Acta Orthop. Belg., 2012, **78**, 279-284

CASE REPORT

Late development of malignant fibrous histiocytoma at the site of a giant cell tumour 38 years after initial surgery

Keiichi MURAMATSU, Koichiro IHARA, Tomoyuki MIYOSHI, Yasuhiro KAWAKAMI, Daisuke NAKASHIMA, Toshihiko TAGUCHI

From Yamaguchi University School of Medicine, Yamaguchi, Japan

The authors report on a patient who developed a malignant fibrous histiocytoma at the site of a benign giant cell tumour, which had been treated by curettage 38 years previously. This latency period is, to their knowledge, the longest yet reported. This female patient was initially treated for a benign giant cell tumour of the proximal tibia when she was 33 years old ; she underwent curettage and Kiel bone grafting. She had not received radiation therapy. Twenty eight years later, she underwent a second operation due to recurrence of a tumour. No specific histological diagnosis was possible : histology suggested a benign tumour, however compatible with a low-grade malignant potential but not associated with giant cell tumour. The patient underwent a third operation, with extensive curettage and total knee arthroplasty 38 years after the initial surgery, because of progressive knee pain. Postoperative histopathology study showed high-grade malignant fibrous histiocytoma. Finally, she underwent above-knee amputation because of uncontrollabloe progression of the tumour. The use of xenogenic bone graft, bone cement and associated bone necrosis potentially contributed to the development of a malignant tumour adjacent to the primary giant cell tumour.

Keywords : giant cell tumour ; malignant fibrous histiocytoma ; malignant transformation ; bone.

INTRODUCTION

Giant cell tumour (GCT) of bone develops adjacent to the subchondral bone of major joints and shows a locally destructive behaviour. GCT is thought to originate at the metaphyseo-epiphyseal junction and may extend into the metaphysis. The distal femur and proximal tibia are most often involved. Although GCT is classified histologically as a benign tumour, its clinical course varies and can sometimes mimic a malignant tumour. Local recurrence rates following surgery have been reported to range from 4 to 50% (*9,10*).

Malignant transformation at the site of a previously treated GCT is a rare but recognized complication. In most cases, the primary GCT was treated with radiation therapy. To our knowledge, only 16 cases have been well documented in the

■ Keiichi Muramatsu, MD, PhD, Orthopaedic surgeon, Associate professor.
■ Tomoyuki Miyoshi, MD, Orthopaedic surgeon, Fellow.
■ Yasuhiro Kawakami, MD, Orthopaedic surgeon, Resident.
■ Daisuke Nakashima, MD, Orthopaedic surgeon, Resident.
■ Toshihiko Taguchi, MD, Orthopaedic surgeon, Professor.
Department of Orthopaedic Surgery, Yamaguchi University School of Medicine, Yamaguchi, Japan.
■ Koichiro Ihara, Orthopaedic surgeon, Chairman.
Department of Orthopaedic Surgery, Kanmon Medical Center, Yamaguchi, Japan.
Correspondence : Keiichi Muramatsu, Department of Orthopaedic Surgery, Yamaguchi University School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. E-mail : muramatu@yamaguchi-u.ac.jp

No benefits or funds were received in support of this study

English literature in which secondary malignancies have arisen in non-irradiated areas (*1-5,7,8,11,12,14*) (Table I). The time interval between primary surgery for GCT and the diagnosis of malignant transformation has been very long, ranging from 7 to 25 years.

We report here a case of malignant fibrous histiocytoma (MFH) that arose at the site of a previously curetted GCT 38 years after initial surgery. This patient had not received radiation treatment. We discuss the aetiology of this MFH and the most appropriate treatment.

CASE REPORT

A 33-year-old woman presented with left knee pain in 1973. She consulted the general hospital in her home town and a bone tumour was identified at the proximal tibia. According to her medical chart, an osteolytic multi-lobular tumour extended into the medial plateau. (Radiographs and histological slides were lost and unavailable for publication because the initial operation was performed 38 years previously). The appearance and epiphyseal location suggested a GCT of the bone. Curettage and xenogeneic Kiel bone grafting was performed in the same year. A yellowish and brown tumour was resected piecemeal. Histologically, the tumour comprised of many multinucleated giant cells arranged in a background of mononuclear stromal cells. There were few findings of mitosis and atypism in the tumour cells. The tumour was diagnosed as a typical benign GCT.

After surgery, the patient was asymptomatic for the following 28 years until 2002, when she began to experience progressive pain in her left knee. She was referred to our university hospital for an unknown bone tumour of the proximal tibia. A radiograph showed an osteolytic lesion with unclear osteosclerotic border, involving the epiphyseal region of the medial tibial plateau (Fig. 1 A & B). Magnetic resonance imaging (MRI) showed a tumour enhanced by gadolinium (Fig. 2). No cortical destruction or extra-osseous lesions were observed. From the pre-operative images, the tumour was suspected of being a recurrence of the GCT, or a low-grade malignancy. We performed extensive curettage and cryosurgery using liquid nitrogen. Cortical and subchondral bones were not damaged and the macroscopic tumour appearance was yellowish. No residual Kiel bone was observed and the intra-operative pathology report did not show any malignancy. The bone defect following tumour curettage was filled with 25 ml of polymethyl methacrylate (Surgical Simplex®). Histological examination revealed spindle-shaped tumour cells with a storiform pattern. Proliferation of multinucleated giant cells associated with osteoclasts was not observed in the specimen, but varying amounts of fibrosis were present. Some cytological atypia, necrosis and atypical mitosis were identified. Based on the overall histopathology findings, the diagnosis was a benign bone tumour compatible with low-grade malignant potential but not associated with GCT (Fig. 3).

The patient was asymptomatic for 7 years until 2010, when she again experienced left knee pain. Radiography showed that bone cement was present just beneath the medial subchondral bone at the tibial plateau (Fig. 4 A & B). Computed tomography revealed a fracture of the subchondral bone. MRI showed an area with abnormal signal adjacent to the bone cement (Fig. 5). Pre-operatively, the diagnosis was late collapse of the subchondral bone at the medial tibial plateau. Removal of the bone cement and reconstruction with total knee arthroplasty and fibula grafting was performed. Surprisingly, the histological findings were completely different to those of the previous lesion treated in 2002. Post-operative histopathological examination showed a high-grade MFH consisting of anaplastic cells with atypical nuclei juxtaposed with zones of the previous lesion (Fig. 6). The Ki67 monoclonal antibody index was approximately 20% positive, thus showing high malignancy. No evidence was found of multinucleated giant cells or GCT.

Following the third surgical intervention, the malignant tumour progressively invaded the tibial canal and the distal end of the tibia, leading to a pathological fracture of the tibia. In February 2011, the patient underwent an above-knee amputation. Post-operative chemotherapy was not given due to her age. She had no local recurrence or distant metastasis at final follow-up of 1 year.

Table I. — Well documented case reports of late development of malignant tumour at the site of a giant cell tumour, not associated with radiotherapy

Author/ year (ref)	Age (Initial) / sex	Location	Primary treatment	Interval (yrs)	Symptom	Radiology	Histology	Final treatment	Metastasis	Prognosis
Rock/ 1986 (*12*)	35/ F	Dist femur	Curettage	22	NR	NR	Fibrosarcoma	Amputation	NR	NR
Gitelis/ 1989 (*3*)	63/ M	Dist femur	Excision	25	Swelling	Osteolytic	Fibrosarcoma	Amputation	Multiple	NR
Hefti/ 1992 (*5*)	31/ M	Prox tibia	Curettage	7	Pain	Osteoblastic	Osteosarcoma	Chemo Amputation	Lung	DOD
Ortiz-Cruz/ 1995 (*11*)	29/ M	Dist femur	Curettage	18	Pain	Osteolytic	MFH	Chemo Wide resect	None	NED
Sakkers/ 1997 (*14*)	25/ M	Prox tibia	Curettage	20	Pain	Osteolytic	MFH	Chemo Wide resect	Multiple	NR
Brien/ 1997 (*2*)	18/ M	Prox tibia	Curettage	6	Chest pain	Healed	Osteosarcoma	Thoracotomy	Lung	DOD
Mori/ 2000 (*8*)	28/ F	Prox tibia	Curettage	25	Pain	Osteolytic	MFH	Chemo Wide resect	None	NED
Marui/ 2001 (*8*)	31/F	Prox tibia	Curettage	15	Pain	Osteolytic	MFH	Chemo Amputation	None	NED
	41/ M	Dist femur	Curettage	13	Pain	Osteolytic	Osteosarcoma	Chemo Amputation	Lung	DOD
Bertoni/ 2003 (*1*)	37/M	Dist femur	Curettage	16	NR	NR	MFH	Chemo Amputation	None	NED
	77/ M	Dist femur	Curettage	27	NR	NR	Osteosarcoma	Radiotherapy	Lung	DOD
	42/ M	Prox tibia	Curettage	16	NR	NR	Osteosarcoma	Amputation	None	NED
	47/ M	Prox femur	Curettage	22	NR	NR	Osteosarcoma	Chemo Radiotherapy	Lung	DOD
	72/ M	Prox tibia	Curettage	27	NR	NR	Osteosarcoma	Amputation	None	NED
	62/ F	Prox radius	Curettage	7	NR	NR	Osteosarcoma	Chemo Resection	None	NED
Grote/ 2004 (*4*)	35/ F	Iliac crest	Resection	10	Swelling	Osteolytic	Osteosarcoma	Chemo Wide resect	None	NED
Present case	33/ F	Prox Tibia	Curettage	38	Pain	Osteolytic	MFH	Amputation	None	NED

NR = not reported ; DOD = dead of disease ; NED = no evidence of disease ; Chemo = chemotherapy ; MFH = malignant fibrous histiocytoma.

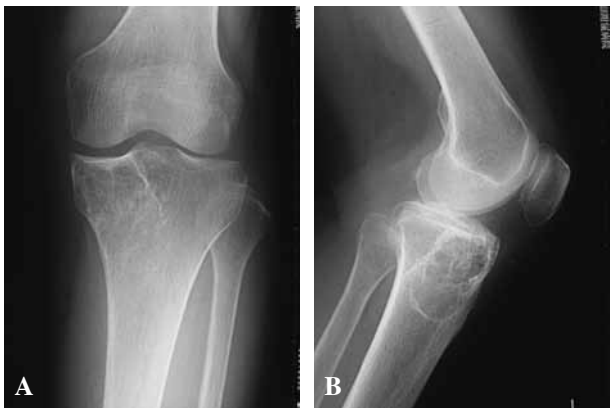

Fig. 1A & B. — Anteroposterior and lateral radiograph of the left knee in 2002, showing an osteolytic lesion with unclear osteosclerotic border involving the epiphyseal region of the medial tibial plateau.

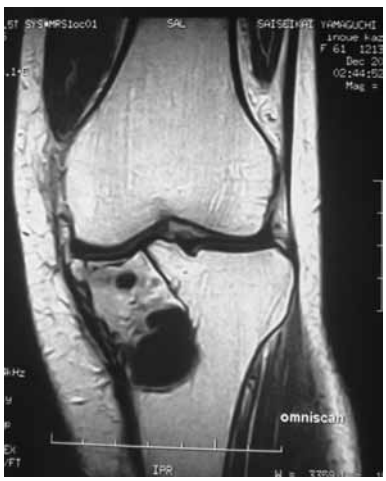

Fig. 2. — Magnetic resonance imaging (MRI) in 2002, showing a tumour with gadolinium enhancement.

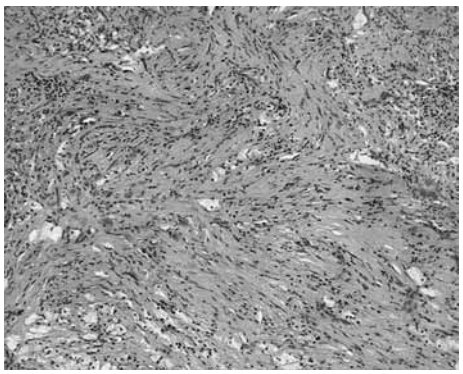

Fig. 3. — Curettage specimen in 2002, showing spindle-shaped tumour cells with a storiform pattern. Proliferation of multinucleated giant cells associated with osteoclasts was not observed. Some cytological atypia, necrosis and atypical mitosis were identified. The diagnosis at the second curettage was a benign bone tumour compatible with low-grade malignant potential but not associated with GCT (haematoxylin and eosin ; original magnification, ×200).

DISCUSSION

Malignant transformation of GCT occurs most frequently after radiation therapy (*1*). The incidence of a secondary malignancy arising at the site of a previously irradiated GCT ranges from 3.6% to 30% (*1*). Previously described malignancies occurring secondary to GCT have been fibrosarcoma, osteosarcoma and MFH (*1-5,7,8,11,12,14*). The survival rate for these patients has been poor due to the aggressive behaviour of such tumours. It is uncertain whether the sarcomas arise as a side-effect of the irradiation, or through malignant transformation of the GCT independently of the irradiation.

A review of the literature by Ortiz-Cruz *et al* (*11*) revealed 16 cases of malignant transformation of GCT without radiation therapy. These cases involved primary malignant GCT and early recurrence within 5 years. To our knowledge, only 16 cases have been documented in which secondary malignancies have subsequently arisen in non-irradiated areas (Table I). Among them, Bertoni *et al* (*1*) reported 5 cases with secondary malignancy after surgical treatment alone. The time interval between primary surgery for GCT and diagnosis of the malignant transformation ranged from 7 to 25 years. There were 7 cases with an interval of more than 20 years.

Similar to cases with irradiated GCT, our case raises the question of whether these tumours represent long-term malignant transformation of the original tumour, or whether they are *de novo* primary tumours. Some authors believe that spontaneous malignant transformation of benign GCT can occur without either radiation or surgery (*3,12*). The only evidence to support malignant transformation of a benign GCT includes documentation of a pre-existing benign GCT, or areas of benign GCT adjacent to sarcomatous elements. In the case

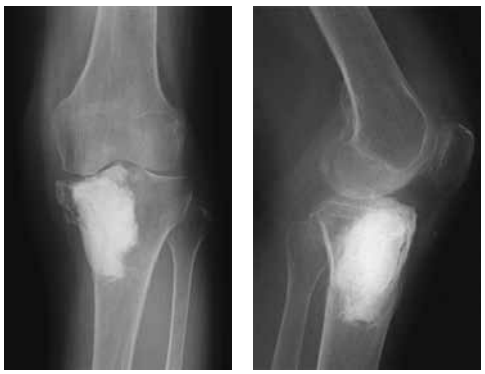

Fig. 4A & B. — Anteroposterior and lateral radiograph in 2010, showing osteolytic lesion surrounding primary lesion. Bone cement was present just beneath the medial subchondral bone at the tibial plateau.

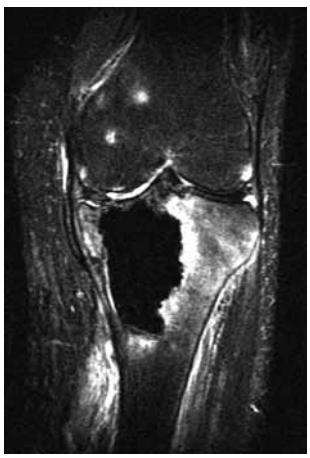

Fig. 5. — MRI in 2010, showing an area with abnormal signal adjacent to the bone cement.

presented here, no residual GCT cells were present at the second operation in 2003. The final tumour diagnosed in 2010 appeared to arise from the bone surrounding the bone cement or from xenogeneic bone graft transplanted 38 years earlier. It seems reasonable to presume that this case may be a *de novo* MFH arising from bone adjacent to the primary lesion, rather than late malignant transformation of a benign GCT.

There are several possibilities as to why MFH occurred adjacent to the primary lesion. Considering the clinical history of the patient, the first possibility is associated with use of the Kiel bone. Kiel bone was frequently used during the

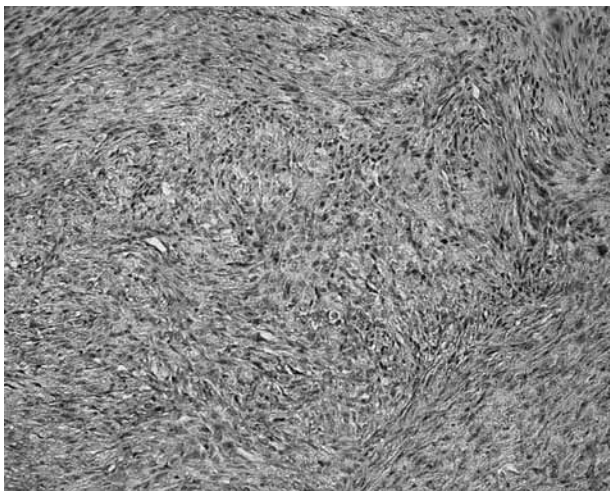

Fig. 6. — Curettage specimen in 2010, showing a high-grade MFH consisting of anaplastic cells with atypical nuclei juxtaposed with zones of the previous lesion. The MIB-index was approximately 20% positive, thus showing high malignancy. No evidence was found of multinucleated giant cells or GCT (haematoxylin and eosin ; original magnification, ×200).

1970's. It was commercially available and consisted of deproteinised bone prepared from freshly killed calves. The bone was extracted with hydrogen peroxide, treated with fat solvents and sterilized by gamma radiation. Salama and Weissman used Kiel bone in 28 patients with benign bone tumour, pseudoarthrosis or traumatic bone defect (*13*). They reported one infection but no malignant transformation after a follow-up period of more than 6 months. To date, there have been no reports describing sarcoma transformation associated with a Kiel bone graft.

Another possibility is the association with bone necrosis and cement. Ortiz-Cruz *et al* (*11*) reported a case with MFH arising in necrotic bone at the site of a previously curetted GCT 18 years after the initial surgery. Histologically, no residual GCT was present and the tumour appeared to arise from the area surrounding the bone graft. To our knowledge, 12 cases have been reported to date describing the presence of sarcoma at the site of total joint replacement using bone cement. Of these, the most frequent tumour type was pleomorphic MFH with abundant giant cells. The time interval between arthroplasty with cementing and malignant transformation ranged from 14 months to 15 years.

Lucas *et al* presented two cases following total hip arthroplasty (*6*). Although the aetiology of arthroplasty-associated sarcoma is uncertain, Lucas *et al* and other authors speculated that a thin mantle of necrotic bone forms at the interface between bone and cement. This is caused by the heat produced during polymerization of the methylmethacrylate bone cement. The necrotic mantle could play a role in carcinogenesis by inducing a chronic repair process and infiltration of histiocytic components that eventually leads to malignancy.

The present case appears to be unique for two reasons. First, most sarcomas that develop from a pre-existing GCT occur within 5 years of treatment of the primary tumour. Our patient experienced late development of MFH after treatment of a pre-existing GCT that was not associated with irradiation, 38 years after the initial diagnosis was made. This latency period is, to our knowledge, the longest yet reported. Second, there has been no previous report associating Kiel bone with the occurrence of a malignant tumour. If the tumour curetted 28 years after the initial GCT surgery had already developed into MFH, the late development of malignant tumour probably has some association with Kiel bone. The use of bone cement and associated bone necrosis potentially contributed to the development of a malignant tumour adjacent to the primary GCT lesion.

REFERENCES

1. **Bertoni F, Bacchini P, Staals EL.** Malignancy in giant cell tumor of bone. *Cancer.* 2003 ; 97 : 2520-2529.
2. **Brien EW, Mirra JM, Kessler S *et al.*** Benign giant cell tumor of bone with osteosarcomatous transformation ("dedifferentiated" primary malignant GCT) : report of two cases. *Skeletal Radiol* 1997 ; 26 : 246-255.
3. **Gitelis S, Wang JW, Quast M, Schajowicz F, Templeton A.** 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* 1989 ; 71-A : 757-761.
4. **Grote HJ, Braun M, Kalinski T *et al.*** Spontaneous malignant transformation of conventional giant cell tumor. *Skeletal Radiol* 2004 ; 33 : 169-175.
5. **Hefti FL, Gächter A, Remagen W, Nidecker A.** Recurrent giant-cell tumor with metaplasia and malignant change, not associated with radiotherapy. A case report. *J Bone Joint Surg* 1992 ; 74-A : 930-934.
6. **Lucas DR, Miller PR, Mott MP, Kronick JL, Unni KK.** Arthroplasty-associated malignant fibrous histiocytoma : two case reports. *Histopathology* 2001 ; 39 : 620-628.
7. **Marui T, Yamamoto T, Yoshihara H *et al.*** De novo malignant transformation of giant cell tumor of bone. *Skeletal Radiol* 2001 ; 30 : 104-108.
8. **Mori Y, Tsuchiya H, Karita M *et al.*** Malignant transformation of a giant cell tumor 25 years after initial treatment. *Clin Orthop Relat Res* 2000 ; 381 : 185-191.
9. **Muramatsu K, Ihara K, Taguchi T.** Treatment of giant cell tumor of long bones : clinical outcome and reconstructive strategy for lower and upper limbs. *Orthopedics* 2009 ; 32 : 491-494.
10. **Ofluoglu O.** Aggressive treatment of giant cell tumour with multiple local adjuvants. *Acta Orthop Belg* 2008 ; 74 : 831-836.
11. **Ortiz-Cruz EJ, Quinn RH, Fanburg JC, Rosenberg AE, Mankin HJ.** Late development of a malignant fibrous histiocytoma at the site of a giant cell tumor. *Clin Orthop Relat Res* 1995 ; 318 : 199-204.
12. **Rock MG, Sim FH, Unni KK *et al.*** Secondary malignant giant-cell tumor of bone. Clinicopathological assessment of nineteen patients. *J Bone Joint Surg* 1986 ; 68-A : 1073-1079.
13. **Salama R, Weissman SL.** The clinical use of combined xenografts of bone and autologous red marrow. A preliminary report. *J Bone Joint Surg* 1978 ; 60-B : 111-115.
14. **Sakkers RJ, van der Heul RO, Kroon HM, Taminiau AH, Hogendoorn PC.** Late malignant transformation of a benign giant-cell tumor of bone. A case report. *J Bone Joint Surg* 1997 ; 79-A : 259-262.