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Case report

Primary bone carcinosarcoma: Chondrosarcoma and squamous cell carcinoma with keratin pearl formation

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Malignant bone tumors with epithelial differentiation are extremely rare. Only one case of primary malignant bone tumor with distinct squamous cell carcinoma and chondrosarcoma has ever been reported. Reported herein is a case of primary malignant bone tumor with distinct squamous cell carcinoma and chondrosarcoma, so-called carcinosarcoma of bone, arising in the femur of a 53-year-old man. The tumor was located within the femur and was diagnosed by curettage as a well-differentiated chondrosarcoma. No primary tumor was detected in any other organ. Within a few months the tumor had rapidly grown toward the soft tissue, and hemipelvectomy was performed. Examination of the surgical specimen revealed that the tumor was mainly composed of undifferentiated spindle sarcoma cells with scattered foci of chondrosarcoma and of squamous cell carcinoma with keratin pearl formation. The patient died approximately 6 months postoperatively. At autopsy multiple metastases were detected in the heart, both lungs, muscles, and lymph nodes. Interestingly, the chondrosarcoma and squamous cell carcinoma components were observed in several metastatic foci. The tumors in both the previously reported case and the present case contained components of chondrosarcoma and squamous cell carcinoma with keratin pearl formation, and this combination of histological features may be a unique characteristic of carcinosarcoma of bone.

Key words: bone, carcinosarcoma, chondrosarcoma, squamous cell carcinoma

Carcinosarcoma is defined as a tumor that contains both a carcinoma component and a sarcoma component, and carcinosarcomas generally occur in the genital organs, urinary systems, and digestive systems. Several different types of bone tumors, including adamantinomas and chordomas, exhibit epithelial features, but carcinomas do not usually originate in bone, and carcinosarcoma of bone is very rare. Only one previous case, a tumor with distinct carcinoma and sarcoma components, reported in 1986, has been documented.[1] That tumor was located in the humerus and was composed of chondrosarcoma and squamous cell carcinoma with keratin pearl formation. The subtypes in that case of the carcinoma and sarcoma component were the same as in the present case. Histological examination of tissue obtained at autopsy revealed the histological features of carcinosarcoma in several metastatic foci.

CLINICAL SUMMARY

A 53-year-old man complained of pain in his right thigh for 1 year, and osteomyelitis was suspected based on the plain radiography findings (Fig. 1a). Plain radiographs showed a mixed osteolytic and sclerotic change in the cortical border of the femoral diaphysis. Periosteal reaction was focally detected. The lesion had relatively distinct margin. Curettage revealed that the bone marrow was filled with whitish jelly-like material, and there was no apparent extraosseous proliferation. The curettage material was diagnosed as a grade 1 chondrosarcoma. The right thigh rapidly increased in size over the next few months, and massive growth toward the soft tissue around the femur was detected by scintigraphy and magnetic resonance imaging (MRI). Multiple small nodules were detected in both lungs on a computed tomography (CT) scan, and metastases were suspected. Hemipelvectomy was performed to secure a safe margin. After the operation, the patient received outpatient chemotherapy because he refused to be treated in the hospital. The chemotherapy regimen consisted of paraplatine (450 mg) once a month. Approximately 1 month later a cutaneous metastasis appeared on his face, and 2 months after that a second

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cutaneous metastasis appeared on his head. A large mass was detected in the right pulmonary artery on CT. The patient's respiration rapidly deteriorated and he died of respiratory failure approximately 6 months after the operation.

No primary lesion except the femur lesion was detected clinically or radiographically. The patient had no history of surgery or chemoradiation therapy prior to the amputation of his right thigh.

MATERIALS AND METHODS

The specimens of biopsy, operation and autopsy were fixed with 10% formalin and embedded in paraffin. Sections were cut 4 μm thick and stained with hematoxylin–eosin. The sections were also immunostained by the avidin–biotin–peroxidase complex method with antibodies to the cytokeratins (pancytokeratin; AE1 + AE3, monoclonal, mouse, DakoCytomation, Glostrup, Denmark, diluted 1:50 and high-molecular-weight keratin; 34βE12, monoclonal, mouse, Enzo Diagnostics, New York, diluted 1:20), epithelial membrane antigen (EMA; E29, monoclonal, mouse, DakoCytomation, diluted 1:200), S-100 protein (polyclonal, rabbit, DakoCytomation, diluted 1:200), desmin (D33, monoclonal, mouse, DakoCytomation, diluted 1:50), smooth muscle actin (1A4, monoclonal, mouse, DakoCytomation, diluted 1:100), and p53 (DO-7, monoclonal, mouse, DakoCytomation, diluted 1:20). Before staining for high-molecular-weight keratin, EMA and desmin, the sections were immersed in citrate buffer at pH 6.0 and placed in a microwave oven for 20 min. Before staining for p53, the sections were autoclaved in citrate buffer at 120°C for 15 min. Before staining for pancytokeratin, S-100 protein and smooth muscle actin, the sections were immersed in 0.1% tripsin at 37°C for 30 min.

PATHOLOGICAL FINDINGS

Curettage specimen

Histological examination of the curettage specimen revealed grade 1 chondrosarcoma (Fig. 2). The specimen consisted of irregularly shaped lobules or a less distinct lobular pattern and had a chondroid matrix. The cellularity was slightly increased, and the nuclei were enlarged and irregular in shape.

Operation specimen

Macroscopic examination of the surgical specimen revealed a whitish tumor measuring 25 × 14 × 13 cm with necrosis and hemorrhage, which was found in the upper and middle part of the right thigh. The destroyed femur was present at

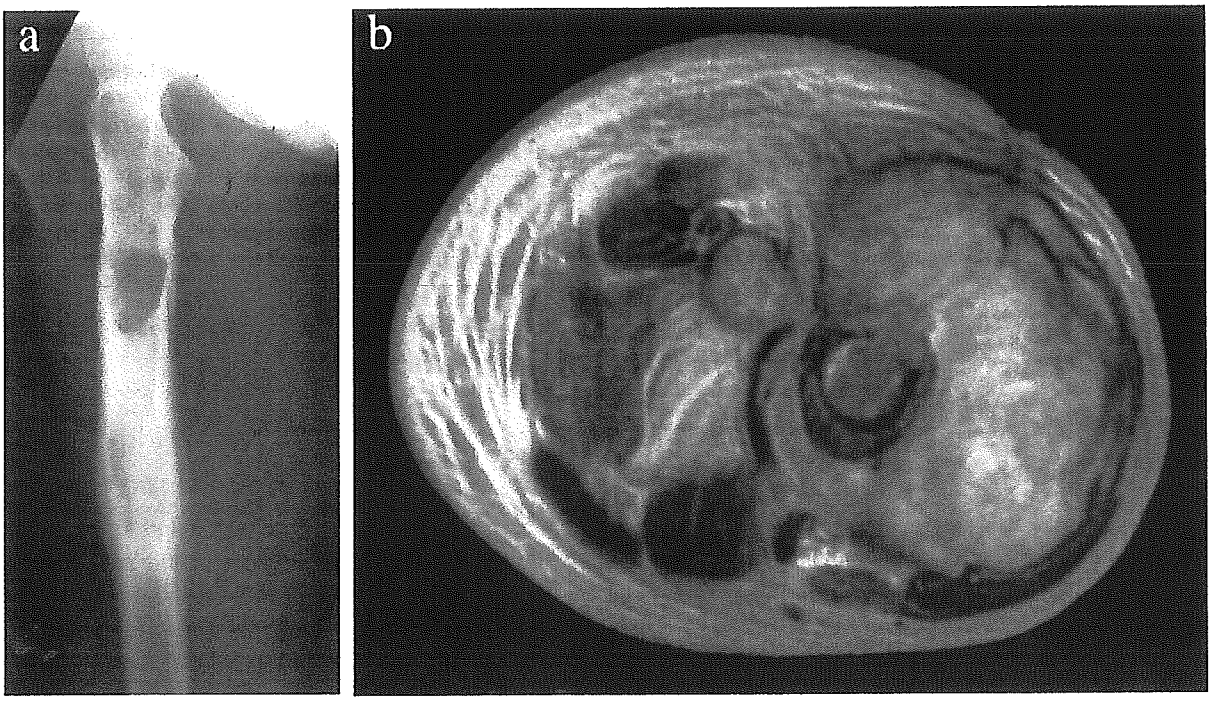

Figure 1 Plain radiograph and T2-weighted magnetic resonance imaging (MRI) of the right thigh. (**a**) Plain radiograph at the time of the first examination showed osteolytic change, sclerosis and periosteal reaction of the femur with no extra-osseous growth of a tumor. (**b**) MRI showed a huge tumor with massive extra-osseous growth.

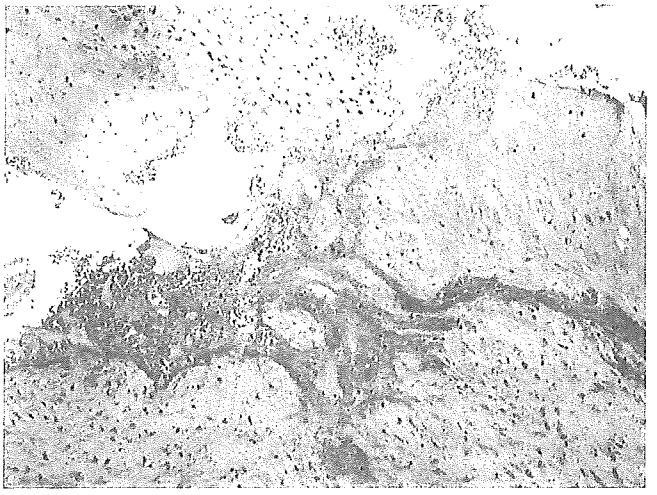

Figure 2 Curettage specimen diagnosed as grade 1 chondrosarcoma with irregularly shaped lobules and increased cellularity.

the center of the tumor (Figs 1b,3a). Several small foci of a chondroid nature were scattered throughout the intraosseous and extraosseous parts of the tumor. Microscopically, the tumor was mainly composed of undifferentiated spindle cell sarcoma with varying cellularity (Fig. 4a). These areas of spindle cell sarcoma were composed of plump or slender spindle cells containing abundant eosinophilic cytoplasm. The spindle cells were arranged in a haphazard, vaguely fascicular or storiform pattern, and they exhibited a moderate degree of nuclear pleomorphism and moderate mitotic activity. Small foci of grade 1 chondrosarcoma were found scattered throughout the tumor (Fig. 4b) as well as small-scattered foci of squamous cell carcinoma with prominent keratin pearl formation (Fig. 4d). The epithelial elements consisted of cancer nests that contained numerous cancer pearls. Occasionally small scattered foci of cancer pearls were seen in the component of spindle cell sarcoma. The areas of squamous cell carcinoma and the areas of chondrosarcoma each accounted for approximately 10% of the tumor. Spindle sarcoma cells were observed between the foci of chondrosarcoma and squamous cell carcinoma. No direct transitions from chondrosarcoma to squamous cell carcinoma were observed. There were no glandular structures or bone formation in the tumor. Immunohistological staining revealed that the squamous cell carcinoma areas were positive for epithelial markers (pancytokeratin and high-molecular-weight keratin, EMA; Fig. 4e), and the spindle cells adjacent to the squamous cell carcinoma foci were focally and weakly positive for epithelial markers. The chondrosarcoma areas were positive for S-100 protein (Fig. 4c), and the majority of the spindle cells were positive for vimentin, and negative for epithelial markers, S-100 protein, desmin, and smooth muscle actin. The surgical margin was negative for malignant cells. The spindle cell sarcoma component had metastasized to a lymph node adjacent to the primary tumor, and the metastatic focus was negative for epithelial markers.

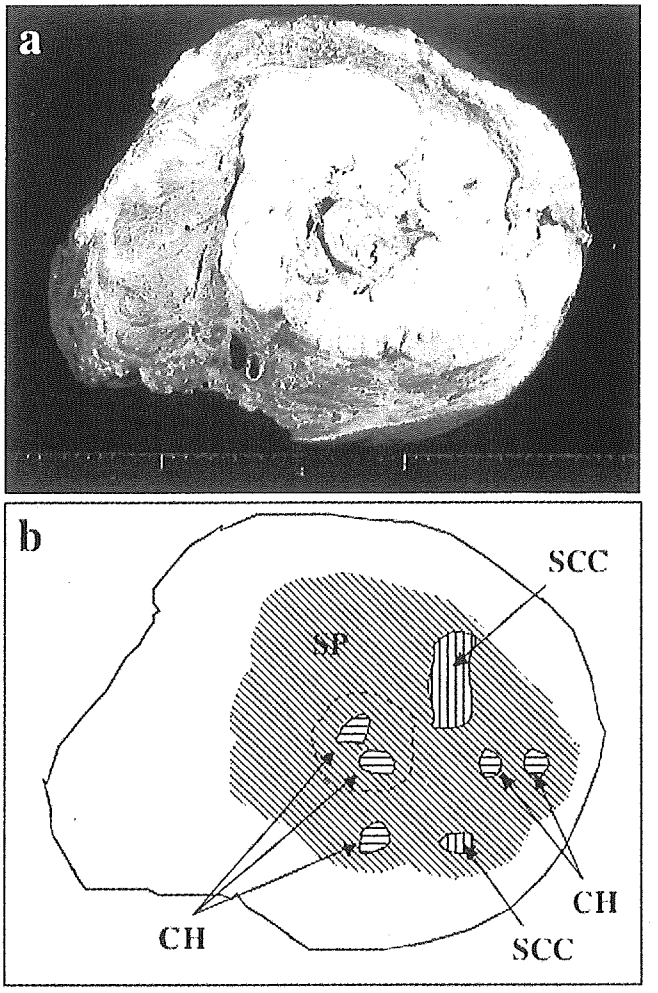

Figure 3 Macroscopic appearance of the cut surface and the schematic diagram of the tumor. (**a**) The tumor exhibited massive growth towards the soft tissue around the femur and had destroyed the femur. (**b**) Schematic diagram of each of the components of the carcinosarcoma on the same cut surface of (**a**). The tumor was composed of undifferentiated spindle cell sarcoma (SP), squamous cell carcinoma (SCC) and chondrosarcoma (CH). The dotted line in the tumor outlines a portion of the destroyed femur.

Autopsy specimen

A large, long whitish tumor was found in the area between the right atrium and the right pulmonary artery and was obstructing blood flow. Multiple metastases were observed in both lungs, the chest wall, the iliopsoas muscle, soft tissue in the pelvis adjacent to the bladder, and in the perigastric lymph nodes. Microscopic examination revealed that the metastatic foci consisted mainly of undifferentiated spindle cell sarcoma. A few foci of epithelial differentiation with trabecular arrangement were observed in the pulmonary metastases,

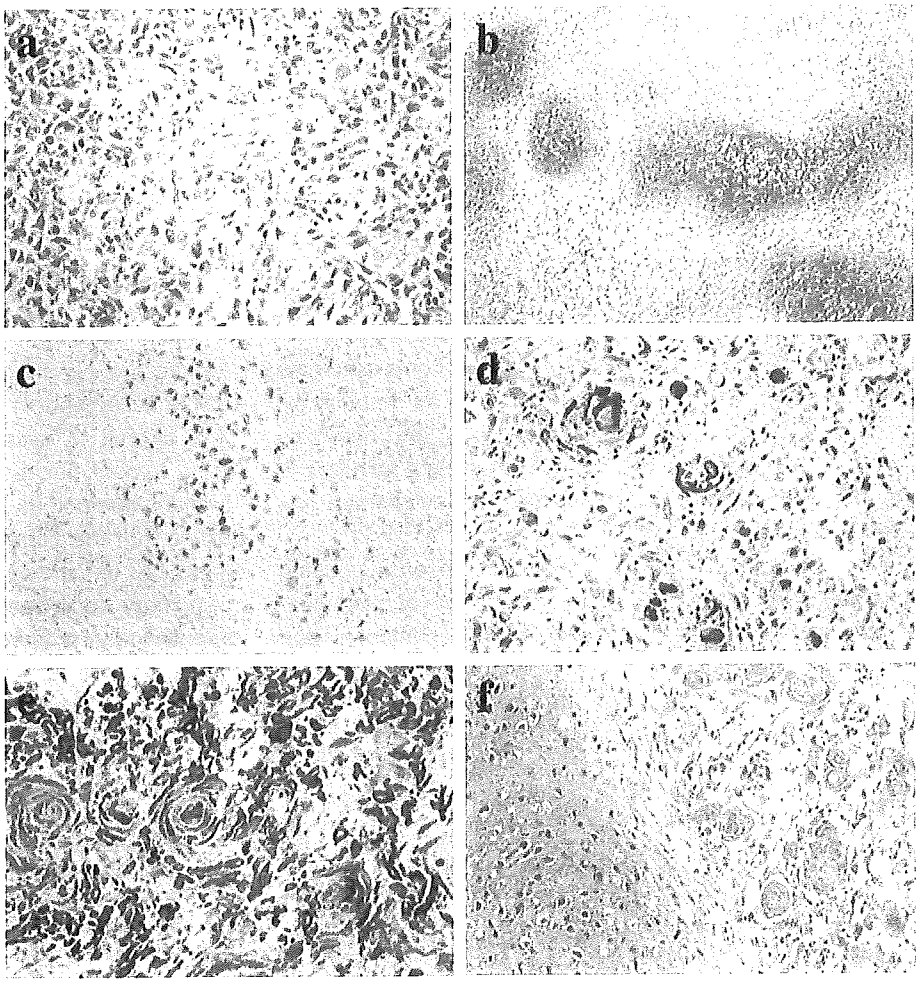

Figure 4 Microscopic appearance of the tumor. The main component of the tumor was (**a**) undifferentiated spindle cell sarcoma. (**b**) Chondrosarcomatous areas were scattered throughout the spindle cell sarcoma. (**c**) The chondrosarcomatous areas were positive for S-100 protein. (**d**) Foci of squamous cell carcinoma with prominent keratin pearl formation were occasionally observed in the spindle cell sarcoma. (**e**) The squamous cell carcinoma foci were strongly positive for pancytokeratin. (**f**) An area of squamous cell carcinoma is seen abutting against an area of chondrosarcoma in this intrapelvic nodule in the metastatic foci at autopsy.

an intrapelvic nodule and perigastric lymph nodes, and they were positive for epithelial markers. Small foci of chondrosarcoma and squamous cell carcinoma were also found in these metastatic lesions. It was particularly noteworthy that a squamous cell carcinoma component was found abutting against a chondrosarcoma component in an intrapelvic nodule (Fig. 4f). The direct cause of death was respiratory insufficiency secondary to tumor embolism.

DISCUSSION

Several cases of multipotential malignant neoplasms of bone have been reported.[2–4] They appeared to consist of undifferentiated cells with multiple differentiation (i.e. bone, cartilage, blood vessels, etc.). Hutter *et al.* proposed the term 'primitive multipotential primary sarcoma',[3] and Jacobson used the term 'polyhistoma' to describe sarcomas of bone that exhibit a broad mixture of histological types and represent multiple lines of differentiation.[4] A few cases of multipotential neoplasm with epithelial differentiation were documented in their reports. There have also been several reports of osteosarcoma and Ewing's sarcoma with epithelial differentiation, and the epithelial differentiation was confirmed by immunohistochemical or ultrastructural studies.[5–11] Primary bone tumors with definite epithelial differentiation, however, are extremely rare, and only one other case of a bone tumor containing definite squamous cell carcinoma and chondrosarcoma components has ever been reported.[1] Interestingly, the present case also contained components of chondrosarcoma and squamous cell carcinoma with keratin pearl formation.

Bone tumor with epithelial differentiation suggests the possibility of an adamantinoma, a rare primary bone tumor known to have an epithelial component. However, there were no components exhibiting a basaloid pattern or tubular pattern in the present case, and the prominent chondrosarcomatous component militated against a diagnosis of adamantinoma. A few cases of mixed tumor of bone have recently been reported, and because they contained a squamous component and a chondroid component[12,13] it was important to differentiate the present case from mixed tumor. Several findings in the present case indicated that it was not a mixed tumor of bone. First, there were no prominent myoepithelial cells or stellate cells. Second, all of the types of

tumor cells were glial fibrillary acidic protein-negative. The spindle cells in the present case were negative or weakly positive for smooth muscle actin immunohistochemically. And there were no tumors in the salivary glands at autopsy. Furthermore, the hypothesis of dedifferentiated chondrosarcoma with epithelial differentiation is considerable in the present case because the curettage material of femur revealed chondrosarcoma, and the operation material was mainly composed of undifferentiated spindle cell sarcoma. Several reports have been made of dedifferentiated chondrosarcoma with other mesenchymal components, such as rhabdomyosarcoma, angiosarcoma, osteosarcoma etc.; and one case of dedifferentiated chondrosarcoma containing a spindle cell area with intense cytoplasmic staining for cytokeratin has been documented.[14–18]

A biclonal and a monoclonal origin have been suggested to explain the histogenesis of two components of carcinosarcoma in many organs. Several molecular techniques have often been used to determine the histogenesis in different organs. In a few cases of carcinosarcoma the lesion was considered to be a biclonal tumor (collision tumor),[19–22] but most have appeared to be monoclonal. Thompson *et al.* determined the clonality of the carcinomatous and sarcomatous components of carcinosarcomas by examining a 511 bp region located within the first intron of the *human hypoxanthine-phosphoribosyl transferase* gene.[23] They demonstrated the comigration of the single homoduplexes generated by both carcinoma cells and sarcoma cells in six different organs. Gronau *et al.* determined the clonality to analyze for gains and losses of chromosomal material by comparative genomic hybridization and loss of heterozygosity analysis.[24] They demonstrated overlapping core aberration losses on the short arm of chromosome 9 and on the long arm of chromosome 11 in carcinosarcomas of the urinary bladder. Dacic *et al.* determined the clonality to perform an extensive comparative genotypic analysis in the six pulmonary carcinosarcomas.[25] Abeln *et al.* performed a loss of heterozygosity analysis in malignant mixed Mullerian tumors.[26] Emoto *et al.* showed that two clones established from a carcinosarcoma of the uterus were capable of differentiating into epithelial, mesenchymal, or both elements.[27] Kounelis *et al.* examined the point mutations in *p53* exons 5 through 8 in nine cases of female genital tract, and detected the loss of the wild-type allele in both carcinoma cells and sarcoma cells.[28] Wada *et al.* examined the mutation in the *p53* gene and *K-ras* gene, and found that the *p53* sequence was identical in both the carcinomatous and sarcomatous components of 21 carcinosarcomas of the uterus.[21] These results in several organs strongly support the theory of monoclonality of carcinosarcoma. In the present case each component must have been monoclonal, because the carcinoma and sarcoma components were intermingled in both the primary tumor and the metastatic lesions.

Two main hypotheses have been proposed to explain the differentiation of monoclonal tumor cells into separate epithelial and mesenchymal directions in carcinosarcoma. The first hypothesis is that both the epithelial and mesenchymal components are derived from totipotent (multipotential) stem cells,[1–3,23,25] and the second hypothesis is that the mesenchymal elements represent metaplastic change of epithelial elements.[22,26,29,30] These hypotheses are accepted in many organs, in which the most common malignant tumors are carcinoma. The hypothesis of totipotent stem cell is acceptable in all organs, including bone. In contrast, it is difficult to accept the metaplastic theory for primary bone tumors because there are no epithelial elements or primary carcinomas in bone tissue. Nevertheless, it is interesting that the combination of chondrosarcoma and squamous cell carcinoma has been observed in only two cases of primary bone carcinosarcoma with distinct epithelial differentiation: the present case and a previously reported case.

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基礎研究成果の臨床応用推進研究事業

ヒト化CD26抗体の難治性免疫疾患
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