Mini Review

Malignant giant cell tumor of bone

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Abstract
Giant cell tumors of bone are locally destructive benign entities that occur predominantly in long bones of post-pubertal adolescents and young adults. The majority are treated by aggressive curettage or resection. Occasionally, Giant cell tumors of bone may undergo malignant transformation to undifferentiated sarcomas. We report a mini review of malignant GCT of the long bones in order to raise awareness of this entity that may mimic the benign form but is more aggressive with poorer prognosis.

Keywords: Giant cell tumor, Long bones, Malignant transformation

Giant cell tumors (GCTs) are primary locally aggressive bone tumors that represent 5% of all bone neoplasms¹. They have a female predominance and they are most common in patients aged 20 to 40 years. In Oriental and Asian populations incidence may reach 20% of bone neoplasms while it is more uncommon in Caucasians². Pain is the most common presenting symptom while pathologic fractures may occur in 11-37% of the cases³. Distal femur, proximal tibia and distal radius are the most common sites involved with 50% of the cases diagnosed around the knee area⁴ (Figure 1). These neoplasms are characterized by osteoclast-like giant multinucleate cells (Figure 2). Thus, radiographically they appear as pure osteolytic eccentric lesions of the epiphysis extending to the articular surface or the diaphysis (Figure 3)⁵. GCTs are usually highly destructive solitary lesions commonly extending to the surrounding soft tissue, however 1% to 2% may simultaneously or sequentially be multicentric⁶.

Although classified as primary benign bone tumors, in 1-3% of GCTs spontaneous transformation to a high-grade...
malignancy may occur. This malignant transformation may be found in both primary and secondary GCTs, but it is more common in secondary GCTs whom recur at the same site years after surgical excision or radiotherapy. The incidence of malignant GCTs has been estimated in the United States at 2.4 per 10000000 persons per year (mainly adults aged 20 to 44 years of age) and malignant transformation unfortunately leads to a poor prognosis, similar to the one of high-grade sarcomas.

The differential diagnosis of malignant GCTs is extremely difficult and important due to their aggressive character and poor prognosis compared to the benign forms. The difficulty in the interpretation of these lesions begins with terminology. The term malignant GCTs has been controversial due to its usage to describe several entities such as giant cell-rich osteosarcomas and malignant fibrous histiocytomas with multinucleated cells which are not GCTs. As a result, throughout the years, various studies and scientific teams...
have attempted to establish criteria to classify malignant GCTs. Turning his focus on the pathophysiology of the lesion rather than its clinical manifestation, Jaffe was the first to identify a unique morphology in which the stromal mononucleated cells showed noticeable atypia. Nachimento later proposed that for the definitive diagnosis of malignant GCTs there should be significant areas of high grade non-osteogenic sarcoma characteristics within the stromal component of the lesion. Atypia, as well as coagulative necrosis, vascular emboli and metastasis which are criteria for malignancy are not applicable in malignant GCTs since even the benign forms may exhibit them. Histologically, cells with hyperchromatic nuclei with variably prominent nucleoli, atypical mitoses and malignant spindle cells may also be found infiltrating the normal bone trabecula. A careful dissection of the pathologic tissue taken to biopsy along with a simple hematoxylin and eosin dye may reveal the malignant areas of transformed GCTs. Furthermore, immunohistochemistry revealing overexpression of PS3, P63 and Ki67 has been associated with malignant transformation.

When investigating malignant GCTs, it is important to underline the separation between primary and secondary malignant GCTs. Primary malignant GCTs are extremely rare, characterized by a spontaneous malignant transformation of conventional GCTs to lesions with sarcomatous features after the initial diagnosis. The most recent term for this entity is “malignancy in giant cell tumor”. On the other hand, secondary malignant GCTs are lesions characterized by malignant transformation in patients previously treated with surgical excision or radiotherapy. The exact pathophysiological mechanism of this transformation remains unknown, but studies have shown that secondary malignant GCTs tend to be more aggressive than the primary ones. Additionally, patients with secondary malignant GCTs post radiotherapy tend to have worst prognosis and thus are monitored closely. For secondary malignant GCTs malignant transformation may take 4 to 40 years. Radiology and clinical evaluation of benign and malignant GCTs may not differentially diagnose one form from the other since they both exhibit signs of osteolysis, cortical erosion and soft tissue involvement. This separation is simplistic though, since benign GCTs demonstrate a 5-year survival of 90% and are treatable, unlike the malignant forms. Even benign metastatic GCTs have better survival rates. On the other hand, distinction from “giant cell-rich” or “osteoclasts-rich” osteosarcomas which are associated with osteoclast-like giant multinucleated cells and hence have similar pathophysiological characteristics, is aided by radiological characteristics such as the site of the tumor, its diaphyseal or meta-diaphyseal location. Other sarcomas containing giant cells that should be included to the differential diagnosis are osteosarcoma, chondrosarcoma, fibrosarcoma and undifferentiated high grade pleomorphism sarcoma.

The treatment of choice is surgery depending on the extension of the lesion but since this is a rare entity no established treatment algorithm has been designed. En block excision is the optimal treatment option which is designed based on modern imaging techniques such as Magnetic Resonance Imaging (MRI) but may be extensive and disabling for the patient. Investigators have used chemotherapy alone in non-operable cases while Denosumab which is a monoclonal antibody to RANKL has been additionally used for palliative treatment. Thomas DJ et al. reported excellent results of denosumab administration in reducing pain in nearly 85% of patients and minimizing radiographic progression of the lesion in almost 90% of the cases. Additionally, in phase II study trials, treatment with Denosumab has been shown to inhibit disease progression and reduce requirement of surgery while inducing tumor necrosis of GCT. However, these were benign GTC cases in which surgical excision due to location and extend was not possible. Furthermore, in all these data, researchers question the duration of Denosumab treatment needed and the recurrence rates of GCT after the mononuclear antibody is stopped. The recurring GCT after Denosumab treatment may be malignant but the exact incidence is unknown thus the eligibility of Denosumab in malignant GCTs remains a question to be answered in future studies.

Conclusion

GCT of long bones is classified as benign neoplasm. Malignant transformation has a difficult clinical and radiographic diagnosis and may only be diagnoses histologically. Malignant components are usually sparse within the benign components and are likely to be missed on biopsy. Thus, careful biopsy supplementation by orthopaedic surgeons and a thorough examination by pathologists is critical for diagnosis. Proper treatment by wide excision should be performed when possible to offer these patients the best possible care. Hopefully, further investigation of agents such as denosumab with excellent results for benign forms of GCTs will add to our treatment options in the future. Currently, awareness, high rates of suspicion and early detection are the key ingredients in the treatment of malignant GCTs.

References


