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CASE REPORT

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Malignancy in giant cell tumor

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Abstract Malignant giant cell tumor is a confusing term that in the past has been used to describe different types of giant cell-rich tumors. We try to clarify this term in this report. We consider two types of malignancy in giant cell tumor of bone: "primary" when it arises in juxtaposition to a benign giant cell tumor and 'secondary' when it arises at the site of a previously treated giant cell tumor. Here we present a case of primary malignancy in giant cell tumor that was initially not recognized as a malignancy. On radiography and histology of frozen sections the lesion had the appearance of a conventional giant cell tumor of bone. After curettage, the permanent histology slides showed areas of highly malignant osteosarcoma juxtaposed to areas of benign giant cell tumor. The patient was treated with chemotherapy and wide resection of the tumor.

Keywords Giant cell tumor of bone · Malignant giant cell tumor · Malignancy in giant cell tumor of bone · Femur · Radiographs

Introduction

Malignant giant cell tumor of bone has become a confusing term because of the inclusion of many giant cell-rich sarcomas not related to giant cell tumor of bone (GCT) [1]. The term "malignancy in giant cell tumor" may overcome this problem in semantics [2]. Malignancy in GCT can be classified as primary when it arises in juxtaposition to a benign giant cell tumor (synchronous malignancy) [3, 4, 5], or secondary when it arises at the site of a previously treated GCT (secondary metachronous malignancy). Most malignancies in GCT are secondary, usually after previous radiation therapy and less commonly after a latent period and previous curettage [6, 7, 8]. We report a case of primary malignancy in GCT. Clinical, radiographic and pathology features are analyzed.

Case report

In March 2000 a 24-year-old man was seen at our institution with a 4-year history of right knee pain. In 1998 imaging studies done elsewhere had shown a lytic lesion in the right distal femur (Fig. 1). After a needle-biopsy the differential diagnosis had been GCT or aneurysmal bone cyst, but no treatment was carried out. On presentation at our institution the lytic lesion in the femoral condyle had an appearance on radiography similar to two years earlier (Fig. 2). Computed tomography (CT) disclosed a lytic lesion with intact cortex and well-defined margins (Fig. 3).

An incisional biopsy with frozen sections was done. The diagnosis of the frozen section was GCT and a thorough curettage was performed. Phenol and cement were used as adjuvants. The permanent histology slides (Fig. 4) showed fields of grade 4 fibroblastic osteosarcoma side by side with areas of GCT (primary malignancy in GCT – synchronous). After a course of neo-adjuvant chemotherapy a wide resection and reconstruction with a prosthesis was performed. No residual tumor was detected on the cement borders with the host bone. The patient was alive and well 15 months after the last surgical treatment. There were no signs of local recurrence or metastasis.

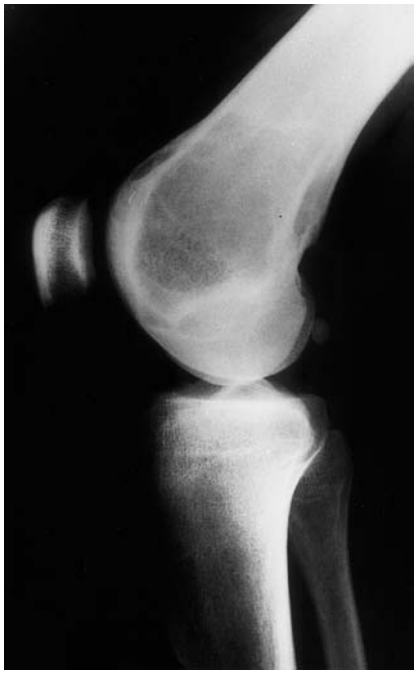

Fig. 1 Lateral radiograph 2 years prior to presentation at our institution showing a lytic lesion in the distal femur

Discussion

In the literature the term "malignant GCT" is confusing, complicated and with many different histological meanings [1]. Sarcomas rich in giant cells (osteosarcoma and malignant fibrous histiocytoma), GCT that metastasize, aggressive locally recurrent GCT and GCT with varying degrees of anaplasia have all been included under the rubric of malignant GCT. Jaffe et al. [9] and Sanerkin [10] tried to overcome this problem by defining a grading system that would predict the prognosis of GCT. However, their grading systems were difficult to apply and did not correlate with the clinical behavior of these tumors. More specifically the grading systems did not appear to predict local recurrence, aggressiveness and/or metastases.

A reproducible diagnostic criteria of malignant GCT was proposed by Hutter et al. [11] and Dahlin et al. [12]. Malignant GCT was considered a sarcoma either in a pre-existing GCT or in conjunction with it. Unni [6] avoided the term "malignant GCT"' because it was confusing, and subdivided "malignancy in GCT" into primary and secondary malignancies. Primary malignancies in GCT are those lesions in which a high-grade sarcomatous component is present de novo in conjunction with a GCT. Secondary malignancies in GCT are represented by high-grade sarcomas occurring as a "recurrence" at the site of a previously treated GCT. Most malignancies in GCT are secondary and occur several years after radiation therapy (radiation-induced sarcomas). A few cases of secondary malignancy in GCT are sarcomas that arise in a previously documented GCT either treated by surgery only or after a long latent period: "evolutionary malignant GCT" [13]. Primary malignancies in GCT are very rare and are considered to represent dedifferentiation in GCT [4, 6]. In the series from the Mayo Clinic in 1996 [6], of the 35 malignancies in GCT 30 were sec-

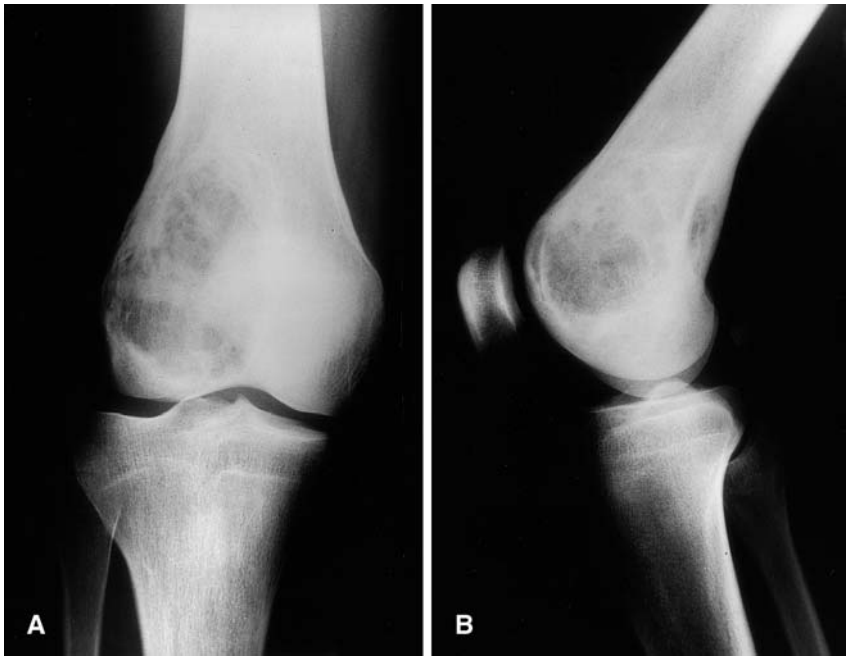

Fig. 2A, B Anteroposterior and lateral radiographs at the time of hospital admission showing the osteolytic lesion involving the meta-epiphyseal region of the distal femur. There were no significant changes in comparison with the radiographs taken 2 years earlier

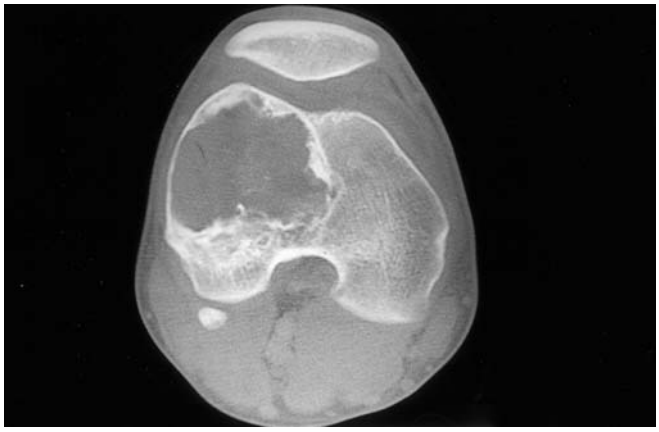

Fig. 3 CT image showing a large area of low signal abnormality in the distal femur. The destructive lesion had well-defined sclerotic borders. No cortical breakthrough or extension into the soft tissue was present. Minimal focal sclerosis was seen in the lytic lesion

ondary. Of the secondary malignancies in GCT 24 were post-radiation sarcomas and six occurred after surgical treatment only. There were five primary malignancies in GCT of which the clinical and radiographic features suggested a diagnosis of benign GCT. Histologically in these cases there were areas of typical GCT juxtaposed to areas of high-grade spindle cell sarcoma. The largest series of primary malignant GCT was studied at the Memorial Hospital by Nascimento et al. [3]. They reported eight cases defined as tumors with characteristic features of GCT but with many fields showing sarcomatous features of the stromal cells. Cases showing limited, focal, microscopic areas of sarcomatous patterns were not included in the study. As only one of the patients died, the authors stated that primary malignant GCT was a separate entity with a more favorable clinical behavior compared with the secondary type.

Meis et al. [4] described one case of primary malignant GCT of the left ischium (GCT and concurrent sarcoma arising de novo). Histologically there was GCT juxtaposed to high-grade malignant fibrous histiocytoma. They recognized this histologic pattern as dedifferentiation or tumor progression and called the lesion "dedifferentiated GCT".

Occasionally GCT show focal anaplasia in the stromal cells. Layfield et al. [14] described two cases with degenerative atypia of the mononuclear stromal cells that lacked mitotic figures.

Primary malignancy in GCT is a very rare problem. There should be histologic coexistence of GCT and stromal cells with highly malignant histologic features in many microscopic fields to make this diagnosis.

At our institute we reviewed the cases of malignancy in giant cell tumor. The series included 17 patients seen at the institute between 1961 and 2001. Five cases were

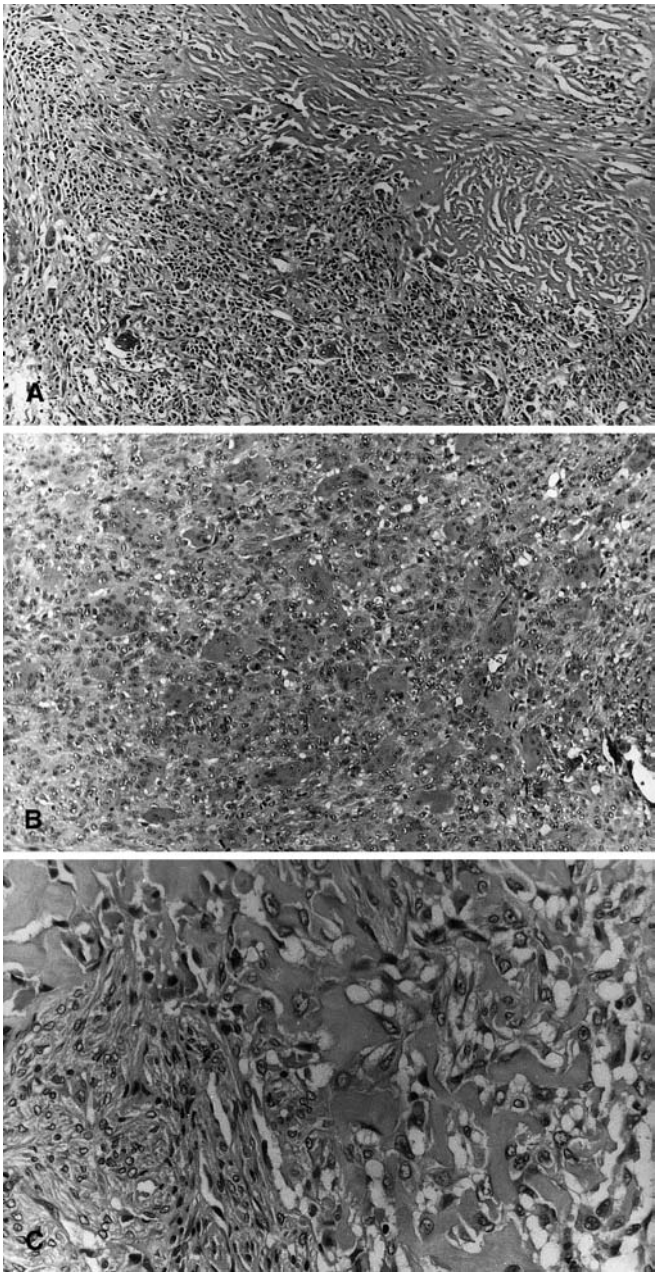

Fig. 4A–C Histology of the curetted specimen. **A** Areas with giant cells close to a sclerotic component. A distinct separation front between the giant cell tumor component and the sarcomatous component was seen (H&E, ×160). **B** High-power view. Giant multinucleated cells were embedded in a round oval cell stroma. These were the morphologic features of the frozen sections and of some areas in the permanent sections (H&E, ×250). **C** High-power view of sclerotic areas close to the giant cell tumor component. Highly malignant cells with collagen and osteoid stroma were present in the grade 4 fibroblastic osteosarcoma component (H&E, ×350)

primary malignancies in GCT and 12 were secondary, of which six occurred after radiation therapy and the other six arose spontaneously. The age at the time of diagnosis of the primary malignancies in GCT ranged from 20 to 68 years (median 62 years). All five patients were male and all lesions occurred in the meta-epiphysis of long bones. The histologic appearance of the malignant areas was that of osteosarcoma in four cases and of malignant fibrous histiocytoma in one case. Two patients had lung metastasis: one died 8 months after the diagnosis, one is alive at 40 months. The other three have no evidence of disease at 2, 15 and 161 months respectively.

The primary malignancies in GCT have to be distinguished from benign GCT. This case report shows that this differentiation can be difficult, as the clinical and radiographic appearances of these lesions can be similar. Moreover it shows that on histology the diagnosis of primary malignancy in GCT can initially be missed when a frozen section or biopsy shows only areas of benign giant cell tumor. Detailed study of the permanent histology slides is necessary to reveal the malignancy in order to start appropriate treatment immediately.

Malignant giant cell tumor, malignancy in giant cell tumor, and dedifferentiated giant cell tumor are all terms that have been used to describe the entity we are reporting. Our preference is "malignancy in giant cell tumor". The critical issue, however, is to recognize this tumor for what it is and treat it as a sarcoma and not a giant cell tumor.

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