Fibrosarcoma Development 15 Years After Curettage and Bone Grafting of Giant Cell Tumor of Bone

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abstract

Malignant transformation of conventional giant cell tumor of bone is rare and usually occurs with irradiation. This article describes a case of malignant transformation of a giant cell tumor 15 years after initial curettage and bone graft. A 35-year-old man was admitted to the hospital with a recurrent giant cell tumor of the distal femur. On presentation, the patient reported the insidious onset of a dull aching pain in the distal part of the left thigh 4 months prior to admission. Radiographs revealed a destructive lesion in the left distal femur. Needle biopsy revealed recurrence of giant cell tumor with suspected malignant transformation. The patient underwent en bloc resection of the distal femur with adequately wide margins and reconstruction of the knee joint with a prosthesis. Pathological findings showed malignant transformation of a giant cell tumor to high-grade spindle cell sarcoma. Immunohistochemistry showed diffuse and strong p53 expression. A diagnosis of secondary fibrosarcoma was made after discussion. Unfortunately, the tumor proved to be highly resistant to the chemotherapy, and the patient died of multiple lung metastases 14 months after the diagnosis of malignant transformation. What has to be stressed in this case is that any late recurrence must be approached considering the possibility of a secondary induced primary tumor. Because of the rarity of this disease, the effective therapeutic strategy for fibrosarcoma secondary to giant cell tumor is lacking. In addition, identification of the p53 mutation may help in diagnosing cases of potential malignant transformation of giant cell tumor.

Figure: Anteroposterior radiograph showing an expansile lytic lesion involving the complete distal femur.

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Secondary sarcoma arising in association with a preexisting benign giant cell tumor (GCT) is a rare phenomenon but is also a well-documented event.\textsuperscript{1-9} Most patients with sarcomas secondary to a GCT have a history of irradiation treatment for the primary lesion. The histologic types of these tumors are most frequently malignant fibrous histiocytoma or osteosarcoma, and fibrosarcoma that develops in a preexisting GCT without radiation is rare.

The authors report a patient with a GCT that transformed into a secondary fibrosarcoma more than 15 years after treatment of the primary tumor; the patient had no history of irradiation. To assess whether this malignant transformation could be attributed to dysfunction of the p53 tumor suppressor, the authors performed immunohistochemistry for the p53 with the aim of characterizing potential biogenetic alterations related to the sarcomatous transformation.

**Case Report**

A 35-year-old man, a machine operator, was admitted to the authors’ hospital in August 2011 reporting pain and functional impairment of his left knee. He reported a primary tumor that had occurred in his left distal femur at age 20 years that was treated with curettage and a bone graft (Figure 1). His previous surgical specimens had been diagnosed as a conventional GCT. Since then, he had been followed for 15 years.

The patient noted the insidious onset of a dull aching pain in the distal part of the left thigh 4 months prior to admission, which had developed without related trauma or infection. The pain was worse at night and was aggravated by activity. At onset, the patient received no medication. As the symptoms increased, he took analgesics. The patient’s history was not remarkable, and he specifically denied any radiotherapy; he did not smoke or drink alcohol.

At admission, physical examination showed swelling and pain at the lateral aspect of the left knee. The physical examination revealed tenderness to palpation over the lower left thigh. Plain radiographs (Figure 2) and computed tomography (Figure 3A) revealed an osteolytic lesion expanding in the grafted area of the left distal femur with immediate signs of aggressiveness (cortical breakthrough, having a large mass permeating the bone and cortex, with extensive soft tissue involvement). On magnetic resonance imaging, a tumor was detected in the distal femur. It was isointense with muscle on T1-weighted images (Figure 3B) and showed high signal intensity on T2-weighted images.
Further staging and screening investigations for metastatic disease, including chest radiographs and computed tomography, abdominal ultrasound, bone scan, blood biochemistry/hematology, and estimation of serum prostate-specific antigen levels, were negative. Needle biopsy of the lesion was performed 2 days after admission. The distal femur was entered using a medial approach. Frozen sections of the tissue were interpreted as showing high-grade spindle cell sarcoma. The patient was diagnosed with a secondary fibrosarcoma and underwent en bloc resection and reconstruction with prosthesis.

The local tumor was grossly 12×8×7 cm. Examination of the specimen revealed that the lesion in the distal femur involved the entire medullary cavity and had eroded through the thin-out cortex of distal femur.

Histological study revealed high-grade spindle cell sarcoma with an elongated nucleus in the tissue. No evidence of osteoid formation by the sarcomatous cells was seen in any of the specimens taken from different areas of the tumor. Uniform spindle cells showing little variation in size and shape and a distinct fascicular (herringbone) pattern were seen (Figure 4A). Tumor osteoid formation and residual areas of GCT were not found. In addition, secondary fibrosarcoma of GCT was diagnosed. Immunohistochemical testing showed that the tumor cells were positive for FN and Ki-67 and negative for smooth muscle actin, S-100 protein, desmin, and CD34. Immunohistochemical testing showed p53 overexpression (Figure 4B).

The patient made an uneventful postoperative recovery and received adjuvant chemotherapy. Six months later, roentgenogram of the chest revealed multiple metastatic nodules throughout both lung fields. The patient died in November 2012, fourteen months after en bloc resection, due to widespread metastases.

**DISCUSSION**

It has been well recognized that some sarcomas may occur in preexisting benign bone tumors or nontumorous conditions. Sarcomatous transformation has been observed in patients with osteochondroma, chondroma, GCT of bone, fibrous dysplasia, Paget’s disease, and bone infarct. Giant cell tumor of bone is a locally aggressive lesion that has a limited propensity for metastasis. Giant cell tumor of bone is a primary benign tumor; late local recurrence of GCT after more than 5 years is rare. Malignant transformation of GCT is relatively rare, with a reported incidence ranging from 1.4% to 6.6%, and it typically occurs after radiation therapy or multiple local recurrences of conventional GCT. Sarcomatous change in a previously histologically typical GCT is seen in less than 1% of cases without previous radiotherapy. The common histologic classification of high-grade sarcomas was osteosarcoma and malignant fibrous histiocytoma. Malignant transformation in GCT typically occurs in a previously irradiated lesion, usually 5 years or more after the initial radiation exposure, making the presence of a sarcoma in the current patient, who did not undergo irradiation, a rare incidence. In addition, the long duration for malignant transformation was also unusual.

A sarcoma secondary to GCT is most frequently located in the long bones around the knee joint, with a preference for the distal femur. Pain and swelling are the most common symptoms of...
the malignancies. On histopathological gross examination, the tumor consists of a solitary, soft to firm, lobulated, fleshy, grayish-white mass. Darker areas of hemorrhage may be found. The margins of the tumor are ill-defined; they often extend with multiple processes into the surrounding tissues or grow in a destructive manner. The predominant tumor cells are spindle-shaped with fine collagen fibers arranged in intertwined bundles, often creating a herringbone pattern with the fascicles crossing at 45° angles. Considerable variation is seen in the amount of fibers, atypical nuclei, and number of mitotic figures. Tumor osteoid formation and residual areas of GCT were not found in this case. Multinucleated giant cells or giant cells of unusual size and shape are rarely features of this tumor. On the contrary, the malignant fibrous histiocytoma shows both histiocytic and fibroblastic features, characterized by elongated spindle cells arranged in a pinwheel or storiform fashion, and cells with histiocytic features, such as pleomorphic folded or grooved nuclei with abundant, often foamy cytoplasm. Multinucleated giant cells and large nuclei are often present.

The pathogenesis of this malignant transformation is still unknown. Losses of heterozygosity on chromosomes 9p and 17p (close to the p53 locus) have been reported in cases of primary and metastatic GCT, and it has been suggested that losses of heterozygosity of these loci might be acquired events in tumors that metastasize. A p53 mutation has also been reported in bone and soft tissue sarcomas. However, a p53 mutation has rarely been reported in malignant or benign GCTs. A p53 point mutation and p53 overexpression in stromal cells were reported in a case of recurrent GCT diagnosed as malignant GCT. Picci et al noted the propensity of excessive cellular proliferation to progress to neoplasia in the proliferating margin of a bone infarct. They suggested that a sarcoma arising at the sites of bone infarct is related to the cells involved in the chronic reparative process and associated with cell organization. They also suggested that histiocytes, osteoblasts, fibroblasts, and endothelial cells play an important role in the reparative process. The fibroblasts may contribute to the transformation of fibrosarcoma. It is well known that the remodeling process in bone is slow and continues during practically the whole life span, as has been demonstrated by histological examination in patients showing active remodelling after more than 7 years since grafting. This might also explain the long latency of secondary sarcomas.

Because it is rarely seen and reported in clinic work, the effective therapeutic strategy for fibrosarcoma secondary to GCT is lacking. In the current case, the authors first used surgical resection to remove the main body of the tumor and then chemotherapy was applied according to clinical practice to treatment of the soft tissue sarcomas and fibrosarcoma. Although a recent report demonstrated that chemotherapy did work for treatment of a fibrosarcoma secondary to a GCT, the current patient’s life was not prolonged and his quality of life did not improve after surgical resection or chemotherapy.

Finally, the prognosis of sarcoma development for GCT of bone is the same as that of high-grade osteosarcoma or malignant fibrous histiocytoma. Anract et al studied the treatment and outcome of patients with malignant GCTs and reported a better 1-year survival rate after surgery combined with chemotherapy compared with surgery alone; however, the 5-year survival rates and actuarial survival curves showed no statistical differences. The prognosis for these patients is relatively poor. Fifty-seven percent of patients died of their disease at an average of 19.2 months after diagnosis. Because the tumor is highly resistant to the therapy, the current patient died of multiple lung metastases 14 months after the diagnosis of malignant transformation.

CONCLUSION

Sarcoma secondary to GCT is an extremely rare and challenging clinical entity for physicians and patients. In the current study, the authors present a patient with a fibrosarcoma that developed in a preexisting GCT without radiation after 15 years. What has to be stressed is that any late recurrence must be approached with consideration for the possibility of a secondary induced primary tumor; it is imperative that they be recognized at an early stage so they can be treated adequately by aggressive surgery and, in some cases, chemotherapy. Because of the rarity of this disease, it is unlikely that prospective studies will reveal the optimal treatment regimen. This means that in practice renewed staging and consideration of tailored therapies must be done, thus offering the patient the best chances of cure. Identification of the p53 mutation may help diagnose potential malignant transformations of GCTs.

REFERENCES


