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 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

Figure 1. Typical and less typical locations of Giant cell tumors of long bones.

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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 1 000 000 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. Nachiamento 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.

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 expression of P53, P63 and Ki67 has been associated with over-expression of P53, P63 and Ki67 has been associated with 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.

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. Malignant components are usually sparse histologically. Malignant GCTs may not differentially diagnose one form from the other since they both exhibit signs of osteolysis, cortical erosion and soft tissue involvement.

Radiology and clinical evaluation of benign and malignant GCTs may not differentially diagnose osteosarcoma, chondrosarcoma, fibrosarcoma, and undifferentiated high grade pleomorphic 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 bloc excision is the optimal treatment option which is designed based on modern imaging techniques such as Magnetic Resonace Imaging (MRI) but may be extensive and disabling for the patient.

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.

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