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Cytogenetic Abnormalities in a Rare Case of Giant Cell Osteogenic Sarcoma

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Abstract

The cytogenetic analysis of a rare, nonirradiated case of giant cell tumor of bone with osteogenic sarcoma transformation is presented for the first time in a 19-year-old female. Telomeric associations involving 4p, 8p, 11p, 14p, 17p, 17q, and 20q were observed. Additionally, monosomy 13, 11p abnormalities and marker chromosomes were identified in tumor cells. Chromosome 11 involvement, particularly 11p translocations and 11p telomeric associations, were frequently observed in the tumor cells obtained from our patient, which suggests that chromosome 11p may play a role in the development of giant cell osteogenic sarcoma.

INTRODUCTION

Giant cell tumor (GCT) is a solid, primary neoplasm of bone. It represents 5% of primary skeletal neoplasms and is characterized by its biologic aggressiveness. It has a reported local recurrence rate after nonaggressive surgical resection that may be as high as 60% and demonstrates the rare ability of benign pulmonary metastases in 2% of affected individuals [1–7]. Malignant transformation occasionally occurs in GCT. For example, giant cell sarcoma occurs in less than 1% of patients with benign GCT but can occur years after the primary lesion has been removed and/or irradiated [8]. Histologically, the transformed neoplasm often appears as a fibrosarcoma, or, when malignant osteoid is produced, an osteogenic sarcoma. The diagnosis of giant cell osteogenic sarcoma (GCT/OGS) is made when histologic zones of typical benign GCT are demonstrated adjacent to the malignant osteoid [9].

Eighty percent of individuals with GCT exhibit the cytogenetic abnormality of telomeric associations (“*tas*”), while approximately one-third of GCT cells demonstrate “*tas*” [9–11]. Four cytogenetic studies of 11 patients with OGS have been reported [12–15], and complex karyotypes with multiple cytogenetic abnormalities, particularly translocations, marker chromosomes, deletions, hyperdiploidy, and hypodiploidy, were identified.

Herein, we report the first cytogenetic study of the rare occurrence of a nonirradiated GCT/OGS from the femur of a 19-year-old white female.

CASE HISTORY

At age 16, a white female presented with progressive left knee pain of 4 months' duration. A lytic metaphyseal-epiphyseal lesion in the medial femoral condyle was noted radiographically. An intralesional resection of this primary bone neoplasm was performed. Forty grams of histologically benign GCT was identified and the curetted cavity filled with bone cement. Figures 1A and B show a representative photomicrograph of this tumor.

Two months later, the patient noted recurrent pain in the left knee. Radiographic examinations identified a tumor recurrence proximal to the cement bolus in the femur, but the chest radiogram was normal. A second operative procedure through the reopened and enlarged previous incision procured 3 grams of histologically benign GCT. The cement bolus was removed and the cavity enlarged.

Two-and-one-half years after the first surgery, the patient presented to the emergency room with acute right-sided chest pain. She had been previously asymptomatic and ambulating normally. Imaging studies of her chest revealed multiple nodules in both lungs. There had been no appreciable change in her femur radiographs. Needle biopsy of a lung nodule revealed tissue histologically identical to that from her original femur surgery, i.e., GCT. Subsequently, she underwent several cycles of multi-agent chemotherapy with Adriamycin, Cisplatin, Ifosfamide, and Mesna. Regression in the size of the lung nodules was observed and a median sternotomy was performed 11 months after onset of the chest pain. Multiple bilateral pulmonary metastasectomies were performed. The histology of the lesions revealed GCT/OGS, as malignant osteoid was identified juxtaposed to benign GCT.

Postoperatively, left knee discomfort with ambulation was noted. Radiographic evaluation of the femur revealed tumor recurrence. Three months post sternotomy, a limb-preserving wide intraarticular distal femoral resection was performed. An allograft-total knee arthroplasty composite was used for reconstruction. Histologic analysis of the multiple recurrent femoral tumor revealed GCT/OGS similar to that identified in the lungs. Figures 2A and B demonstrate a representative photomicrograph of this neoplasm.

At 1 year after GCT/OGS resection from the femur there has been no evidence of locally recurrent disease clinically or radiographically. She is an independent ambulator. Unfortunately, her chest disease has progressed despite radiotherapy.

MATERIALS AND METHODS

The GCT/OGS tumor cells from the femur were sterilely harvested, cultured, and cytogenetically analyzed. The solid tumor (1 cc) was minced and digested in an enzyme solution containing collagenase. The tumor cell suspension was centrifuged and the enzyme solution removed. The cells were placed in sterile T-25 flasks containing 4 ml RPMI 1640 cell culture medium supplemented with 20% fetal calf serum, penicillin, streptomycin, and L-glutamine. Short-term cultures (less than 4 weeks) and long-term cultures (greater than or equal to 4 weeks) were harvested when the cells reached confluency. Cells were detached with trypsin, centrifuged, and placed in T-75 flasks containing 10 ml RPMI 1640 medium for 48 hours. Colcemid (2 mcg final concentration) was added to each flask for the final 3

hours. Microscope slides were made, and the chromosomes banded with trypsinization and Giemsa stain.

RESULTS

The cytogenetic findings of the short-term cultures were significantly different from those of the long-term cultures. Twenty metaphases were analyzed from each of the short- and long-term cultures. Altogether, 15 of 20 cells from the short-term culture showed a normal female karyotype, whereas no normal cells were observed in the long-term cultures. Complete karyotypes are listed in Table 1. Of the 40 cells investigated, 25 showed an abnormal karyotype with a total of 21 telomeric associations (“*tas*”) observed (Figs. 3 and 4; Table 2). In addition, 25 structurally abnormal chromosomes, including five nonidentical marker chromosomes, were found.

Telomeric associations, translocations, and other structural chromosomal abnormalities were identified in GCT/OGS with a preponderance of alterations involving chromosome 11. Chromosome 11 was involved in nine “*tas*” and, furthermore, the breakpoint 11p15 was involved in two of six translocations. Two different 11p+ chromosomes were identified: 11p+ was identified four times and der(11)t(11;?)(p15;?) seen three times, respectively (Fig. 5). In total, 17 of the 40 cells studied (42%) contained a chromosome 11 abnormality and 18 of 47 structural abnormalities (38%) also involved chromosome 11 (Table 3).

Aside from chromosomal loss, which could be interpreted as random occurrence, an additional cytogenetic abnormality observed more than once and involving a chromosome other than chromosome 11 was a chromosome 14p+. The chromosome 14p+ was identified in six cells. Two of the six cells contained a “*tas*” involving chromosome 14p+. The termini of the short arm of chromosomes 4, 8, 14, and 17 and the long arm of chromosome 17 were each involved in three “*tas*”. There were no structural changes involving the long arm of chromosome 13; however, monosomy 13 was identified in one cell.

DISCUSSION

Cytogenetic findings of a rare case of nonirradiated GCT with OGS malignant transformation is presented for the first time. Cytogenetic analysis of cells from the recurrent tumor site in the femur was performed and multiple telomeric associations and translocations were observed. Interestingly, the cytogenetic abnormalities demonstrated from GCT/OGS tissue were similar to those seen individually in GCT and OGS tumor cells alone.

Telomeric associations (“*tas*”) are defined as end-to-end fusion of chromosomes without the loss of DNA. Rarely, telomeric associations are observed in human solid tumors such as GCT, atrial myxomas, and renal oncocyomas [10, 16–23]. GCT cells exhibit “*tas*” in approximately 80% of patients [10, 11]; however, their “*tas*” appear non-random, involving only a few chromosomes. We have analyzed cytogenically 15 patients with GCTs and found the involvement of 19q, 11p, and 20q (in descending frequency) in “*tas*” [10]. Similarly, Bridge et al. also described 11p (35 cells, most common) and 19q (10 cells, fifth most common) telomeric associations in GCTs [11]. Our patient described in this report also showed 11p involvement in eight “*tas*,” which was more frequent than any other terminus.

Multiple cytogenetic abnormalities have been identified in OGS, including complex translocations, marker chromosomes, deletions, and hyper- and hypodiploidy. The 11 reported cases of OGS studied cytogenetically suggest that the complexity of the karyotypes and numerous markers indicate a high level of chromosomal instability in these tumors [12–15]. Biegel et al. noted monosomy 13 in all of their abnormal cases, further implicating involvement of the tumor suppressor gene mapped to the long arm of 13 [14]. However, the complexity of OGS karyotypes may mask other chromosome abnormalities fundamental to this malignant neoplasm. In our study of GCT/OGS, only one cell was missing a chromosome 13 and no 13q structural abnormalities were identified.

Cytogenetic examination of our patient implicates chromosome 11 involvement, which is further supported by five reported cases of OGS with chromosome 11 abnormalities. Three reported cases demonstrated an 11p+ comparable to the 11p+ seen in our patient and one individual each showed the following karyotypes: t(1;11)(q11;p11) and del(11)(p11p13). Thus, cytogenetic findings from previously studied OGS demonstrate chromosome 11 abnormalities and show overlap with the chromosomal alterations identified in our cytogenetic analysis of GCT/OGS. It is also important to note that our patient had received chemotherapy which is known to cause cytogenetic abnormalities.

Perhaps not coincidental is the finding that the H-ras gene is mapped to 11p15. The human ras oncogene family consists of three genes, Harvey (H), Kirsten (K), and N-ras, which encode for closely related 21-kd proteins. Interestingly, H-ras has been implicated in human malignancies of the lung and colon [24]. Molecular studies are needed to identify if H-ras serves a similar role in the oncogenesis of GCT/OGS and OGS.

Cytogenetic analysis of GCT/OGS may offer the unique opportunity to study early chromosome changes in OGS. The cytogenetic analysis of neoplasms transformed into malignancies—for example, GCT into OGS—may identify structural chromosomal abnormalities fundamental to oncogenesis that are later obscured by chromosomal instability seen in established malignancies.

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Figure 1.
Photomicrograph of original femoral giant cell tumor of bone. Note multiple mononuclear stromal cells surrounding the multinuclear giant cells **A** ($\times 50$), **B** ($\times 125$).

Figure 2. Photomicrographs of recurrent femoral giant cell tumor of bone demonstrating the production of neoplastic osteoid. **A** ($\times 50$), **B** ($\times 125$).

Figure 3.

Karyotype from long-term culture of giant cell tumor/osteogenic sarcoma of the femur demonstrating a telomeric association and an 11p+. 86,XXXX, +3,-4,-6,-10,-10,tas(11p; 14p),11p+,-14,-14,-14,-17, +21, +mar.

Figure 4.

Three telomeric association examples observed in giant cell tumor/osteogenic sarcoma, from left to right: $\text{tas}(1\text{p};20\text{q})$, $\text{tas}(4\text{p};11\text{p})$, $\text{tas}(\text{Xp};11\text{p})$.

Figure 5.

Examples of the two different 11p chromosomes (e.g., 11p+, der(11)t(11;?)(p15;?) identified in giant cell tumor/osteogenic sarcoma. Two examples of 11p+ on the left and three examples of der(11) on the right (as described in the text).

Table 1**Complete karyotype analysis of Giant Cell Osteogenic Sarcoma**

Short-term cultures (N = 20)	
46,XX = 15 cells	
46,XX,t(3;7)(q25;q11)	
46,XX,t(1;11)(q21;p15),t(6;14)(p21;q32)	
46,XX tas(8p;18p)	
46,XX tas(4p;11p)	
46,XX tas(8q;17q),11p+	
Long-term cultures (N = 20)	
46,XX,11p+,-22	
46,XX,tas(4p;11p)	
46,XX,i(4p),14p+,-21	
45,XX,tas(1p;20q),-8,17p+	
46,XX,der(11)t(11;?)(p15;?)14p+,-20	
44,XX,tas(8p;10p),tas ins(11;?)(p?;?) ins(14;?)(p?;?)	
41,XX,11p+,-17,17q+,-18,-19,19q+,-20,-22,	
42,X,-7,tas(11p;12p),-13,14p+,-19	
46,XX,tas(11p;ins(14)(p?;?))	
46,XX,t(4;11)(q11;p15)	
46,XX,tas(11p;20q)	
46,XX,t(4;9)(q11;p11)	
46,XX,tas(4p;18q)	
46,XX,4q+,tas(14p;17p)	
45,X,tas(8p;15p),tas(Xp;11p),14p+,-21	
44,X,-5,t(7;9)(q11;p11),8p+,10p+,-14,20q+	
45,XX,tas(3p;5p),-5-9,-10,der(11)t(11;?)(p15;?),-13,+3mar	
86,XXXXX,+3,-4,-6,-10,-10,tas(11p;14p),11p+,-14,-14,-14,-17,+21,+mar	
45,XX,-11,tas(14p;16q),tas(17p;17q),tas(19q;22q),+ace	
46,XX,tas(11p;17q),tas(17p;19p)	

Table 2

List of telomeric associations observed in 40 cells from patient with GCT/OGS

Frequency	Chromosome Terminus
8	1Ip
3	4p,8p,14p,17p,17q
2	20q,14p+
1	Xp,1p,3p,5p,8q,10p,12p,15p,16q,18p,18q,19p,19q, 22q,der(11)t(11;?)(p15;?)

Table 3

List of chromosome 11 abnormalities observed in 40 cells from patient with GCT/OGS

t(1;11)(q21;p15)
t(4;11)(q11;p15)
11p+ (4 cells)
der(11)t(11;?)(p15;?) (3 cells)
tas(4p;11p) (2 cells)
tas(11p;12p)
tas(11p;14p+)
tas(11p;20q)
tas(11p;Xp)
tas(11p;14p)
tas(11p;17q)
tas[der(11)t(11;?)(p15;?);14p+]