Case Report
Primary bone carcinosarcoma of the fibula with chondrosarcoma and squamous cell carcinoma components

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Abstract: Carcinosarcoma is defined as a malignant neoplasm that is composed of both carcinomatous and sarcomatous components. The occurrence of carcinosarcoma in the bone is extremely rare. In this report, we describe the third documented de novo case of carcinosarcoma of the bone. A 59-year-old Japanese female presented with a painful tumor in her right lower leg. Plane radiography revealed an osteolytic destructive lesion with periosteal reaction and mineralization in the right fibula. Resection of the fibula tumor was performed under a clinical diagnosis of chondrosarcoma. Histopathological study revealed that the tumor was comprised of three components. The main component was proliferation of small round to short spindle cells (approximately 50%), and the remaining components were chondrosarcoma (30%) and squamous cell carcinoma (20%). Immunohistochemically, SOX9 was expressed in the small round to spindle cells and chondrosarcoma component, and p63 and p40 were expressed in all three components. Accordingly, an ultimate diagnosis of carcinosarcoma of the bone was made. The clinicopathological analysis of carcinosarcoma of the bone revealed that this type of tumor affects the middle-aged to elderly persons and occurs in the long bone. All three de novo cases had chondrosarcoma and squamous cell carcinoma components. One of the 3 patients died of the disease. The histogenesis of carcinosarcoma of the bone remains a matter of controversy, although a multipotential stem cell theory has been proposed. Additional studies are required to clarify the clinical behavior and histogenesis of carcinosarcoma of the bone.

Keywords: Carcinosarcoma, bone, chondrosarcoma, squamous cell carcinoma

Introduction
Carcinosarcoma, also referred to as sarcomatoid carcinoma, is defined as a malignant neoplasm that is composed of both carcinomatous and sarcomatous components, and generally occurs in the genital organs, urinary system, and rarely in the digestive system [1-10]. Carcinosarcoma of the bone is extremely rare, and only two de novo cases and one secondary case have been reported in the English-language literature [11-13]. The two de novo cases had chondrosarcoma and squamous cell carcinoma components located in the humerus and femur, respectively [11, 12], and the secondary case had osteosarcoma and squamous cell carcinoma components located at the site of a previously diagnosed giant cell tumor of the femur [13]. Herein, we report the third documented case of de novo carcinosarcoma of the bone and discuss the clinicopathological features of this extremely rare tumor.

Case report
A 59-year-old Japanese female without a past history of carcinoma or sarcoma presented with a painful tumor in her right external side of the lower leg, which had been noticed approximately one year earlier. Plane radiography revealed an osteolytic destructive lesion invading into the surrounding soft tissue of the right fibula. Periosteal reaction and slight mineralization within the tumor were also observed (Figure 1). According to these findings, chondrosarcoma was suspected. Computed tomography and
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immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [14-16]. Proliferating chondrocytes were positive for S-100 protein and SOX9, and negative for cytokeratin (AE1/AE3), p63, and p40. AE1/AE3, p63, and p40 were expressed in the atypical cells showing trabecular growth and pearl formation, but SOX9 was not expressed.

According to these results, a tentative diagnosis of chondrosarcoma with squamous cell carcinoma component was made.

Operative specimen

Histopathologically, the resected fibula tumor was composed of three components (Figure 3A). The main component was proliferation of small round to short spindle cells, accounting for approximately 50% of the tumor. These cells had round to oval nuclei containing coarse chromatin and small nucleoli (Figure 3B). A few mitotic figures were observed (1/10 high-power fields). Continuous to this component was proliferation of irregular-shaped lobules of cartilage (approximately 30% of the tumor) (Figure 3A, 3C). At the periphery of the lobules, small round cells with a high nuclear/cytoplasmic ratio and round to oval nuclei containing small nucleoli were present, and obvious lacuna and chondroid matrix formation were noted at the center of the lobules (Figure 3C). The nuclei of the atypical chondrocytes were large, and binucleated cells were scattered. No mitotic figures were noted in this component. The third component was a squamous cell carcinoma, which accounted for approximately 20% of the tumor (Figure 3A). Within the small round to short spindle cells, variable-sized epithelial nests were observed. These atypical epithelial cells had rich eosinophilic cytoplasm and large round to oval nuclei containing small nucleoli (Figure 3A, 3B). Keratinization was obvious.

Most of the tumor, especially in the extraosseous lesion, showed the above-mentioned histopathological features. Moreover, the samples from the intraosseous lesion demonstrated the same histopathological features as the biopsy specimen.
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Table 1 summarizes the immunohistochemical results of the present case. Cytokeratin (AE1/AE3) was expressed in the squamous cell carcinoma component, but not in the other two components (Figure 4). p63 and p40 were expressed in all three components (Figure 4). In the squamous cell carcinoma component, p63- and p40-positive cells were preferentially observed at the periphery of the nests. SOX9 and S-100 protein were expressed in the small round to spindle cells and chondrosarcoma component (Figure 4).

According to these results, an ultimate diagnosis of carcinosarcoma of the fibula with chondrosarcoma and squamous cell carcinoma components was made.

Discussion

In this report, we described the third documented case of de novo carcinosarcoma of the bone. Table 2 summarizes the clinicopathological features of the two previously reported de novo cases and one secondary case of carcinosarcoma of the bone as well as the present one. This extremely rare tumor affects middle-aged to elderly persons and occurs in the long bones. The most common symptom is pain of the lesion. Interestingly, all three de novo cases had chondrosarcoma and squamous cell carcinoma components (Table 2). Ling et al. first reported a de novo case of carcinosarcoma of the bone in 1985 [11]. This humerus tumor was composed of squamous cell carcinoma (>50%) and chondrosarcoma (30%) [11]. Moreover, the second de novo case reported by Shiraishi et al. was a femur tumor, which was mainly comprised of an undifferentiated spindle cell component, and chondrosarcoma (10%) and squamous cell carcinoma (10%) were also observed within the tumor [12]. In the present case, the tumor was composed of small round to short spindle cell component (50%), chondrosarcoma (30%), and squamous cell carcinoma (20%). This histopathological feature resembled that of the previous case by Shiraishi et al. [12]. In addition, all three de novo cases had pearl formation in the squamous cell carcinoma. Further, Machinami et al. reported a case of carcinosarcoma (osteosarcoma and squamous...
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cell carcinoma) arising at the site of a previously diagnosed giant cell tumor of bone [13].

A few cases of multilineage malignant neoplasm of the bone have been reported. Hutter et al. first described this extremely rare tumor as “primitive multipotential primary sarcoma of the bone” in 1966 [17]. This type of tumor is characterized histopathologically by the presence of undifferentiated mesenchymal and epithelial components, including osteoid, vascular, chondroid, and squamous cells [17]. Subsequently, Jacobson coined the term “polyhistioma” to designate a malignant small round cell tumor with the ability to differentiate into various mesenchymal structures [18]. Bono reported a case of primary small round cell tumor with foci of bone formation and squamous differentiation accompanied by skin and lymph node metastases [19]. Moreover, a few cases of osteosarcoma accompanying squamous cell carcinoma of the bone have been reported [16, 20, 21].

The histogenesis of carcinosarcoma and multipotential sarcoma of the bone remains a matter of controversy. Two main theories regarding the histogenesis of carcinosarcoma have been proposed in some organs. Some researchers believe that this type of tumor represents a collision tumor comprised of two independent but simultaneously occurring epithelial and mesenchymal monoclonal neoplasms, whereas others suggest that carcinosarcoma has a common clonal origin with divergent differentiation into the two components. Recent molecular analyses have demonstrated that the carcinomatous and sarcomatous components are of monoclonal origin in some organs, and carcinosarcoma may progress through multistep carcinogenesis with accumulation of genetic alterations, genetic instability, and generation of multiple subclones, followed by secondary transdifferentiation from an epithelial to a mesenchymal phenotype [22]. Moreover, two main hypotheses have been proposed to explain the differentiation of a monoclonal neoplasm with epithelial and mesenchymal components in carcinosarcoma. The first hypothesis is that both components are derived from multipotent (totipotent) stem cell origin, and the second one is that the mesenchymal component repre-

Figure 3. Histopathological features of the surgical specimen of the fibula tumor. A: The tumor is composed of three components: small round to short spindle cells, chondrosarcoma, and squamous cell carcinoma, HE, x 40. B: Small round to short spindle cell component. These cells have round to oval nuclei containing small nucleoli. Nests of squamous cell carcinoma are also observed, HE, x 200. C: Chondrosarcoma component. Obvious lacuna and chondroid matrix formation are present. The nuclei of the chondrocytes are large, and binucleated cells are scattered. HE, x 200.
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![Image of immunohistochemical features](image_url)

**Figure 4.** Immunohistochemical features of the fibula tumor. Cytokeratin (AE1/AE3) is expressed only in the squamous cell carcinoma component. p63 is expressed in all three components. Positive immunoreactivity for SOX9 is observed in the small round to spindle cells and chondrosarcoma component. x 40.

**Table 1.** Summary of immunohistochemical results

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Small round to short spindle cell component</th>
<th>Chondrosarcoma component</th>
<th>Squamous cell carcinoma component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin (AE1/AE3)</td>
<td>DAKO</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>p63</td>
<td>Novocastra</td>
<td>+</td>
<td>+ (periphery of the nests)</td>
<td>+</td>
</tr>
<tr>
<td>p40</td>
<td>Calbiochem</td>
<td>+</td>
<td>+ (periphery of the nests)</td>
<td>-</td>
</tr>
<tr>
<td>SOX9</td>
<td>Santa Cruz</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>S-100 protein</td>
<td>Nichirei</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

sent metaplastic change from an epithelial element [12]. The hypothesis of multipotent (totipotent) stem cell is highly plausible in carcinosarcoma of the bone because no epithelial component is present in the bone [12].

The prognosis of carcinosarcoma of the bone has not been established yet because of the rarity of this tumor. The present case has been free from recurrence 1 month after the surgery, and the case reported by Ling et al. had been free from recurrence 3 years and 3 months after the surgery (the patient died of another cause) [11]. However, the patient reported by Shiraishi et al. died of disease 6 months after the surgery by multiple lung and cutaneous metastases [12]. Moreover, the patient with secondary carcinosarcoma reported by Macchinami et al. died of pulmonary metastases [13]. Additional case studies are needed to clarify the behavior of this type of tumor.

Differential diagnostic considerations of the present case should include bone tumors with epithelial differentiation. Adamatinoma is a rare malignant bone tumor comprising of clusters of epithelial cells surrounded by a relatively bland spindle-cell osteofibrous component [23]. Although adaminoma has a squamous cell component, chondrosarcoma component is not present [23]. Moreover, a few cases of myoepithelioma/mixed tumor of the bone have
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Table 2. Clinicopathological features of primary carcinosarcoma of the bone

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Location</th>
<th>Symptom</th>
<th>Histopathological characteristics</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>68/Female</td>
<td>Humerus</td>
<td>Pain in the left shoulder</td>
<td>Chondrosarcoma (30%) and SCC components (&gt;50%), Keratinization (+). Undifferentiated spindle cell component is dominant.</td>
<td>Free from metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>53/Male</td>
<td>Femur</td>
<td>Pain in the right thigh</td>
<td>Chondrosarcoma (10%) and SCC (10%) components, Keratinization (+).</td>
<td>Died of another cause. Died of disease 6 months after surgery. Multiple lung, cutaneous metastases.</td>
</tr>
<tr>
<td>Case 3</td>
<td>45/Male</td>
<td>Femur</td>
<td>Swelling of the right knee</td>
<td>Osteosarcoma and squamous cell carcinoma arising at the site of a previous giant cell tumor of the bone.</td>
<td>Died of pulmonary metastases</td>
</tr>
<tr>
<td>Present case</td>
<td>59/Female</td>
<td>Fibula</td>
<td>Pain in the right lower leg</td>
<td>Small round to short spindle cells (50%), chondrosarcoma (30%) and SCC components (20%), Keratinization (+).</td>
<td>Free from recurrence and metastasis 1 month after surgery</td>
</tr>
</tbody>
</table>

SCC, Squamous cell carcinoma.

been documented [24]. Although myoepithelioma of the bone shows chondroid matrix formation, this type of tumor typically has spindle, stellate cells interspersed within myxoid or myxochondroid stroma [24]. These histopathological features can facilitate the differential diagnostic considerations of carcinosarcoma of the bone.

This case report is the first to examine the immunohistochemical expression of SOX9, p63, and p40 in carcinosarcoma of the bone. SOX9 is a transcription factor playing a crucial role in normal chondrogenesis, and SOX9 antibody has been used as a diagnostic tool for neoplasms with chondroid differentiation, such as chondrosarcoma and chordroblastoma [25, 26]. In the present case, the small round to spindle cell component showed positive immunoreactivity for SOX9 as well as the chondrosarcoma component. This suggests that the small round to spindle cell component has an immature cartilaginous character. p63 is a p53 homologue that is expressed in various normal epithelial tissues, such as squamous epithelium, urothelium, basal cells/myoepithelial cells of the salivary gland, breast, and prostate, and epithelial malignancies including squamous cell carcinoma, urothelial carcinoma, and myoepithelial component of salivary gland neoplasms. Positive immunoreactivity for p63 has been reported in some types of soft tissue tumors [27], as well as all cases of giant cell tumor of the bone and some cases of chordroblastoma and aneurysmal bone cyst [28]. In addition, p40 (DeltaNp63) is an isoform of p63 and has been recently used as a superior antibody for diagnosis of pulmonary squamous cell carcinoma [29]. In the present case, both p63 and p40 were expressed in the small round to spindle cells and chondrosarcoma component as well as the squamous cell carcinoma component (Table 2). The mechanism and significance of the expression of p63 and p40 in the small round to spindle cells and chondrosarcoma component have not been resolved yet. Therefore, additional studies are required to clarify the significance of p63 and p40 expression in chondrosarcoma.

Disclosure of conflict of interest

None.

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