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Original contribution

Denosumab-treated giant cell tumor of bone. Its histologic spectrum and potential diagnostic pitfalls☆,☆☆

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Summary Giant cell tumor (GCT) of bone is a locally aggressive, rarely metastasizing primary bone neoplasm that occurs most frequently in the epiphysis of long bones of young adults. It is composed of round, oval, or elongated mononuclear cells admixed with osteoclast-like giant cells that express receptor activator of nuclear factor κB (RANK). The mononuclear stromal cells express RANK ligand, a mediator of osteoclast activation. Denosumab, a monoclonal antibody that reduces tumor associated bone lysis by inhibiting the action of RANK ligand, has been used to treat selected cases of GCT. We reviewed the clinical records and histologic slides of 9 patients with GCT who had received denosumab therapy and were subsequently surgically treated. There were 5 men and 4 women aged 20 to 66 years (mean, 36 years). Duration of treatment varied from 2.5 to 13 months (mean, 5.9 months). In all cases, different degrees of ossification, fibrosis, depletion of giant cells, and proliferation of mononuclear cells were seen. With this combination of changes, denosumab-treated GCT may mimic other lesions such as fibrous dysplasia, juvenile ossifying fibroma, nonossifying fibroma, and osteoblastoma. Less frequent but more relevant is the presence of cellular atypia or patterns of ossification that resemble an undifferentiated pleomorphic sarcoma, a conventional osteosarcoma, or a low-grade central osteosarcoma. The presence of clinical and radiologic response to denosumab, along with the lack of high mitotic activity, atypical mitotic figures, extensive necrosis, or a permeative pattern of growth, represents clues to achieve a correct diagnosis.

1. Introduction

Giant cell tumor (GCT) of bone is a locally aggressive, rarely metastasizing primary bone neoplasm that occurs most frequently in the epiphysis of long bones of young adults [1]. GCT usually arises in the appendicular skeleton, with the most common site being the distal femur, followed by the proximal tibia and distal radius. Histologically, it is composed of round, oval, or elongated mononuclear cells admixed with several osteoclast-like giant cells. Mitotic figures are usually present, and there may be foamy cells, areas of fibrosis, bone

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Table 1 Clinical features of 9 patients with denosumab-treated GCT of bone

Case	Age (y)	Sex	Location	Primary or recurrent [a]	Length of therapy (mo) [a]
1	66	M	Distal radius	Recurrent (recurrence in soft tissue)	9
2	41	M	Distal radius	Recurrent	6
3	20	F	Proximal tibia	Recurrent	13
4	36	M	Distal radius	Recurrent	8
5	22	M	Distal ulna	Primary	5
6	31	M	Proximal Humerus	Primary	2.5
7	40	F	Distal femur	Primary	4
8	29	F	Distal radius	Primary	3
9	39	F	Distal ulna	Primary	3

Abbreviations: F, female; M, male.
[a] Before first post-denosumab surgery.

formation, and foci of necrosis [2]. The osteoclast-like giant cells, which play a clear role in the aggressively lytic behavior of GCT, express receptor activator of nuclear factor κB (RANK). The mononuclear stromal cells express RANK ligand (RANKL), a key mediator of osteoclast activation [3].

Denosumab, a human monoclonal antibody that specifically inhibits RANKL, reducing tumor-associated bone lysis, has shown considerable activity regarding disease control in selected cases of GCT [4-6]. Radiologically, lack of progression, calcification, and better delineation of the target lesion were demonstrated. At the histologic level, the changes include a decrease in the number of giant cells as well as replacement by fibrous and osseous tissue [7]. As a result, histology of treated tumors may differ significantly from the original lesion and even resemble other lesions of soft tissue or bone, which can lead to confusing situations, particularly if the pathologist is not aware that denosumab neoadjuvant therapy was performed. Moreover, as was recently recognized, some of this denosumab-treated GCT may have histologic overlap with malignant GCT [8].

Herein, we describe the full histologic findings in 9 cases of GCT who had received neoadjuvant denosumab therapy. We focus on the potential diagnostic pitfalls, including several benign and malignant lesions. We also discuss pseudomalignant features and true malignancy in these tumors.

2. Materials and methods

Each author certifies that his institution has approved the reporting of this study and that all investigations were conducted in conformity with ethical principles of research. This work was performed at the Italian Hospital of Buenos Aires, Buenos Aires, Argentina.

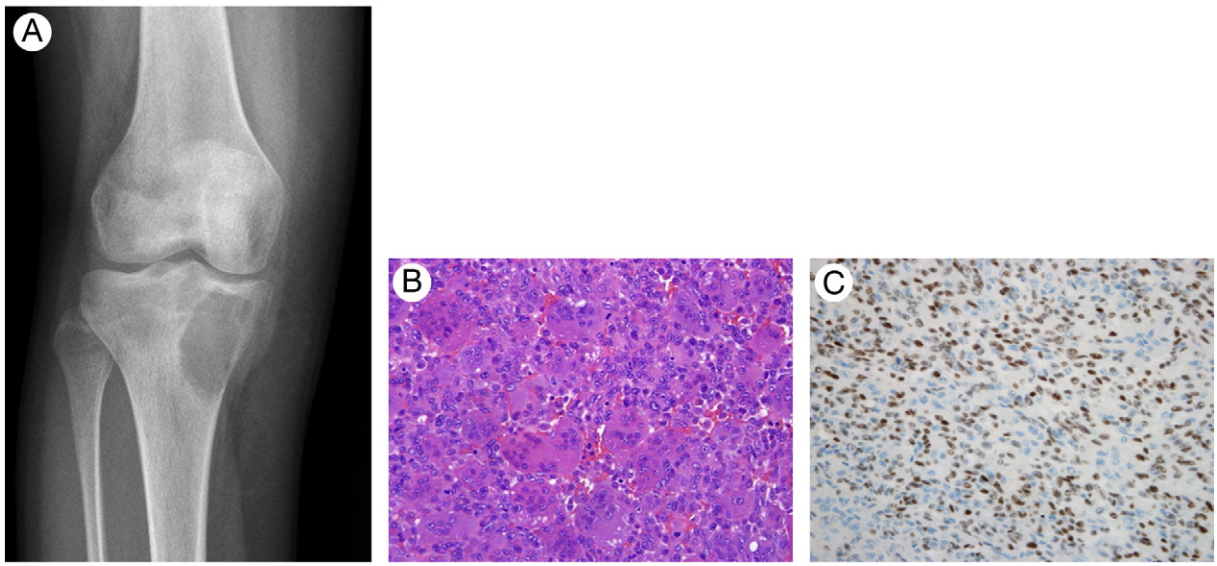

Fig. 1 Radiologic and histologic features of GCT of bone: case 3. A, Radiograph shows a large, lytic, eccentric lesion involving the proximal epiphysis and metaphysis of the tibia. B, Histology (hematoxylin and eosin stain, original magnification ×40) reveals mononuclear cells and multinucleated giant cells, with similar nuclear features, scattered in a uniform manner. C, Immunohistochemistry shows mononuclear cells diffusely and strongly positive for p63.