Late Malignant Transformation of Giant Cell Tumor of Bone 41 Years After Primary Surgery

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Abstract

Giant cell tumor of bone is an uncommon benign tumor that frequently recurs locally. Spontaneous 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 41 years after initial curettage and subsequent resection. A 68-year-old man presented with a 6-month history of left hip pain. He had been diagnosed 41 years previously with giant cell tumor in the left femoral neck treated by simple curettage and bone grafting, followed by resection of the femoral head 1 year later for local recurrence. On presentation, radiographs revealed a destructive lesion in the left proximal femur. Incisional biopsy revealed recurrence of giant cell tumor with suspected malignant transformation. The patient underwent en bloc resection of the proximal femur with adequately wide margins and reconstruction of the hip joint with a prosthesis. Pathological findings showed malignant transformation of a giant cell tumor to osteosarcoma and leiomyosarcoma. No recurrence or metastasis developed during 2-year follow-up. Benign local recurrences usually arise in the first 3 postoperative years, whereas malignant transformation tends to take longer than 3 years. To the authors’ knowledge, the 41-year interval from primary surgery to diagnosis of malignancy for the current patient is the longest interval reported among cases in which patients received no radiation therapy.

Figure 1: Anteroposterior (A) and Lauenstein (B) plain radiographs after primary surgery–curettage and bone grafting.

Figure 2: Anteroposterior (A) and Lauenstein (B) plain radiographs showing an osteolytic lesion in the left proximal femur.

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Giant cell tumor of bone is a rare primary skeletal lesion accounting for approximately 5% of all primary bone tumors except multiple myeloma in adults. Although classified as a primary benign bone tumor, a giant cell tumor of bone has a high recurrence rate reaching 65%, along with the potential for malignant transformation. Malignant transformation usually develops after radiation of the primary tumor; judging by reports on giant cell tumor, malignant change occurring postoperatively in the absence of adjuvant radiotherapy is a rare phenomenon. This article describes a case of late malignant transformation of benign giant cell tumor of bone 41 years after resection in the absence of adjuvant radiation therapy.

**CASE REPORT**

A 68-year-old man presented with a 6-month history of left hip pain. He was diagnosed with a giant cell tumor in the left femoral neck at age 27 years (41 years previously). The tumor was curetted, and the autologous bone was grafted at another hospital (Figure 1). Pathological findings revealed a benign giant cell tumor of bone (confirmed with a findings sheet written by the pathologist). His tumor recurred 1 year later, and a pathological fracture occurred; therefore, the tumor was treated surgically by resection of the femoral head and curettage of the tumor was treated surgically by resection of the proximal femur with marginal resection of the proximal femur with margins of more than 3 cm and reconstruction of the hip joint with an oncology modular prosthesis. The tumor was white and elastic, measuring 10.5×8.0×5.5 mm. Pathological findings revealed that the tumor contained spindle cells in a predominantly disorderly pattern intermixed with herringbone or pericytomatous patterns in some areas. Although the presence of multiple multinucleated giant cells and histiocytes (cluster of differentiation-68 positive) in the lesion suggested a possible recurrence of giant cell tumor, the immunohistochemical findings that the spindle tumor cells were negative for S100, desmin, cluster of differentiation-34, and cluster of differentiation-99 but positive for smooth muscle antibody and vimentin were indicative of malignant transformation to osteosarcoma. In addition, a few tumor cells produced osteoid, indicating their transformation to osteosarcoma (Figure 4).

Although the patient received no postoperative chemotherapy for the same reason that he received no preoperative che-

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**Figure 1:** Anteroposterior (A) and Lauenstein (B) plain radiographs after primary curettage (A) and bone grafting (B).

**Figure 2:** Anteroposterior (A) and Lauenstein (B) plain radiographs showing an osteolytic lesion in left proximal femur.
motherapy, no recurrence or metastasis developed during 2-year follow-up.

**DISCUSSION**

Giant cell tumors rarely transform into malignant tumors. The reported incidence of secondary malignant giant cell tumors ranges from 0.5% to 5% of all giant cell tumors. Most secondary malignant giant cell tumors are postirradiation sarcomas; malignant transformation without previous irradiation is rare. In the largest series of secondary malignant giant cell tumor cases by Bertoni et al., malignant transformations occurred in 6 of 924 patients after surgery alone. Other studies reported malignant transformation rates after surgery alone ranging from 0.5% to 2% of all secondary malignant giant cell tumors.

Primary malignant giant cell tumor is also rare, perhaps in part due to difficulties of diagnosing such tumors as primary rather than secondary. In particular, because of the heterogeneity in many primary malignant giant cell tumors that results in the tumor containing areas of benign giant cells, a biopsy may not initially detect the presence of a malignant tumor if the sample comes from benign portions of the tumor. In such cases, the lesion would initially be misdiagnosed as a benign giant cell tumor; reliance on this initial erroneous diagnosis of benign giant cell tumor would subsequently result in a diagnosis of secondary malignant giant cell tumor when the tumor is identified as malignant at recurrence. The consequence would be that the number of reported primary malignant giant cell tumor cases would be lower than the actual number and also that the number of cases of reported early transformation of a giant cell tumor into a secondary malignant giant cell tumor would be erroneously high compared with the actual number. In addition, a primary malignant giant cell tumor needs to be differentiated from a giant cell–rich osteosarcoma, but differentiation between these 2 lesions is difficult because the cytologic evidence of malignancy can be subtle in certain areas, such as the mononuclear cells of giant cell–rich osteosarcomas. Although the primary tumor may have already been malignant or not a giant cell tumor, as in the current case, it cannot be confirmed because no primary pathologic specimen remains.

Published studies of secondary malignant giant cell tumor have reported widely varying intervals from initial treatment to...
malignant transformation: 1 to 36 years after surgery alone and 4 to 42 years after irradiation.\textsuperscript{3} To the current authors’ knowledge, the 41-year elapse between the initial treatment and diagnosis of malignant transformation in the current patient is the longest such interval reported for patients not receiving radiation therapy. A closer examination of the published data revealed that most benign recurrences of giant cell tumor occur within the first 2 years after initial treatment, whereas malignant changes usually take longer than 3 years to manifest after the initial treatment of a benign giant cell tumor.\textsuperscript{6} These findings indicate that late recurrences arising more than 3 years after the initial treatment of a giant cell tumor should prompt careful investigation of potential malignant transformation.

Local recurrence rates of giant cell tumor depend on the aggressiveness of the initial surgery.\textsuperscript{1} Intralesional curettage, the preferred treatment for most giant cell tumors, is associated with reported recurrence rates from 20% to 65%.\textsuperscript{7,10} Several studies have reported improved tumor control in conjunction with adding local adjuvants (e.g., polymethylmethacrylate, phenol, hydrogen peroxide, and cryo-therapy) to intralesional curettage.\textsuperscript{7,9-13} In contrast, wide resection, which is currently reserved for tumors with extensive destruction or cases where joint salvage is impossible, is associated with a lower risk of recurrence (range, 0%-12%) than intralesional surgery.\textsuperscript{1,7,9,10,13}

Although wide resection also reduces the risk of malignant transformation following initial treatment, most cases of secondary malignant giant cell tumor are treated by curettage and bone grafting.\textsuperscript{4} Sakkers et al\textsuperscript{4} reported a case of malignant fibrous histiocytoma developing in a bone grafting area, a situation that may be comparable with malignant fibrous histiocytoma developing in an area of bone infarction.\textsuperscript{14,15} In both instances, the reparative proliferative changes in the border surrounding an area of dead bone served as the nidus for the formation of a malignant tumor. The current patient also was treated initially by curettage and bone grafting, but the additional resection performed 1 year after bone grafting made it impossible to investigate the histology of the bone grafting site.

Recent reports showed successful systemic therapy with denosumab (a monoclonal antibody against receptor activator of nuclear factor kappa-B [RANK] ligand) as other choice of treatment. Thomas et al\textsuperscript{16} reported that 30 of 35 patients, including some who had lung lesions, showed a tumor response with systemic denosumab. Because denosumab has inhibited osteoclast function via the RANK–RANK ligand pathway,\textsuperscript{17} it might also inhibit the osteoclast-like giant cells of a giant cell tumor of bone. Surgery that causes major functional deficits is not justifiable for a lesion that is typically benign, although promising alternatives are lacking in some cases. The authors hope denosumab will change clinical practice in the treatment of complicated giant cell tumor of bone.

Prognoses for primary and secondary malignant giant cell tumor are poor, although some studies have identified better outcomes for primary rather than secondary malignant giant cell tumor (especially postradiation secondary malignant giant cell tumor).\textsuperscript{3} The improved outcomes for primary malignant giant cell tumor could be the consequence of more unfavorable tumor locations in the postradiation secondary malignant giant cell tumor group. However, Anract et al\textsuperscript{1} reported equally poor outcomes for both groups. However, because of the small number of cases, no reliable statistical analysis of survival has been performed.

**CONCLUSION**

The current article describes an unusual case of a secondary malignancy in giant cell tumor occurring 41 years after initial surgery in the absence of radiation therapy. Although malignancies in giant cell tumors are rare and because of the poor prognosis of these sarcomas, early recognition of these cancers is important so they can be treated adequately. Although definitive diagnosis requires histological examination of the tumor, a diagnosis of malignancy could initially go undetected if a frozen section or biopsy specimen happens to sample only areas of classic (i.e., benign) giant cell tumor. Clinically, recurrences occurring 3 years or longer after initial surgery or radiotherapy of a primary giant cell tumor of bone should raise the level of suspicion for secondary malignancy.


