

Osteosarcoma Arising from Giant Cell Tumor of Bone Ten Years After Primary Surgery: A Case Report and Review of the Literature

KO HASHIMOTO, MASAHITO HATORI, MASAMI HOSAKA, MIKA WATANABE,¹
TADASHI HASEGAWA² and SHOICHI KOKUBUN

Department of Orthopaedic Surgery, ¹Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan, and ²Department of Surgical Pathology, Sapporo Medical University School of Medicine, Sapporo, Japan

HASHIMOTO, K., HATORI, M., HOSAKA, M., WATANABE, M., HASEGAWA, T. and KOKUBUN, S. *Osteosarcoma Arising from Giant Cell Tumor of Bone Ten Years After Primary Surgery: A Case Report and Review of the Literature.* Tohoku J. Exp. Med., 2006, **208** (2), 157-162 — Giant cell tumor of the bone (GCT) is a relatively uncommon tumor. It is characterized by the presence of multinucleated giant cells. GCT is a primary benign tumor but may evolve into a malignant tumor, usually after irradiation. We report a rare case of osteosarcoma arising ten years after the primary surgery for GCT without radiation. A 45-year-old woman presented with severe right knee pain after suffering contusion. Roentgenogram revealed a bone tumor in the lateral femoral condyle of the right knee. Histopathological examination demonstrated the features of GCT, and treatment consisted of curettage and bone grafting. Four months after the operation, multiple lung metastases of GCT occurred, which were treated by partial lobectomy. Ten years after the primary treatment, severe knee pain recurred. Roentgenogram and magnetic resonance imaging (MRI) demonstrated a destructive lesion in the lateral condyle of the right knee. Histopathological examination demonstrated a lacy pattern of osteoids and abnormal mitoses in the aggregated atypical mononuclear cells, indicating osteosarcoma. Despite above-knee amputation and chemotherapy, scapular and lung metastases developed and the patient died five months after above knee amputation. One may question whether the primary GCT contained some malignant cells. However, given the aggressiveness of the malignant tumor, this is unlikely. The recurrence of pain and aggravation of bone destruction many years after the primary treatment suggest malignant transformation of GCT. ——— giant cell tumor; osteosarcoma; malignant transformation; long term

© 2006 Tohoku University Medical Press

Received August 22, 2005; revision accepted for publication November 4, 2005.

Correspondence: Masahito Hatori, M.D., Assistant Professor, Department of Orthopaedic Surgery, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

e-mail: mhato@mail.tains.tohoku.ac.jp

Giant cell tumor of the bone (GCT) is a relatively uncommon tumor. It is characterized by the presence of multinucleated giant cells. GCT is categorized as a primary benign tumor, but it is known that it may evolve into a malignant tumor. Although there are many reports of GCT in which the cases showed malignant transformation, most of those cases had been treated primarily by radiation. On the other hand, secondary malignant tumor without radiation therapy is very rare (Dahlin et al. 1970; Campanacci et al. 1987).

We report a case of osteosarcoma arising ten years after the primary surgery for a benign GCT that was not treated with additional radiation therapy:

CASE REPORT

In 1994 a 45-year-old woman visited a clinic with gait disturbance due to right knee pain after

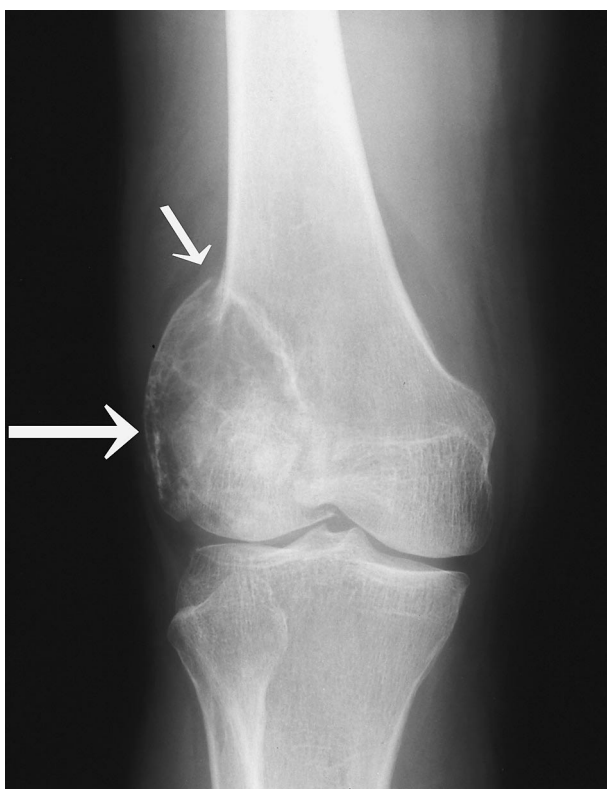


Fig. 1. Anteroposterior radiograph before primary treatment, in 1994. An osteolytic lesion (long arrow) and pathological fracture (short arrow) were shown in the lateral condyle of the right femur.

suffering a contusion. A pathological fracture due to a bone tumor was noted in the lateral condyle of the right femur (Fig. 1). A needle biopsy revealed the lesion have a GCT histologically, and class 2 cytologically. Then the patient was referred to our hospital. The lesion was curetted and autogenous bone graft with artificial bone packing was performed. The histological diagnosis of the operative specimen was benign GCT (Fig. 2).

Four months after the operation, dozens of metastatic tumors appeared in both lungs. Partial lobectomy was performed in the right lung. Histopathological examination demonstrated the metastatic tumors to be GCTs. In 2001, recurrent tumors were found in the right distal femur and both lungs, which were observed periodically without treatment because of the slow growth. The recurrent tumors of both lungs were irradiated in 2003 for control of the lesions.

In 2004 the patient was admitted to our clinic because she became unable to walk again due to severe right knee pain. Marked swelling and tenderness were noted. Laboratory data showed no inflammatory changes, while alkaline phosphatase (Al-P) was elevated to an abnormally high value

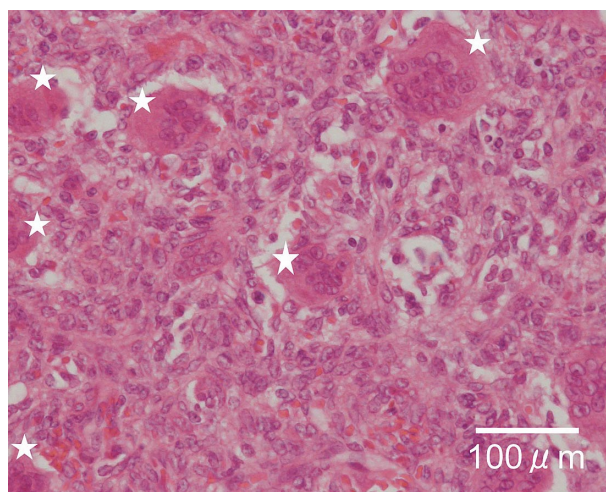


Fig. 2. Histopathological study of the specimen from open biopsy of the primary lesion. Multinuclear giant cells (★) were scattered in dense aggregations of uniform mononuclear cells without atypical nuclei or abnormal mitoses ($\times 200$).

of 1,059 IU/liter. A roentgenogram demonstrated a large osteolytic lesion approximately 5 × 4 cm in size occupying most of the lateral condyle of the right femur (Fig. 3). Computed tomography (CT) demonstrated multiple osteolytic lesions occupying most of the lateral femoral condyle (Fig. 4). On MR images the osteolytic lesion extended into the soft tissue. The lesion was heterogeneous on T2-weighted images and clearly enhanced by Gadolinium enhancement (Fig. 5).

Macroscopically, specimens of open biopsy were soft, grayish-white. Light microscopy showed dense aggregation of mononuclear cells with highly anaplastic nucleus and mitoses more than 50 cells per 10 high-power fields (HPF).



Fig. 3. Anteroposterior radiographs at the time of admission in 2004 showing an expanded destructive lesion (arrow) in the lateral condyle of the right femur.

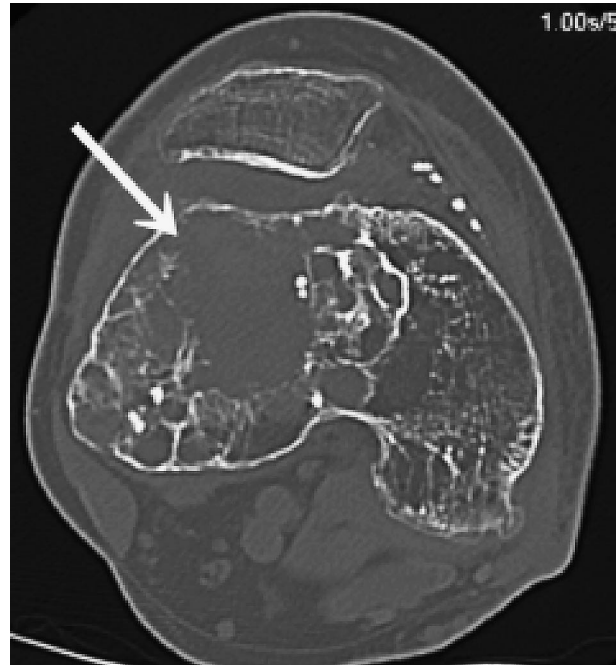


Fig. 4. CT scan shows multiple osteolytic lesions occupying most of the lateral femoral condyle. The lateral condyle of the distal femur was destroyed by tumor invasion (arrow).

Multinuclear giant cells were scattered throughout the specimens and osteoid formation was also remarkable (Fig. 6). The tumor was diagnosed as high-grade osteosarcoma secondary to a benign GCT. Despite above-knee amputation and chemotherapy, scapular and lung metastases developed. The patient died five months after the above knee amputation.

DISCUSSION

GCT is known to be able to evolve into malignant tumor. McGrath (1972) classified such tumors into three types: primary, evolutionary and secondary. “Primary” is for tumors that are malignant from the outset, “evolutionary” for typical tumors that progress to a malignant form within a short period, and “secondary” for typical tumors that undergo sarcomatous changes after a relatively long symptom-free period, and usually developed after irradiation. In the literature the classification “evolutionary” has been applied for spontaneous malignant transformation of GCTs after a symptom-free period, whilst “secondary”



Fig. 5. Coronal T1-weighted fat suppressed MR image of the right distal femur after gadolinium enhancement, in 2004. Enhancement (arrow) was apparent and irregular in the lateral femoral condyle.

has been used for post-irradiation malignancy. In reports of malignant transformation of GCTs the tumors were irradiated at the primary treatment. On the other hand, malignant transformation without radiation therapy, as in our case, is very rare. Referring to the literatures, our case would be classified as evolutionary malignancy.

There have been 29 cases of malignancy in GCTs without radiation therapy in the English literature (Mnaymneh et al. 1964; Johnson et al. 1969; Dahlin et al. 1970; McGrath 1972; Nascimento et al. 1979; Sanerkin 1980; Sundaram et al. 1982; Boriani et al. 1986; Rock et al. 1986; Campanacci et al. 1987; Gitelis et al. 1989; Meis

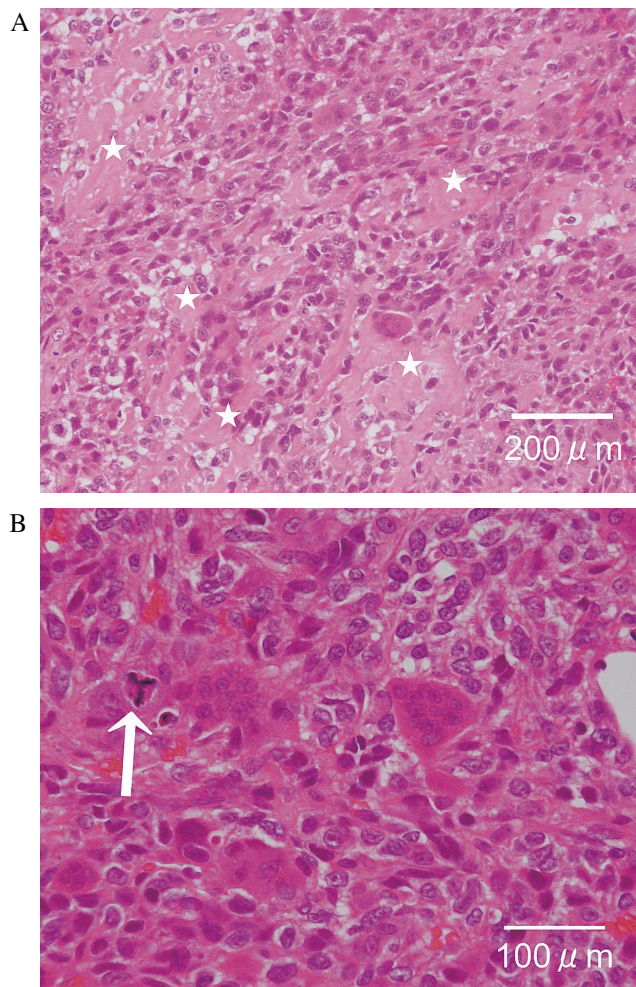


Fig. 6. Histopathological study of the specimen from open biopsy of the secondary lesion. Atypical nuclei, anisokaryosis and a lacy pattern of osteoids (★) indicating osteosarcoma. (A: $\times 100$). Multinuclear giant cells are scattered in dense aggregations of mononuclear cells with highly atypical nuclei. An abnormal mitosis can be observed (arrow) (B: $\times 200$).

et al. 1989; Zhu et al. 1990; Hefti et al. 1992; Ortiz-Cruz et al. 1995; Brien et al. 1997; Sakkars et al. 1997; Mori et al. 2000; Marui et al. 2001; Bertoni et al. 2003; Grote et al. 2004). In those cases, 8 were primary and 21 were evolutionary malignancy. In the cases of evolutionary malignancy, the interval between the discovery of GCTs and malignant transformation ranged from 1.4 years to 25 years (average 9.9 years). Nine of the patients experienced malignant transformation more than 10 years after the initial diagnosis of

GCTs. In this sense the 10 year interval of the present case would not be so uncommon. It is questionable about when such tumors underwent malignant transformation. In other words, there may have been malignant portions in the primary lesion. However, considering the aggressiveness of these tumors after malignant transformation, this would seem unlikely.

In the secondary malignant transformation in GCTs with or without radiation therapy, Rock et al. (1986) reported that fibrosarcoma developed three times more frequently than osteosarcoma. On the other hand, in the 21 cases of evolutionary malignancy in GCTs in the literature, histopathological diagnoses were fibrosarcoma in eight cases, osteosarcoma in seven, and malignant fibrous histiocytoma in six. No specific affinity was indicated concerning the histological type in evolutionary malignancy as compared with secondary malignancy. The histological examination in the present case demonstrated high-grade osteosarcoma. Hutter et al. (1962) and Dahlin et al. (1970) defined "malignant giant-cell tumor" as a sarcoma either juxtaposed to the zone of a typical giant-cell tumor or occurring at the site of the previous benign GCT. Although such a juxtaposition was not clearly noted in the present case, the osteosarcoma had definitely occurred at the site of the previous benign GCT. The fact that osteoclastic giant cells were abundant in the tumor, also confirmed the point.

The prognosis of secondary malignancy in GCTs has been reported to be poor. Nascimento et al. (1979) reported that the prognosis of secondary malignant GCT is worse than primary malignant GCT. However, the reported prognosis seemed to vary according to the generation. In the reports during the 1980s and earlier (Dahlin et al. 1970; Sanerkin 1980; Sundaram et al. 1982; Boriani et al. 1986), most patients with evolutionary malignancy in GCTs died 1 year or less after the malignancy had been discovered, while such patients survived 1 year or longer in the reports from the 1990s or later (Ortiz-Cruz et al. 1995; Sackers et al. 1997; Mori et al. 2000; Marui et al. 2001; Bertoni et al. 2003; Grote et al. 2004). Improvements in chemotherapy seem to contrib-

ute to the better prognosis. On the other hand, the prognosis after the appearance of malignancy is independent of the primary treatment, the histological type of the malignancy, or the duration between the onset of the primary benign GCT and the appearance of malignancy.

Although osteosarcoma arising from a benign GCT without radiation in the primary lesion is very rare, this should be considered as a differential diagnosis of recurrent benign GCT.

References

- Bertoni, F., Bacchini, P. & Staals, E.L. (2003) Malignancy in giant cell tumor. *Skeletal Radiol.*, **32**, 143-146.
- Boriani, S., Sudanese, A., Baldini, N. & Picci, P. (1986) Sarcomatous degeneration of giant cell tumours. *Ital. J. Orthop. Traumatol.*, **12**, 191-199.
- Brien, E.W., Mirra, J.M., Kessler, S., Suen, M., Ho, J.K. & Yang, W.T. (1997) Benign giant cell tumor of bone with osteosarcomatous transformation ("dedifferentiated" primary malignant GCT): report of two cases. *Skeletal Radiol.*, **26**, 246-255.
- Campanacci, M., Baldini, N., Boriani, S. & Sudanese, A. (1987) Giant-cell tumor of bone. *J. Bone Joint. Surg. Am.*, **69**, 106-114.
- Dahlin, D.C., Cupps, R.E. & Johnson, E.W., Jr. (1970) Giant-cell tumor: a study of 195 cases. *Cancer*, **25**, 1061-1070.
- Gitelis, S., Wang, J.W., Quast, M., Schajowicz, F. & Templeton, A. (1989) Recurrence of a giant-cell tumor with malignant transformation to a fibrosarcoma twenty-five years after primary treatment. A case report. *J. Bone Joint. Surg. Am.*, **71**, 757-761.
- Grote, H.J., Braun, M., Kalinski, T., Pomjanski, N., Back, W., Bleyl, U., Bocking, A. & Roessner, A. (2004) Spontaneous malignant transformation of conventional giant cell tumor. *Skeletal Radiol.*, **33**, 169-175.
- Hefti, F.L., Gachter, A., Remagen, W. & Nidecker, A. (1992) Recurrent giant-cell tumor with metaplasia and malignant change, not associated with radiotherapy. A case report. *J. Bone Joint. Surg. Am.*, **74**, 930-934.
- Hutter, R.V., Worcester, J.N., Jr., Francis, K.C. & Foote, F.W., Jr., S.F.W. (1962) Benign and malignant giant cell tumors of bone. A clinicopathological analysis of the natural history of the disease. *Cancer*, **15**, 653-690.
- Johnson, K.A. & Riley, L.H., Jr. (1969) Giant cell tumor of bone. An evaluation of 24 cases treated at the Johns Hopkins Hospital between 1925 and 1955. *Clin. Orthop. Relat. Res.*, **62**, 187-191.
- Marui, T., Yamamoto, T., Yoshihara, H., Kurosaka, M., Mizuno, K. & Akamatsu, T. (2001) De novo malignant transformation of giant cell tumor of bone. *Skeletal Radiol.*, **30**, 104-108.
- McGrath, P.J. (1972) Giant-cell tumour of bone: an analysis of fifty-two cases. *J. Bone Joint. Surg. Br.*, **54**, 216-229.
- Meis, J.M., Dorfman, H.D., Nathanson, S.D., Hagggar, A.M. & Wu, K.K. (1989) Primary malignant giant cell tumor of bone: "dedifferentiated" giant cell tumor. *Mod. Pathol.*, **2**, 541-546.
- Mnaymneh, W.A., Dudley, H.R. & Mnaymneh, L.G. (1964) Giant-Cell Tumor Of Bone. An Analysis And Follow-Up

- Study Of The Forty-One Cases Observed At The Massachusetts General Hospital Between 1925 And 1960. *J. Bone Joint. Surg. Am.*, **46**, 63-75.
- Mori, Y., Tsuchiya, H., Karita, M., Nonomura, A., Nojima, T. & Tomita, K. (2000) Malignant transformation of a giant cell tumor 25 years after initial treatment. *Clin. Orthop. Relat. Res.*, **381**, 185-191.
- Nascimento, A.G., Huvos, A.G. & Marcove, R.C. (1979) Primary malignant giant cell tumor of bone: a study of eight cases and review of the literature. *Cancer*, **44**, 1393-1402.
- Ortiz-Cruz, E.J., Quinn, R.H., Fanburg, J.C., Rosenberg, A.E. & Mankin, H.J. (1995) Late development of a malignant fibrous histiocytoma at the site of a giant cell tumor. *Clin. Orthop. Relat. Res.*, **318**, 199-204.
- Rock, M.G., Sim, F.H., Unni, K.K., Witrak, G.A., Frassica, F.J., Schray, M.F., Beabout, J.W. & Dahlin, D.C. (1986) Secondary malignant giant-cell tumor of bone. Clinico-pathological assessment of nineteen patients. *J. Bone Joint. Surg. Am.*, **68**, 1073-1079.
- Sackers, R.J., van der Heul, R.O., Kroon, H.M., Taminiau, A.H. & Hogendoorn, P.C. (1997) Late malignant transformation of a benign giant-cell tumor of bone. A case report. *J. Bone Joint. Surg. Am.*, **79**, 259-262.
- Sanerkin, N.G. (1980) Malignancy, aggressiveness, and recurrence in giant cell tumor of bone. *Cancer*, **46**, 1641-1649.
- Sundaram, M., Martin, A.S. & Tayob, A.A. (1982) Case report 182: osteosarcoma arising in giant cell tumor of tibia. *Skeletal. Radiol.*, **7**, 282-285.
- Zhu, X.Z. & Steiner, G.C. (1990) Malignant giant cell tumor of bone: malignant transformation of a benign giant cell tumor treated by surgery. *Bull. Hosp. Jt. Dis. Orthop. Inst.*, **50**, 169-176.
-