Malignancy in Giant Cell Tumor of Bone: Benign Metastatic, Borderline, or Malignant? A Case Report of a Challenging Diagnosis, and Review of Literature

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Abstract

Giant cell tumors of the bone (GCTB), while often benign, are regarded as locally aggressive and highly unpredictable with the capability to recur, metastasize, and even undergo sarcomatous transformation into a malignant variant. There have been inconsistent views regarding histomorphology, radiography and local occurrence of GCTB, and metastatic malignant GCTB. Herein, we describe the histological features of a case of GCTB with such atypical foci in which the initial diagnosis of malignancy was amended to a benign metastatic giant cell tumor. Whether the creation of a “borderline” or “atypical” GCTB category is necessary is yet to be determined.

KEYWORDS: Giant, Malignant, Borderline, Atypia, metastasectomy

ABBREVIATION

GCTB: Giant cell tumor of the bone, MGCT: Malignant Giant cell tumor

INTRODUCTION

Giant cell tumor of the bone (GCTB) is a rare, locally aggressive osteolytic tumor that is responsible for up to 6% of all primary bone tumors [1,2]. Patients typically present in their third and fourth decades of life, with a slightly higher incidence among females. Symptoms range from vague tenderness, swelling, and reduced joint mobility to severe pathologic fractures [1, 2]. GCTB affects the axial and distal skeletal bone, most commonly involving the meta-epiphyseal region of the distal femur, distal radius, sacrum, and proximal humerus [3]. GCTB can remain local, metastasize, or undergo malignant transformation. In less than 5% of all cases, giant cell tumors of the bone can undergo malignant transformation, also known as sarcomatous transformation or dedifferentiation of GCTB [4,5]. Malignant GCTB (MGCT) is then categorized in one of two ways: a primary de novo type and a secondary type [5]. Primary malignant GCTBs usually arise juxtaposed to the typical GCTB, often evident at initial diagnosis [5-7].

Local benign recurrence occurs anywhere from 25% to 50% of patients following curettage [7, 8]. Further, benign metastasis of GCTB, often to the lungs, occurs in upwards of 9% of patients and, while normally indolent, can compromise pulmonary function and be fatal [1,7]. Lung metastases have a higher risk of occurring in patients that have undergone radiative treatment or surgical curettage of the primary tumor or those that have a higher Campanacci stage [7,9]. Campanacci et al. classified the GCTB into three grades depending on their radiographic appearance: a grade one lesion is considered latent and consists of a tumor with a well-defined margin and intact cortex; a grade two lesion is active and has a relatively well-defined margin but in the absence of a radiopaque rim, and the cortex is thinned and moderately expanded; the most aggressive is a grade three lesion which has indistinct borders and cortical destruction [10].

Furthermore, the latency period between the time of primary tumor and the detection of pulmonary infiltrates can vary significantly and has been shown to vary based on the treatment and the location of the primary tumor [7, 9, 11]. It is the histological nature of the lesion that differentiates between metastasis of the benign tumor and malignancy, thus it is of clinical importance to detect and distinguish between malignancy and metastasis early on to begin treatment accordingly because the prognosis of metastatic GCTB is more favorable than that of malignant GCTB [7].

In the literature, the proposed criteria for malignancy adopts the dedifferentiation theory and describes an undifferentiated sarcomatous overgrowth devoid of giant cells juxtaposed to a typical GCTB, or in a previously diagnosed GCTB. Atypia is generally accepted in GCTB. However, cytologic and architectural atypia beyond the permissible level of benign GCTB and short of malignancy can cause serious diagnostic dilemmas as to its benign degenerative or malignant significance. Additionally,
there have been disputes regarding radiography and local occurrence of GCTB, and no correlation between the two has yet been established [8]. Herein, we describe the histological features of a case of GCTB with such atypical foci in which the initial diagnosis of malignancy was corrected to a benign metastatic giant cell tumor.

**CASE PRESENTATION**

This is a case of a 45-year-old man who presented with a solitary distal epiphyseal femoral mass, which was curedtted and replaced by cortical bone after a diagnosis of giant cell tumor of bone (GCTB). Three years later, the patient presented with bilateral multiple lung nodules, largest measuring 2.8 cm, compatible with metastasis. Biopsy from the largest lung nodule showed typical features of GCTB within which were small foci of increased stromal cellularity, mild to moderate pleomorphism, scattered atypical mitoses, and variably prominent nucleoli. There was also a minute focus of stromal overgrowth of mildly atypical spindle cells with decreased number of giant cells (Figure 1 A-B-C). There was no hyperchromasia or frank high-grade sarcomatous growth. Histomorphology of prior femoral GCTB was reviewed and showed identical features to the current lung metastasis. Before referral to our institution, the submitted outside opinion was a GCTB with areas of malignant transformation. Our review came to the final diagnosis of a benign GCTB metastatic to the lung with no evidence of malignant transformation. The final diagnosis for which treatment was based upon was benign GCTB. Surgical metastasectomy was not an option due to widespread bilateral lung metastasis. In addition, the patient refused aggressive lung surgery, and was treated with whole lung radiotherapy. Patient was free of recurrence or additional metastasis for 14 months follow up, after which he was lost to follow up.

**DISCUSSION**

Giant cell tumors of the bone, while often benign, are regarded as locally aggressive and highly unpredictable, with the capability to recur, metastasize, and even undergo sarcomatous transformation into its malignant counterpart. As highlighted in our case, distinguishing between benign metastases and malignancy can be challenging in cases of GCTB, owing to their highly unpredictable nature, and atypical histomorphology. Neither histopathological grading, nor radiography, has proven a reliable diagnostic tool nor prognostic indicator for determining clinical outcome and aggressiveness of tumor [8]. The challenges proposed by our case suggest a need for consensus in diagnosing and differentiating between benign and malignant GCTB. This is especially important for malignant GCTB because it has a poor prognosis and prompt appropriate management is essential to provide optimal treatment [7].

Benign metastases are histologically defined as multinucleated osteoclast precursor cells that are highly pleomorphic and form scattered spindle cells in a syncytium-like sheet [7, 12]. Atypical nuclei or high mitosis are not commonly seen; however, it is typical to find common GCTB findings of fibrosis, osteoid, collagenization, etc. [12, 13]. This contrasts with malignant sarcoma malignancies which consists of high grade sarcomatous growth in unison with benign GCTB or malignant proliferation at a site of previously documented benign giant cell tumor or a new metastatic site. Malignant GCTB has also been described as “giant multinucleated cells alternating with stromal cells with sarcomatous morphology”, consistent with Jaffe’s histological grade III, primary and secondary malignancy respectively [14]. Examples of common sarcomatous transformations include osteosarcoma, fibrosarcoma, or undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma [7]. Because of the variability in malignant transformation, past medical history is an important consideration.

From the prognostic value, primary malignant GCTB has a better outcome and 5-year survival rate than secondary malignant GCTB, yet both subsets of MGCT have a worse prognosis when compared to benign local or metastatic GCTB [7]. Moreover, prior exposure to radiation, curettage and/or bone graft increases the risk for secondary malignancy GCTB [7, 15]. The latency period between time of initial diagnosis of benign GCTB and diagnosis of secondary malignant GCTB is also shorter for patients that were managed by radiotherapy than those that
Immunohistochemical analyses have shown that benign GCTB expresses the vitronectin receptor, calcitonin receptor, tartrate-resistant acid phosphatase (TRAP) and a high expression of receptor activator of nuclear factor kappa K (RANK) on many large osteoclast-like multinucleated giant cells within a nest of neoplastic mesenchymal stromal cells expressing RANK ligand and mononuclear cells of monocyte/macrophage lineage [2, 4, 16]. However, unique to benign GCTB, researchers have discovered a genetic mutation in the H3F3A gene that has been highly associated with benign GCTB but less so with giant cell-rich secondary sarcomas [6, 17]. In contrast, mutations of TP53 and HRAS have been noted in secondary malignant GCTB and amplification of 20q11.1 in cases of GCTB have correlated with metastatic disease [17]. The presence of a H3F3A mutation, accompanied by aggressive radiologic and histological features not compatible with conventional benign GCTB features, produces an avenue for future researchers to examine the genetic differences and further differentiate between benign GCTB and malignant sarcomatous transformation. Molecular studies were not performed on our patient tumor due to insurance payment issues.

**CONCLUSION**

The traditional histologic criteria of malignant giant cell tumor do not include a subset of GCTB that exhibits focal architectural and cytologic atypia beyond the degenerative changes sometimes seen in this tumor. Yet, some of these tumors are variably called malignant and treated accordingly. The behavior and prognosis of such tumors need to be studied in more detail and in large series in order to be correctly classified. Moreover, if they are to be considered malignant, reproducible criteria for MGCT that include this group should be clearly established. Whether the creation of a "borderline" or "atypical" GCTB category is necessary is yet to be determined.

**ACKNOWLEDGEMENT**

Special thanks to Rona Bakri, Ebenezer Rosiji, and Zachary Edler MD candidates, American University of the Caribbean for their assistance in reviewing the final manuscript.

**REFERENCES**


