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Pathological Anatomy

Giant Bone Cell Tumors: Experience of Ibn Sina Hospital in Rabat, Morocco

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Abstract **Case Report**

***Introduction*:** GCT of the bone are a rare benign but locally aggressive tumors showing histologically mononuclear neoplastic cells associated with multinucleated giant cells. The objective of this work is to relate the anatomo-pathological aspects of this entity and to discuss its differential diagnoses. ***Case Reports*:** We conducted a descriptive retrospective study, comprising a series of 42 patients spread over 76 months, from January 2016 to May 2022, including all the patients with bone tumors rich in giant cells. ***Results*:** Our results showed 15 cases of GCT, 8 cases of aneurysmal cyst, 7 cases of Chondroblastoma, 4 cases of non-ossifying fibroma, 4 cases of brown tumor 2 cases of osteoblastoma and 2 cases of osteoid osteomas. ***Discussion*:** GCT, formerly called osteoclastomas, make up 5% of primary bone tumors. The clinical and radiological features are nonspecific. Microscopic studies show the presence of mononuclear neoplastic cells associated with macrophages and multinucleated "osteoclast-like" giant cells. The differential diagnosis is made with Giant cell-rich osteosarcoma, brown tumor, osteoblastome, osteoid osteomas, Chondroblastoma, aneurysmal cyst and non-ossifying fibroma. GCT has been traditionally treated surgically with curettage and placement of cement, and recently, the use of the new chemotherapeutic drug Denosumab is resulting in a dramatic treatment response. ***Conclusion*:** Giant cells bone tumors are a rare locally aggressive benign tumors that can be a real diagnostic challenge due to the large number of bone lesions rich in giant cells. Due to the recent molecular studies, GCT are already benefiting from a targeted anti-RANKL therapy that is particularly useful for locally advanced or metastatic forms.

Keywords: Giant Cells Tumors, Giant Cells Rich Tumors, Bone, Case Series.

INTRODUCTION

Giant bone cell tumors (GCTs), formerly called osteoclastomas, make up 5% of primary bone tumors [1]. They are characterized histologically by the presence of mononuclear neoplastic cells associated with macrophages and multinucleated "osteoclast-like" giant cells.

The objective of this work is to relate the anatomo-pathological aspects of this entity and to discuss its differential diagnoses.

This case report has been reported in line with the SCARE Criteria [2].

CASE REPORTS

We conducted a descriptive retrospective study, comprising a series of 42 patients spread over 76 months, from January 2016 to May 2022, carried out at the pathological anatomy laboratory of the Ibn Sina University Hospital in Rabat. The patients included are all patients with a bone tumor rich in giant cells, whose biopsy was received during the period described above.

Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by Editor-in-Chief of this journal on request.

Table 1 : Summary of epidemiological, clinical, paraclinical, therapeutic and evolutionary characteristics

PATIENT	SEX	AGE	HISTORY	CLINICAL FEAUTURES	SITES	RADIOLOGY DESCRIPTION	HISTOLOGY	TREATMENT	EVOLUTION
1	M	41	Smoking	pain, swelling	Distal femur	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
2	M	19	0	pain	distal femur	well defined l lesion with a thin sclerotic rim	chrondroblastoma	excision	Favourable
3	M	23	0	pain, swelling	Femur	multiloculated lesion	Aneurysmal bone cyst	curettage	local recurrence
4	M	19	0	swelling	distal tibia	well defined l lesion with a thin sclerotic rim	non ossifiant fibroma	curettage	Favourable
5	M	34	0	pain, swelling	proximal tibia	lytic lesion	TCG	Curettage+ bisphosphonates	local recurrence
6	M	18	0	pain	sacrum	dense shell of bone surrounding the lesion	osteoblastoma	bloc resection	local recurrence
7	M	27	0	Pathological fracture	Distal femur	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
8	M	19	0	nocturnal pain	femoral neck	radiolucent nidus and surrounding sclerotic changes	osteoid osteoma	curettage	Favourable
9	F	33	0	pain, swelling	proximal tibia	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
10	F	30	0	pain, swelling	Distal femur	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
11	F	65	renal failure	Pathological fracture	clavicle	well defined lytic lesion with reactive bone	hyperparathyroidism	parathyroidectomie, dialysis	local recurrence
12	F	40	Diabetes	restricted joint movement	proximal tibia	lytic lesion	TCG	Curettage+ bisphosphonates	local recurrence
13	F	80	renal failure	pain	rib	well defined lytic lesion with reactive bone	hyperparathyroidism	parathyroidectomie, dialysis	Favourable
14	M	25	0	pain	distal femur	well defined l lesion with a thin sclerotic rim	chrondroblastoma	excision	Favourable
15	F	26	0	pain, swelling	Distal femur	lytic lesion	TCG	Curettage+ bisphosphonates	
16	F	30	0	pain, swelling	femur	multiloculated lesion	Aneurysmal bone cyst	curettage	local recurrence
17	F	72	renal failure	pain	rib	well defined lytic lesion with reactive bone	hyperparathyroidism	parathyroidectomie, dialysis	Favourable
18	M	36	Smoking	pain, swelling	tibia	multiloculated lesion	Aneurysmal bone cyst	curettage	Favourable
19	M	17	0	pain	spine	dense shell of bone surrounding the lesion	osteoblastoma	bloc resection	local recurrence
20	F	22	0	pain, swelling	humerus	multiloculated lesion	Aneurysmal bone cyst	curettage	local recurrence
21	M	36	Smoking	pain, swelling	distal radius	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
22	M	17	0	pain	proximal humerus	well defined l lesion with matrix calcifications	chrondroblastoma	curettage	local recurrence
23	M	26	0	pain, swelling	femur	multiloculated lesion	Aneurysmal bone cyst	curettage	local recurrence
24	M	40	Hypothyroidism	restricted joint movement	proximal humerus	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
25	M	17	0	swelling	Distal femur	well defined l lesion with a thin sclerotic rim	non ossifiant fibroma	curettage	Favourable
26	M	21	0	pain	proximal humerus	well defined l lesion with a thin sclerotic rim	chrondroblastoma	excision	local recurrence
27	M	35	0	pain, swelling	Distal femur	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
28	F	20	0	swelling	distal femur	well defined l lesion with a thin sclerotic rim	non ossifiant fibroma	curettage	Favourable

29	F	25	0	Pathological fracture	tibia	multiloculated lesion	Aneurysmal bone cyst	curettage	local recurrence
30	M	42	0	pain, swelling	proximal tibia	lytic lesion	TCG	Curettage+ bisphosphonates	local recurrence
31	F	22	0	pain	proximal humerus,	well defined l lesion with matrix calcifications	chrondroblastoma	curettage	Favourable
32	M	15	0	pain, joint effusion	femoral neck	radiolucent nidus and surrounding sclerotic changes	osteoid osteoma	ablation	Favourable
33	F	44	0	pain, swelling	proximal tibia	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
34	F	32	smoking	pain, swelling	femur	multiloculated lesion	Aneurysmal bone cyst	curettage	Favourable
35	F	23	0	pain	proximal tibia	well defined l lesion with a thin sclerotic rim	chrondroblastoma	curettage	Favourable
36	F	38	0	pain, swelling	distal radius	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable
37	F	66	renal failure	pain	rib	well defined lytic lesion with reactive bone	hyperparathyroidism	parathyroidectomie, dialysis	local recurrence
38	F	19	0	swelling	distal tibia	well defined l lesion with a thin sclerotic rim	non ossifiant fibroma	curettage	Favourable
39	M	29	0	pain, swelling	proximal humerus	lytic lesion	TCG	Curettage+ bisphosphonates	
40	M	18	0	pain	proximal humerus	well defined l lesion with a thin sclerotic rim	chrondroblastoma	curettage	Favourable
41		35	0	pain, swelling	humerus	multiloculated lesion	Aneurysmal bone cyst	curettage	Favourable
42	F	32	0	pain, swelling	Distal femur	lytic lesion	TCG	Curettage+ bisphosphonates	Favourable

RESULTS

After the histological analysis of the 42 bone tumors rich in giant cells, we distinguished between several entities:

- 15 cases of Giant cell tumors of the bone, constituting 36% of all tumors

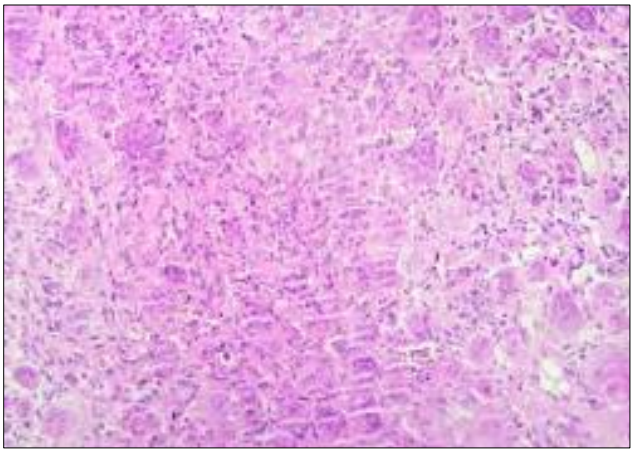

Figure 1: Giant cell tumor

- 8 cases of Aneurysmal cyst, showing cystic cavities filled with blood and separated by thick fibrous septa. These latter contained plump fibroblasts associated with giant cells. Cytological atypia and mitosis were absent.
- 7 cases of Chondroblastoma, showing a benign proliferation made of chondroblastic round cells, with incissurate, kidney-shaped nuclei with rare mitosis and giant multinucleated cells. In places, a chondroid matrix giving a gridded appearance around the chondroblasts was also noted.
- 4 cases of Non-ossifying fibromas; showing a densely cellular fusiform proliferation made of fibrohistiocytic cells with ovoid nuclei without atypia and cytoplasms with imprecise boundaries. Multinucleated giant cells and rare foci of bone metaplasia are also noted.
- 4 cases of Hyperparathyroidism, showing a benign proliferation consisting of a double contingent, mononuclear fibrohistiocytic cells, mixed with multinucleated cells, and xanthelasmised cells, with a focal storiform architecture.
- 2 cases of Osteoblastomas, showing a benign proliferation of fibroblastic cells with vascular structures of variable size and mature osteoid.
- 2 cases of osteoid osteomas, showing thickened spans of compacted bone with regular osteoblasts without atypia.

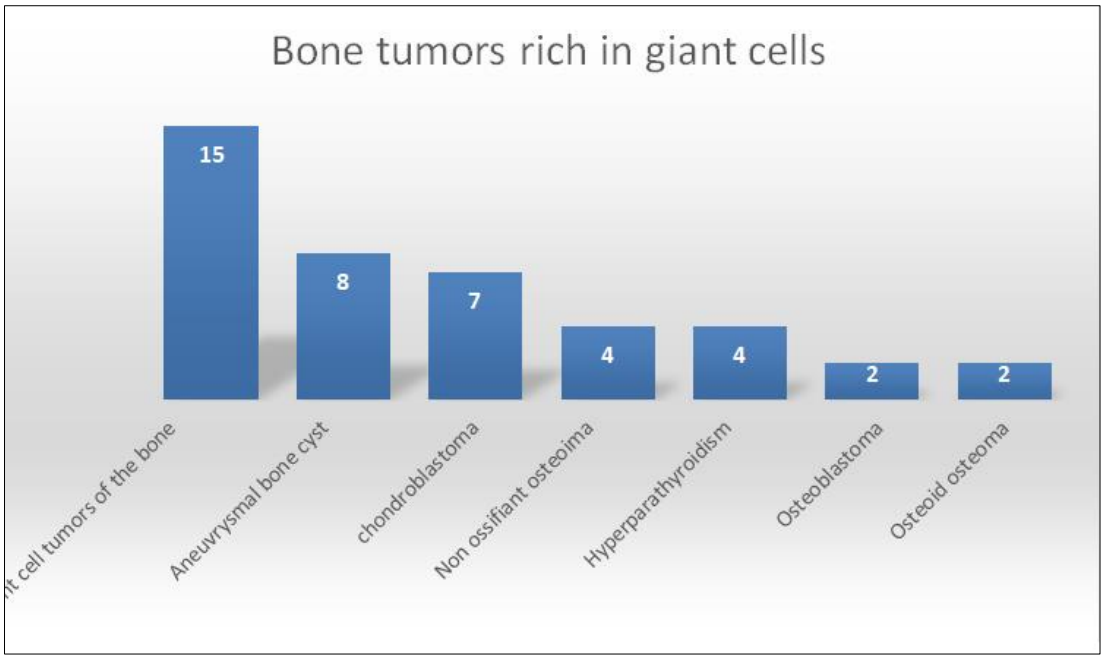

Figure 2: Distribution of histological types of bone tumors rich in giant cells

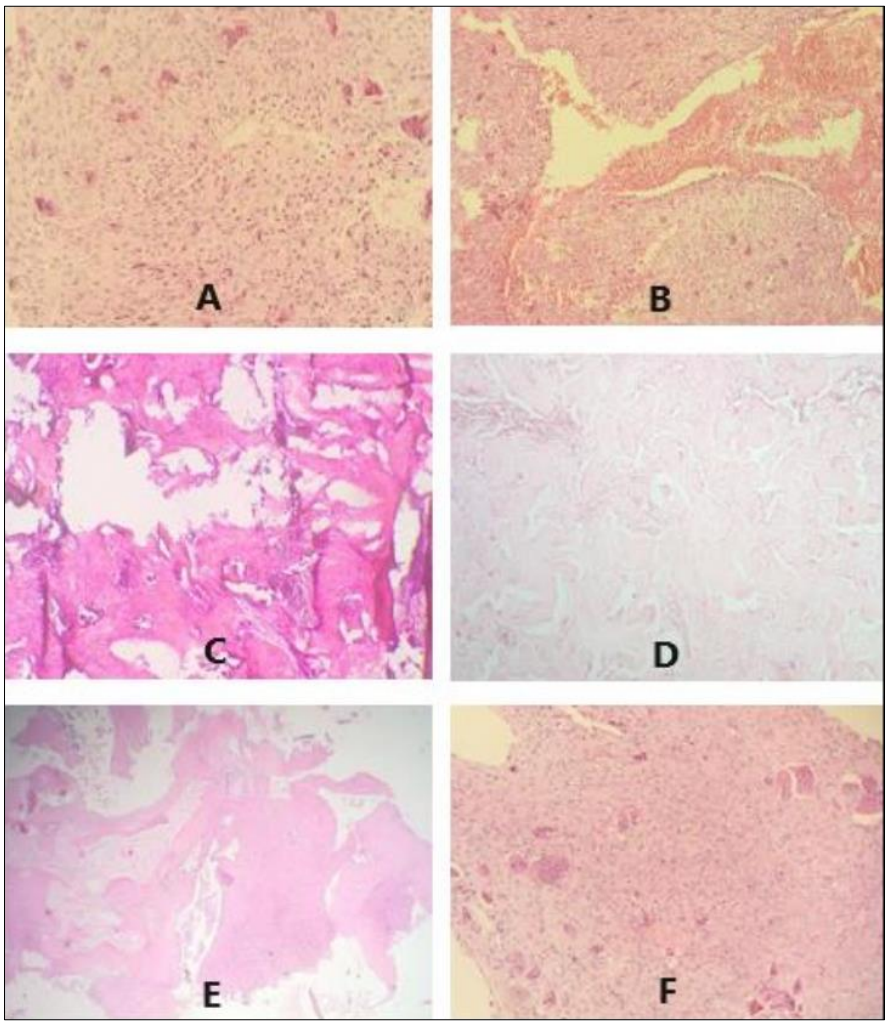

Figure 3: Histological appearance of Brown tumor (A), Aneurysmal cyst (B), Osteoblastoma (C), Non-ossifying fibroma (D), Chondroblastoma (E) and Osteoid osteoma (F)

DISCUSSION

Bone GCTs are locally aggressive but rarely malignant tumors. The mean age is 35 years with a slight female predominance. The most common site is represented by the epiphyses and metaphysis of the long bones, including the distal femur and proximal tibia. Clinical features include bone pain with restricted joint movement and can be complicated by pathological fractures in 5-12% of cases [1].

Radiological examination shows lytic lesions with a variable cortical: intact or thinned or even destroyed, corresponding to the classification of Campanacci [2].

On macroscopic examination, the tumor is generally friable, brown and poorly limited. A firm and fleshy surface is suspected of malignancy.

Histologically, the tumor is formed by a double component; the first is composed of mononuclear, round, oval or fusiform neoplastic cells with a pale eosinophilic cytoplasm and nuclei with dispersed chromatin, and small nucleoli. The second is made up of macrophages and multi-nucleated giant cells, surrounding the tumor cells. Necrotic or hemorrhagic changes as well as mitotic figures are often noted.

Malignancy in GCTs can be primary or secondary, appearing during the evolution of benign GCT. This transformation is either spontaneous or secondary to treatment with Denosumab.

Malignant GCT can, histologically, take the form of undifferentiated sarcoma, fibrosarcoma, chondrosarcoma or osteosarcoma. The presence of necrosis, marked cytonuclear atypia and atypical mitosis is very suggestive of malignancy.

The Jaffé-Lichtenstein histological classification [3], has a therapeutic and prognostic interest, and proposes a scheme distinguishing into three grades: Grade 1 is characterized by the abundance of giant cells, the absence of nuclear abnormalities and rare mitosis. In grade 2, mononuclear cells are abundant with discrete nuclear abnormalities and marked mitotic activity, but without atypical forms. And finally the grade 3 corresponds to a malignant TCG.

Immunohistochemical studies demonstrated that the tumor cells shows positive staining for anti-SALL4, anti-SATB2 and anti-p63. The detection of the H3F3A mutation by immunohistochemistry, or molecular biology, is very characteristic [4]. Histiocytic cells shows positive staining for anti-CD68.

The differential diagnosis corresponds to other bone lesions rich in giant cells, regrouping a large number of bone tumors with a very varied prognosis. Chondroblastoma, aneurysmal cyst, non-ossifying fibroma, osteoid osteomas, hyperparathyroidism and giant cell-rich osteosarcoma are the main differential diagnoses.

On histopathological analysis, chondrosarcoma is characterized by sheets of chondroblasts imbedded in an eosinophilic chondroid matrix and lace-like calcifications. Giant cells and cellular atypia may be present [6]. Secondary aneurysmal bone cyst-type degeneration can be observed especially in tumors of the hand and feet [7].

Aneurysmal cyst is a multiloculated lesion showing blood filled cystic spaces separated by cellular septa containing fibroblasts, giant cells and woven bone. Necrosis and cytological atypia are not common but mitotic activity is easily identified.

Non-ossifying fibroma is classically characterized by a storiform or whirled pattern of fibroblastic spindle cells with fibroblastic connective tissue in the background. Numerous lipophages and giant cells are also present.

Osteoid osteomas is benign proliferation with well-defined borders; It is composed of a central nidus, which contains sheets of immature woven bone, occasionally with osteoblastic rimming, scattered osteoclasts in the fibrous connecting tissue that separates the osteoid trabeculae, and vascular spaces of small and intermediate size. There is a zone of solid, mature bone in the periphery of the lesion that surrounds the nidus [8].

Hyperparathyroidism or brown tumor shows a lobular pattern composed of groups and clusters of osteoclast-like multinucleated giant cells with vascular fibroblastic stroma. Hemorrhage and hemosiderin deposits are also present.

Giant cell-rich osteosarcoma is an undifferentiated sarcoma consisting of a diffuse infiltration of a larger population of giant cells almost covering up the tumor cells. The tumor also consists of sheets and fascicles of anaplastic stromal cells or atypical spindled cells with marked cellular pleomorphism, pale chromatin, conspicuous nucleoli and numerous mitotic figures [9-11].

GCT has been traditionally treated surgically with curettage and placement of cement (polymethylmethacrylate). However, the recurrence rates have been relatively high, ranging from 15% to 25% [12-15]. Recently, the new chemotherapeutic drug Denosumab has been used to treat GCT of bone, resulting in a dramatic treatment response; however, further research is still needed to improve prognosis.

CONCLUSION

Giant cells bone tumors are a rare locally aggressive benign tumors that can be a real diagnostic challenge due to the large number of bone lesions rich in giant cells.

Finally, the identification of specific molecular abnormalities in GCT of the bone increases the reliability of morphological diagnosis and opens up new therapeutic perspectives. GCT are already benefiting from a targeted anti-RANKL therapy that is particularly useful for locally advanced or metastatic forms.

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Ethical Approval: The study is exempt from ethnical approval

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author Contribution

L BENBELLA, F ZOUAIDIA: Identification and write up of case.
M BENBELLA, A. JAHID, Z. BERNOUSSI, K. ZNATI: Review of pathology pertaining to the case.
M. MOUHSSANI: Operating surgeon.

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Guarantor: L BENBELLA.

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