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CASE REPORT

Cytogenetic study of secondary malignancy in giant cell tumor

Taketsugu Fujibuchi · Seiichi Matsumoto · Takashi Shimoji · Keisuke Ae · Taisuke Tanizawa · Tabu Gokita · Keiko Hayakawa · Noriko Motoi · Hiroyuki Mukai

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Introduction

Giant cell tumor (GCT) is classified as a benign bone tumor, but it is locally aggressive, and sometimes metastasizes in a benign state. In addition, malignant transformation occurs once in a while. Most of the secondary malignancies in GCT occur after treatment of benign GCT that has included radiation therapy [1, 2].

As a cytogenetic characteristic of GCT, telomeric associations (tas) were reported [3, 4]. Tas may generate dicentric chromosomes (dic) and chromatoid breakage-fusion-bridges, which lead to chromosomal instability and tumorigenesis [5, 6]. Recently, the relationship between cytogenetic abnormalities and clinical behavior in GCT has begun to be elucidated. For example, the DNA ploidy pattern may predict the recurrence potential of GCT, chromosomal abnormalities superimposed on tas are responsible for an aggressive clinical course [7], and centrosome amplification may be useful in predicting the clinical behavior of GCT [8].

Here we report a case of secondary malignancy in GCT. Malignant transformation occurred in a relatively early period, and any radiation therapy was not administered to the primary lesion. Malignant transformation was demonstrated not only by histopathological study but also by cytogenetic analysis. The recurrent tumor, which was a secondary malignancy in GCT, had a near-triploid karyotype with multiple structural abnormalities as observed in pleomorphic sarcoma, while the primary benign GCT had a near-diploid karyotype with tas and dic.

Case report

A 32-year-old woman was referred to our institute from a nearby clinic with a sacral tumor detected during a gynecological examination. She had suffered from recurrent severe buttock pain for 4 years. At the first visit, her buttock pain was being self-controlled. On physical examination, there were no motor or sensory deficits, no paresthesia in the lower extremities, and no dysfunction of bladder or bowel. Laboratory investigations showed normal values for the bone-alkaline phosphatase, and leukocytes, except for elevation of the total acid phosphatase (59.8 U/l, normal range: 0.0–14.4 U/l) and C-reactive protein (3.7 mg/dl). Plain radiography (Fig. 1a) and computed tomography (CT) demonstrated a massive osteolytic change of the sacrum. MRI demonstrated a massive tumor in the sacrum, which projected anteriorly and compressed the pelvic viscera including uterus, ovary and urinary bladder. Gadolinium-diethylenetriamine pentaacetic acid (Gd)-enhanced T1-weighted images showed the tumor was enhanced

T. Fujibuchi (✉) · S. Matsumoto · T. Shimoji · K. Ae · T. Tanizawa · T. Gokita · K. Hayakawa
Department of Orthopaedic Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto, Tokyo 135-8550, Japan
e-mail: f-buchi@ya2.so-net.ne.jp

Present Address:
T. Fujibuchi
Department of Bone and Joint Surgery, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan

N. Motoi
Division of Pathology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto, Tokyo 135-8550, Japan

H. Mukai
FML Laboratory Tokyo, 1-20-8 Kamiikedai, Ohta, Tokyo 145-0064, Japan

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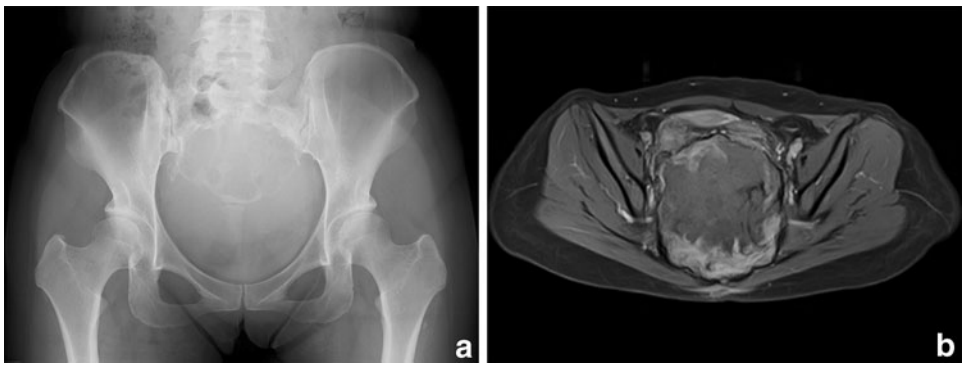

Fig. 1 **a** Anteroposterior plain radiograph and **b** axial view of Gd-enhanced T1-weighted MRI. A massive tumor with heterogenous enhancement localized at sacrum

heterogeneously (Fig. 1b). CT of the lung at the first visit showed multiple nodules, and these nodules showed no change throughout this clinical course (Fig. 2a–d).

Incisional biopsy was performed. Histopathological examination revealed the tumor was composed of osteoclast-like multinuclear giant cells and mononuclear cells with ill-defined cytoplasm. Cellular polymorphism was not obvious. The pathologic diagnosis of the biopsy specimen was giant cell rich lesion, suggesting GCT (Fig. 3a). Cytogenetic analysis was also performed. Cell cultures and preparation for cytogenetic analysis was performed according to procedures described previously [3]. Samples were stained with quinacrine and the karyotypes were described according to ISCN 2009. Cytogenetic analysis of this biopsy specimen showed a near-diploid karyotype with tas and dic, that were characteristics of GCT. In addition, this case showed a high incidence of cytogenetic abnormality, that was found in 95 % of karyotyped cells (21 cells out of 22 cells). No clonal abnormality was found (Fig. 3b, c).

After the fourth administration of zoledronic acid (4 mg) that was given once a month, and the fourth therapeutic embolization, curettage of the tumor and alcohol treatment were performed 4 months after the first visit. Radiation therapy was not applied in the first treatment of this case. After these treatments, recurrence of the tumor was not observed in MRI at 9 months and 1.5 years after the initial operation (Fig. 4a, b).

Two years and 8 months after the initial operation, MRI detected recurrence of the tumor (Fig. 4c). A reoperation was performed followed by a therapeutic embolization. The tumor was curetted again. A histopathological examination of the specimen at the time of recurrence showed proliferation of spindle cells with polymorphism. Partially dysplastic, osteoclast-like giant cells were scattered through the specimen; these findings were not inconsistent with GCT, but suggested a malignant tumor (Fig. 5a). Immunohistochemical studies showed that tumor cells were negative for cytokeratin AE1/3 and EMA, desmin, alpha-smooth muscle actin (SMA), muscle specific actin (HHF35), CD34, CD31, factor VIII, S-100 protein and anaplastic large cell lymphoma kinase (ALK). These immunohistochemical findings revealed that this tumor had no specific differentiation, suggesting it was most likely to be a poorly differentiated sarcoma (MFH). High p53 expression and Ki-67 labeling index were observed in the recurrent tumor, but even the primary tumor showed p53 and Ki-67 expression moderately (Fig. 6a–d). Mutation of the p53 gene was examined

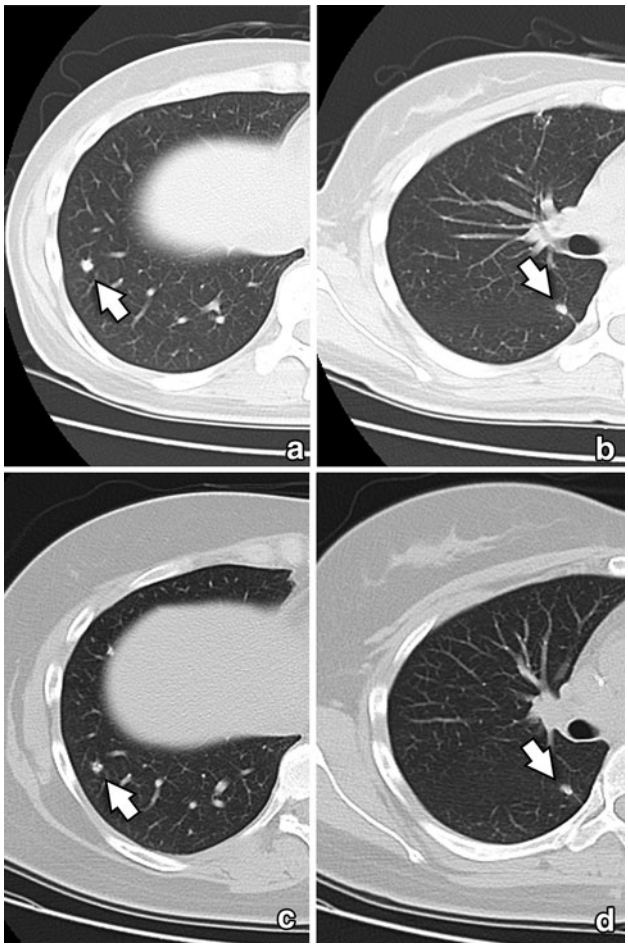

Fig. 2 **a**, **b** Plain CT of the lung at the first visit showed multiple nodules. **c**, **d** Plain CT of the lung at the last follow-up. The size and number of these nodules showed no change throughout this clinical course (*arrows*)