Rare features of giant cell tumors of the bone: A case report

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Abstract. Giant cell tumors of the bone are local invasive diseases that are mainly composed of neoplastic monocytes and nonneoplastic multinucleated giant cells, mostly in the long bones of patients with mature bones. A specific H3F3A mutation is the key to its diagnosis. The present paper reports a case of giant cell tumor of the bone (GCTB) characterized by diffuse cholesterol crystals with few multinucleated giant cells. Imaging examination combined with immunohistochemical H3.3 G34W positivity was used to diagnose the patient with GCTB. Understanding the unique histological morphology of this patient will help doctors correctly diagnose giant cell tumors of bone and avoid misdiagnosis.

Introduction

Giant cell tumor of the bone (GCTB) is a common primary bone tumor that is potentially malignant and rarely metastasizes, accounting for 20% of benign tumors analyzed by biopsy (1). Pain is the initial symptom of the patient, and other manifestations include soft tissue swelling, skeletal deformity and pathological fractures. Surgical treatment is the first choice for treating GCTB. When the surgical plan is not feasible, other treatment methods can be considered, such as radiotherapy, ablation therapy and embolization therapy (2). The expression of RANKL is closely related to that of GCTB, but its specific role is still poorly understood. GCTB has numerous oval monocytes and osteoclast-like multinucleated giant cells at the cellular level. During pathological examination of the resected lesion, different degrees of cortical bone expansion and destruction, as well as a relatively complete periosteum, may be observed. (3) The differential diagnosis includes non-ossifying fibroma, aneurysmal bone cyst, chondroblastoma and cholesterol granuloma (4). GCTB characterized by diffuse cholesterol crystal formation is rare and is, to the best of our knowledge, described in the present case for the first time.

Case report

A 50-year-old man underwent sigmoidectomy for colon adenocarcinoma in April 2015. The pathological AJCC stage was pT2aN0M0, and no treatment was administered after the operation. In August 2020, the patient underwent surgical exploration at Xijing Hospital (Xi'an, China) for a left femur lesion, which revealed a GCTB. X-ray imaging revealed a soluble destructive lesion in the lateral condyle of the femur (Fig. 1), which was consistent with GCTB. CT revealed a large, patchy, low-density area on the medial side of the left distal femur, which was transversely expansive and ~7.1x5.2 cm in size. The edge contour was blurred, and the density was uneven. Chest X-ray and other routine examinations showed no abnormalities. The resected specimen of the left distal femur consisted of grayish red, grayish yellow and broken tissue that was soft and crunchy, with a volume of 7x6x2 cm.

The specimens were fixed in 10% neutral formalin at room temperature for 24 h, dehydrated in a conventional series of gradient alcohols, made transparent with xylene, dipped in wax, paraffin embedded into paraffin tissue blocks and sectioned to 4 μm. Staining with hematoxylin for 5 min at room temperature (20-25˚C) highlighted the nucleus, while eosin staining for 2 min highlighted the cytoplasm. After gradient dehydration and xylene transparency, the sections were sealed using neutral resin and then visualized using a light microscope. Immunohistochemical staining was performed via the EnVision two-step method (5). Sections of 4-μm thickness were cut and then immersed in a 10-mM sodium citrate buffer (pH 6) for 20 min at 97˚C for dewaxing and antigen retrieval. An appropriate amount of 3% endogenous peroxidase blocking agent was added and incubated at room temperature (20-25˚C) for 10 min. Blocking was achieved with 10% bovine serum

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albumin (cat. no. ZLI-9027; ZSGB-BIO) for 15 min at room temperature (20-25˚C). The following primary antibodies were used: H3.3 G34W (clone RM263; cat. no. 31-1145-00; RevMab BioSciences), SATB2 (clone EP281; cat. No. RMA-0750; Fuzhou Maixin Biotech, Co., Ltd.), CD163 (clone MX081; cat. no. MAB-0869; Fuzhou Maixin Biotech, Co., Ltd.), CD68 (clone KP1; cat. no. Kit-0026; Fuzhou Maixin Biotech, Co., Ltd.), Ki-67 (clone SP6; cat. no. RMA-0542; Fuzhou Maixin Biotech, Co., Ltd.). Slice sections were incubated with a primary antibodies (diluted 1:100) at 37˚C for 2 h. Subsequently, the sections were incubated with HRP-labeled goat anti-mouse IgG and goat anti-rabbit antibodies secondary antibody (diluted 1:500; cat. no. PV6000; ZSGB-BIO) at room temperature for 30 min for labeling (H3.3, G34W, SATB2, CD163, CD68, Ki-67), followed by staining with DAB substrate at room temperature (20-25˚C) for 8 min and counterstaining with hematoxylin for 20 sec. After dehydration through a graded alcohol series and clearing in xylene, the sections were mounted with neutral resin. Under the light microscope (magnification, x10 and x40), the tumor cells were oval or spindle-shaped, with diffuse cholesterol crystals (Fig. 2A) and macrophage infiltration but no obvious osteoclast-like giant cells (Fig. 2B). Immunohistochemistry (IHC) showed that the tumor cells were positive for H3.3G34W (Fig. 2C) and negative for SATB2. The Ki-67 proliferation index was ~10%. Macrophage cells were positive for cluster of differentiation (CD)163 (Fig 2E) and CD68 (KP1) (Fig 2F).

In summary, the patient was diagnosed with GCTB (left femur) with diffuse cholesterol crystal formation. After surgical excision treatment, the patient recovered well. During his 3-year follow-up, the patient reported that his physical condition had remained normal without any abnormalities.

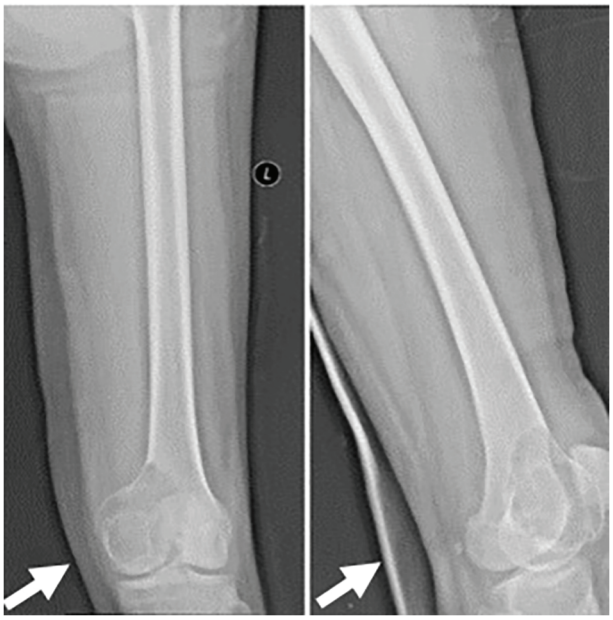

Figure 1. Plain X-ray image showing soluble destructive lesions in the lateral femoral condyle.

Discussion

GCTB is usually composed of numerous osteoclast-type multinucleated giant cells and mononuclear interstitial cells. Fibrosis, cystic degeneration, hemorrhage and hemosiderin deposition can be observed in GCTB, which is characterized by the uniform distribution of oval mononuclear tumor cells between large giant cell-like osteoblasts (6). While GCTB is a common primary bone tumor, GCTB containing fewer multinucleated giant cells and numerous cholesterol crystals has, to the best of our knowledge, not been previously reported in the literature.

The genetic characteristics of GCTB include highly periodic and specific mutations in the H3F3A gene, which encodes histone H3.3 (7). The H3F3A mutation on chromosome 1 can be detected in 69-96% of patients with GCTB. As a specific molecular pathological change in GCTB, the H3F3A mutation has good specificity for distinguishing GCTB from other giant cell bone tumors (8). H3.3G34W mutant-specific antibodies are valuable surrogate markers for the H3F3A genotype, aiding in the diagnosis of GCTB and its variants (9,10). CD163 and CD68 are markers commonly used in immunohistochemical detection to confirm the presence and activity of macrophages. However, these two markers lack specificity between diseases such as GCTB and chondroblastoma (11,12). In the present case, there were no typical histological features of GCTB, but the tumor could be clearly identified as GCTB according to the imaging findings combined with H3.3G34W positivity on IHC.

GCTB can be differentiated from non-ossifying fibroma (NOF), aneurysmal bone cyst (ABC), chondroblastoma and cholesterol granuloma (CG) as follows: i) NOF is a benign tumor composed of spindle cells with an early onset age that often manifests as single lesions with typical radiological features. It is more common in the metaphysis of the mandible and exhibits round or oval eccentric expansion, a clear boundary and a thin cortex; it is often accompanied by a sclerotic margin on the medullary side of the tumor and no periosteal reaction, with an irregular shape and a fan-shaped, sclerotic margin. Microscopically, spindle cells, foam cells and focally aggregated osteoclasts are arranged in a spoke-like pattern. However, the genetic background is still unclear. KRAS or FGFR1 activation mutations are often found in sporadic cases of NOF (13-15). GCTB is composed of neoplastic monocytes, some spindle cells and evenly distributed multinucleated giant cells. It is mostly found in individuals with mature bones. The incidence of GCTB before epiphyseal closure is low. It often manifests as different degrees of pain at the ends of the long bones of the limbs, with local tumors and limited activity. The lesions are located at the metaphysis end and exhibit eccentric, osteolytic and expansive bone destruction; clear boundaries; hemosiderin deposition; and bleeding (3).

ii) ABC is composed of fibroblasts, spindle cells, multinucleated osteoclasts and osteoblasts and has a moderate proliferation density. It mostly manifests as a single lesion and causes no obvious pain. It is more likely to occur in the vertebrae and the epiphysis of the flat shaft in adolescents (under 20 years old) before epiphyseal closure (16). Computed tomography and magnetic resonance imaging typically reveal multiple liquid-liquid planes, with symmetrically distributed lesions with obvious hardened edges, fewer solid components and less separation. Histology typically reveals multiple blood-filled cavities separated by a capsule wall composed

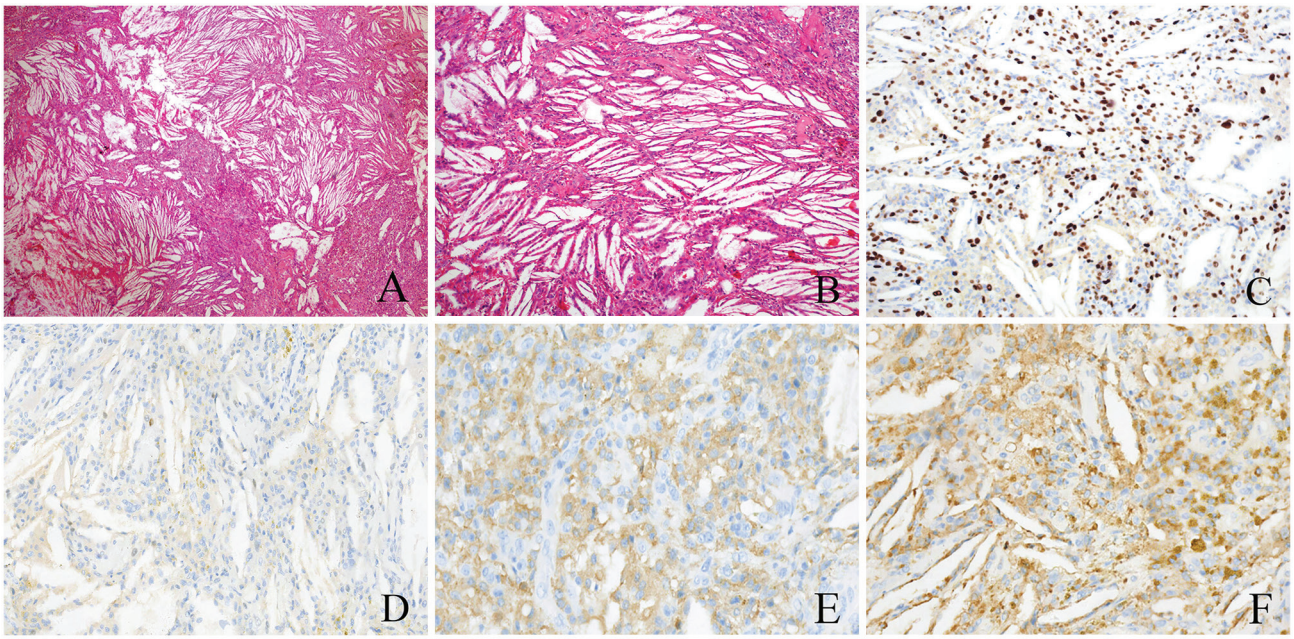

Figure 2. (A) Under low-power magnification, the tumor tissue was spindle-shaped and a small number of multinucleated giant cells could be observed. A number of cholesterol crystals and foreign body granulomas were observed (magnification, x10). (B) Numerous cholesterol crystals were observed under high magnification (magnification, x40). (C) The tumor mononuclear stromal cells showed diffuse positive nuclear H3.3G34W expression, and cholesterol crystals and foreign body granulomas were observed (magnification, x40). (D) Negative control for H3.3G34W immunohistochemistry (magnification, x40). (E) Positive expression of CD163 (magnification, x40). (F) Positive expression of CD68 (KP1) (magnification, x40). CD, cluster of differentiation.

of fibroblasts and osteoclasts, with small multinucleated giant cells distributed around the capsule wall (17). Molecular pathology has shown that patients with ABC often exhibit USP6 gene translocation (18). When GCTB occurs in older individuals, imaging shows fewer liquid-liquid planes, clear lesion boundaries and often complete and continuous cortical bone around the lesion, generally with no marginal localized sclerosis. The multinucleated giant cells of GCTB are large and evenly distributed. During the process of diagnosis, ABCs should be carefully distinguished from other bone cysts with cystic changes (3).

iii) Chondroblastoma is composed of obvious polygonal cells and occurs in individuals aged 10 to 20 years. It is often accompanied by pain and limited activity at the site of onset and often occurs in the epiphysis. The boundary of the lesion is clear, showing map-like bone destruction, eccentric growth and, commonly, calcification. The lace-like calcification area is referred to as 'chicken wire' calcification, and is capable of penetrating the bone cortex to form soft tissue masses and periosteal reactions (19,20). The surrounding bone is slightly sclerotic. Generally, T1- and T2-weighted images show enhancement and uneven signals, with a smooth interface (21). Tumors proliferate and are formed by chondroblast-like cells (20). The nucleus of the tumor is lobulated, the nuclear membrane is thick, mitotic figures are rare, there is relatively little cartilage matrix and some multinucleated giant cells are scattered among the cells. Immunohistochemistry shows positivity for SOX9, S100 and discovered on GIST 1 and specific H3.3 protein mutations, with strong, diffuse K36M expression (22). By contrast, GCTB can invade the surrounding soft tissue and the lesions are mainly soft tissue with uneven density. Cystic degeneration, hemorrhage and hemosiderin deposition can be observed, but there are no calcification points in the lesions and the number of multinucleated giant cells is large and evenly distributed (6).

iv) CG is a benign tumor-like lesion that is common in the middle ear or mastoid in patients with chronic inflammation-related diseases such as cholesteatoma and otitis media. It consists of fibrous granulation tissue filled with cholesterol crystals, and hemosiderin deposition and keratotic substances can appear around it (23).

GCTB is a locally invasive tumor with a high recurrence rate. The distal femur is the most common site of this tumor, and the treatment strategy varies according to the stage of the tumor. Intralesional curettage is the most commonly used treatment (24). Denosumab is a human monoclonal antibody that inhibits RANKL and has been approved for the treatment of adults and skeletally mature adolescents with GCTB (25). Decreased tumor size and calcification are observed after treatment with denosumab, which may reduce blood loss, promote tumor resection and reduce surgical difficulty. Denosumab is used not only for patients who plan to undergo curettage but also for patients who plan to undergo resection (26). The introduction of denosumab therapy represents a milestone in the treatment of GCTB.

In conclusion, understanding the unique histological features of GCTB in the present case report is helpful for pathologists to correctly diagnose GCTB and avoid misdiagnosis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CW and QY made substantial contributions to the conception and design of the study. CW, YG, and ZZN were primarily responsible for writing the manuscript. YG, LW, ZN, JZ and QY were responsible for collecting the patient's clinical data and data analysis. CW and QY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of anonymized data and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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