<td>ADR + IFM</td>
<td>30 Gy/10 fraction</td>
<td>Wide resection</td>
<td>W(1)</td>
<td>Chondroblastic grade 3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ADR</td>
<td>BCD × 2</td>
<td>MTX × 2</td>
<td>Tumor prosthesis</td>
<td></td>
<td></td>
<td>Lung (16 months)</td>
</tr>
<tr>
<td>4</td>
<td>CDDP</td>
<td>ADR + IFM</td>
<td>30 Gy/10 fraction</td>
<td>Wide resection</td>
<td>W(3)</td>
<td>Osteoblastic grade 3</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ADR</td>
<td>BCD × 2</td>
<td>MTX × 2</td>
<td>Tumor prosthesis</td>
<td></td>
<td></td>
<td>Lung (19 months)</td>
</tr>
<tr>
<td></td>
<td>ADR</td>
<td>ADR × 2</td>
<td>MTX × 2</td>
<td>Tumor prosthesis</td>
<td></td>
<td></td>
<td>AWD (35 months)</td>
</tr>
</tbody>
</table>

CDF, continuous disease free; NED, no evidence of disease; AWD, alive with disease.

MTX: 8–12 g/m², CDDP: 100 mg/m², ADR: 30 mg/m² × 2 days, IFM 2 g/m² × 5–7 days, BCD (bleomycin 15 mg/m² × 2 days, cyclophosphamide 500 mg/m² × 2 days, dactinomycin 0.5 mg/m² × 2 days).

All four cases were judged relatively poor responders to the pre-operative chemotherapy regimen.

The oncological outcome at the last follow-up showed that two cases (Cases 1 and 2) were continuous disease free (CDF), one case (Case 3) showed no evidence of disease (NED), and one case (Case 4) was alive with disease (AWD). Distant metastases of lung occurred in two cases (Cases 3 and 4); both cases underwent resection of these metastases in the lung, but recurrence of lung metastases was found in Case 4, who was undergoing systemic chemotherapy at the last follow-up.

**REPRESENTATIVE CASE**

**CASE 3**

An 18-year-old female was referred to us after a 2 month history of severe pain and swelling after she sprained her right ankle. On a visit to another hospital, an abnormal shadow was evident on plain film, and she was referred to our hospital. Laboratory data showed a slightly increased value of alkaline phosphatase. In terms of her past history, at the age of 9 years, she had been diagnosed with Turner’s syndrome, and she had received hormone therapy. Her parents had let her know about her disorder, but her family did not permit us to analyze any possible chromosomal aberration during this more recent event. Physical examination during the initial visit to our hospital showed no characteristic symptoms related to Turner’s syndrome, except cubits valgus. Radiologically, a juxtacortical mass was mainly located on the bone cortex of the posterior aspect of the ankle, with faint calcification shown on plain film (Fig. 3a). Regional CT demonstrated a low-density mass with faint ossification in peripheral regions. Moreover, underlying cortical bone showed a small degree of thickening. Minimal invasion was seen on the medial side of the tibia (Fig. 3b). At first, a biopsy was done, and the pathological diagnosis was osteosarcoma, Grade 3. Cytological study of the same specimen confirmed osteosarcoma, Class V. Treating this as high-grade surface osteosarcoma rather than periosteal osteosarcoma, we administered four courses of chemotherapy consisting of cisplatin and adriamycin, and two courses of ifosfamide, pre-operatively. At this point, plain film showed the entire body of the tumor clearly, and patchy calcification within the tumor was evident.

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**Figure 1.** (a) Lateral plain film of Case 1 with high-grade bone-forming sarcoma, (b) anteroposterior plain film of Case 2 with high-grade bone-forming sarcoma, (c) lateral plain film of Case 4 with well-demarcated ossified low- or intermediate-grade bone tumor, (d) MRI finding of Case 4 without medullary involvement.

**Figure 2.** Histopathological findings of the resected specimen. (a) Fibroblastic osteosarcoma (Case 1; ×200) and (b) osteoblastic osteosarcoma (Case 4; ×200).
Regional CT showed a marked sclerotic change in the peripheral regions. The patient hoped for limb salvage, so wide resection of the tumor was performed and reconstruction with a custom-made prosthesis for the ankle and free vascularized fibula grafting was attempted. Macroscopically, a white to grayish tumor composed of cartilaginous neoplasm was removed, and minimal medullary involvement was found. As judged by the resected specimens, a 1 cm wide margin was achieved. On the microscopical findings, moderately differentiated chondroblastic elements which produced malignant osteoid, consistent with conventional osteosarcoma, were found on routine H&E staining, and prominent ossification was also found. The chemotherapeutic effect was judged as Grade 1, despite the marked sclerotic change radiologically after pre-operative chemotherapy. After tumor resection, two minor post-operative complications, including dislocation of the prosthesis of the ankle joint and screw trouble, occurred. Six courses of post-operative chemotherapy were performed. Nevertheless, 16 months after tumor excision, a solitary pulmonary metastasis was discovered in the left lung. This lesion was surgically removed using thracoscopy. Sixty months have passed since the initial tumor resection. At the last follow-up, this patient shows no further evidence of disease. Limb salvage was achieved (Fig. 3d), and the patient was satisfied. The patient was evaluated as 78% functional according to the score of the Musculoskeletal Tumor Society (8).

DISCUSSION

High-grade surface osteosarcoma is the rarest of the three subtypes of surface osteosarcoma. This disease was first described by Francis (9) in 1964, and nine cases were reported by Wold et al. (10) in 1984. Radiologically, the appearance of this tumor on plain film, CT and MRI was recently analyzed (11,12). Typical cases of this disorder display dense-to-moderate mineralization with fluffy and immature appearance. This mineralization appears predominantly at the base of the lesion. The tumor has a broad base attached to the underlying bone. Periosteal reaction is commonly present. The differential diagnosis of high-grade surface osteosarcoma is radiologically parosteal osteosarcoma, periosteal osteosarcoma, dedifferentiated parosteal osteosarcoma and extramedullary extension from a conventional osteosarcoma. Three of the four cases (Cases 1, 2 and 3) were clearly highly consistent with high-grade bone-forming malignant sarcoma, but only one case (Case 4) showed a relatively dense, ossified mass without periosteal reaction, which suggested low- to intermediate-grade malignant and slow-growing characteristics. It has been reported that it is impossible to differentiate high-grade surface osteosarcoma clinically or radiologically from periosteal osteosarcoma (13). Therefore, a biopsy may be essential. In terms of medullary involvement, at the first medical investigation, three cases (Cases 1, 2 and 4) presented no medullary involvement radiologically, and one case (Case 3) presented minimal involvement. Medullary involvement may be considered fundamentally to contradict a definition of high-grade surface osteosarcoma (2), but some authors have interpreted the definition in a broad sense and minimal involvement is regarded as permissible (12).

In the treatment of high-grade malignant bone tumors, wide resection with adequate surgical margin is required because of local recurrence (6,7). In the past, limb salvage was impossible in some difficult cases. In our cases, above-the-knee amputation was selected in Case 1, which was operated on in 1991, because of progressive disease in spite of the pre-operative treatment. Nowadays, based on the rapid development of various kinds of medical modalities such as imaging techniques, anticancer drugs and reconstruction methods, limb salvage with prosthesis after wide resection of the tumor has become possible (14). Limb salvage with prosthesis was selected in the remaining three cases. In Case 2, the tumor was close to neurovascular structures. An in situ preparation method (ISP) (15), which makes it possible to prepare the nerves and vessels intra-operatively to evaluate the surgical margin without contamination, was used and limb salvage was accomplished. In Case 3, the patient and her family refused leg amputation (Fig. 3c). Regional CT showed a marked sclerotic change in the peripheral regions. The patient hoped for limb salvage, so wide resection of the tumor was performed and reconstruction with a custom-made prosthesis for the ankle and free vascularized fibula grafting was attempted. Macroscopically, a white to grayish tumor composed of cartilaginous neoplasm was removed, and minimal medullary involvement was found. As judged by the resected specimens, a 1 cm wide margin was achieved. On the microscopical findings, moderately differentiated chondroblastic elements which produced malignant osteoid, consistent with conventional osteosarcoma, were found on routine H&E staining, and prominent ossification was also found. The chemotherapeutic effect was judged as Grade 1, despite the marked sclerotic change radiologically after pre-operative chemotherapy. After tumor resection, two minor post-operative complications, including dislocation of the prosthesis of the ankle joint and screw trouble, occurred. Six courses of post-operative chemotherapy were performed. Nevertheless, 16 months after tumor excision, a solitary pulmonary metastasis was discovered in the left lung. This lesion was surgically removed using thracoscopy. Sixty months have passed since the initial tumor resection. At the last follow-up, this patient shows no further evidence of disease. Limb salvage was achieved (Fig. 3d), and the patient was satisfied. The patient was evaluated as 78% functional according to the score of the Musculoskeletal Tumor Society (8).

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amputation, and the custom-made prosthesis for the ankle made it possible to achieve limb salvage.

It has not previously been well known whether adjuvant chemotherapy is actually effective for high-grade surface osteosarcoma. In our case, systemic chemotherapy was performed pre-/post-operatively, according to the modality for conventional intramedullary osteosarcoma. As a result, pathologically, all four cases were unfortunately judged as poor responders. Two cases (Cases 3 and 4) underwent resection for distant metastasis of the lung. Wold et al. (10) reported that ablative surgery alone, without pre-operative chemotherapy at diagnosis, could not improve the clinical course of this type of tumor, and Okada (12) concluded that the prognosis of a good responder with systemic chemotherapy is better than that of a poor responder. High-grade surface osteosarcoma closely resembles intramedullary conventional osteosarcoma, which has a high capacity for distant metastasis and a high rate of local recurrence and mortality. We still believe that the administration of effective chemotherapy can improve the prognosis of this disease.

In one case there was a previous diagnosis of Turner’s syndrome (16). To our knowledge, this is the first report of osteosarcoma in a patient being diagnosed as Turner’s syndrome. Turner’s syndrome is a female phenotype and is clinically characterized by, among other things, short stature, cubits valgus, webbed neck, low hairline, low-set ears, slight ocular ptosis, widely spaced, preadolescence nipples, infantile genitalia and complete absence of pubic hair, and no mental retardation is usually recognized. The genetic abnormality is due to a sex chromatin abnormality. Moreover, the karyotype is generally XO (80%). In this study, according to the wishes of her family, the leukocyte karyotype in the patient’s peripheral blood was not analyzed. In Turner’s syndrome, the occurrence of some types of soft tissue tumor, such as epithelioid sarcoma (17) and synovial sarcoma (18), has been reported. Speculating on the possibility of a relationship between Turner’s syndrome and osteosarcoma, the karyotype of Turner’s syndrome is 45X0, and the SSX gene is located on the X chromosome. This gene plays an important role in the occurrence of synovial sarcoma, with forming fusion gene of t(X;18) (p11.2;q11.2) translocation (19). Overexpression of the SSX gene in high-grade osteosarcoma was recently reported to occur at a high rate (20). Thus, owing to the lack of investigation, it remains uncertain in our study. Additional data will be required in the future.

In conclusion, we presented four cases with high-grade surface osteosarcoma. One case had a previous diagnosis of Turner’s syndrome. The radiological appearance seemed characteristic, except in one case that was difficult to differentiate from other, lower-grade juxtacortical sarcomas. Our treatment for high-grade surface osteosarcoma was a combination of wide resection and chemotherapy. At the last follow-up, two cases were CDF, the remaining two cases were living with NED and AWD after resection of lung metastasis.

References