Original Article
Primary hemosiderotic fibrolipomatous tumor in bone: a case report and review of the literature

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Abstract: *Background and aim*: Hemosiderotic fibrolipomatous tumor (HFLT) is a locally invasive tumor composed of mature adipocytes accompanied by spindle cells containing hemosiderin deposition. In 2013, it was categorized by WHO as a soft tissue tumor with uncertain differentiation. So far, the literature has reported 60 cases but primary HFLT in bone has never before been reported. We set out to investigate the clinicopathological features of primary HFLT in bone. *Methods*: We retrospectively reviewed the clinical, imaging, histological, and immunophenotypic features and treatment of 1 case of primary HFLT in bone, and combined this with literature discussion. Results: HFLT occurred in the lateral femoral condyle of a 50-year-old male patient, which might have been overlooked were it not for the knee-joint pain and dysfunction. CT and MRI showed osteolytic bone destruction with a clear 4.0-cm diameter boundary, diagnosed as cystic damage of the lateral condyle of the left femur. SPECT metabolism was not active. Histologically, the lesion was composed of different proportions of mature fat cells, spindle cells, and hemosiderin. Immunohistochemistry revealed spindle cells expressing vimentin, p63, but not CD34, calponin, and others. The tumor tissue was thoroughly removed by curetting, and a bone graft was carried out after immersion in anhydrous ethanol. At the 11-month postoperative follow-up, the patient was recovering well. *Conclusions*: Primary HFLT in bone is extremely rare. In imaging, it can easily be misdiagnosed as a bone cyst. Histological morphology of the current case is similar to that of soft tissue HFLT.

Keywords: Femur/Bone, hemosiderin, fibrous tissue cells, lipoma

Introduction

Hemosiderotic fibrolipomatous tumor (HFLT) is a locally invasive tumor composed of mature adipocytes accompanied by spindle cells containing hemosiderin deposition, which is also known as fibrohistiocytic lipoma [1]. It was first reported by Marshall-Taylor and Fanburg-Smith [1] in 2000, but is relatively rare. Including our report, a total of 60 cases HFLT have been published in the scientific literature [1-14]. In 2013, it was categorized by WHO as a soft tissue tumor with uncertain differentiation [15].

HFLT occurs mainly in middle-aged female patients, with lesions often located on the ankle or superficial soft tissue of limb extremities [1-14]. HFLT in bone has never before been reported. We now report a case of a 50-year-old male patient with HFLT diagnosed on the lateral femoral condyle of the left femur. The clinical, imaging, morphologic, and immunohistochemical features, and the treatment of this patient, are described and discussed along with a review of the literature to improve understanding of this type of tumor.

Case presentation

Clinical manifestation

The patient was a 50-year-old male farmer who had suffered pain in the left knee joint without apparent cause for 15 days. The pain was persistent, being aggravated by fatigue and alleviated after resting, without any other discomfort such as fever or morning stiffness. The patient was admitted to our hospital (People's Liberation Army 152 Hospital), due to aggravated pain and limited joint motion for the past 4
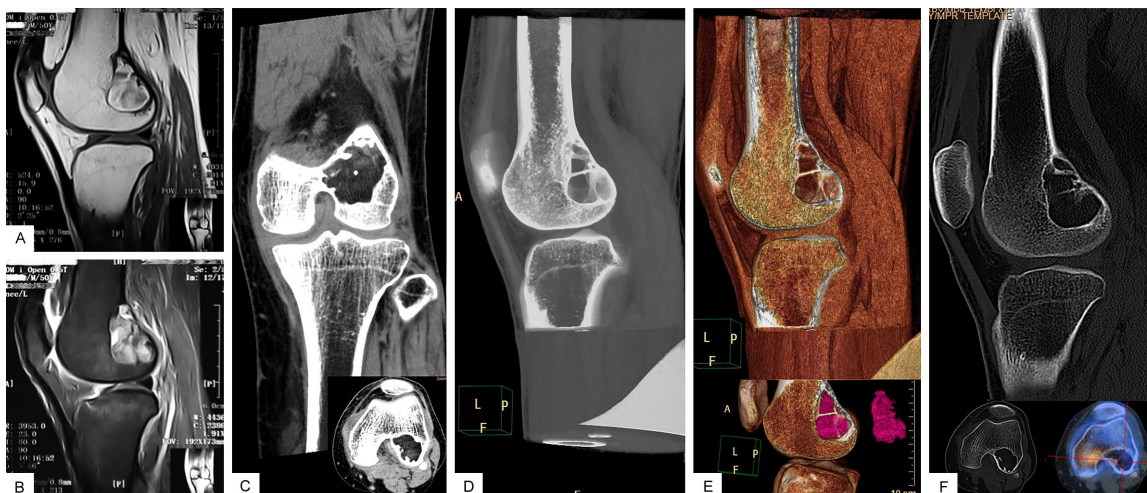
Figure 1. Primary HFLT in bone. A. MRI T1WI showing osteolytic destruction of lateral condyle of left femur with a clear boundary; lesion area shows a hybrid image shadow of slightly higher and slightly lower signal. B. MRI adipose-suppression, PD-weighted images showing hybrid image shadow of slightly higher and slightly lower signal. C. CT-reconstructed coronal and transverse planes (inserted image) of soft tissue and left lateral femoral condylar lesions showing cystic low-density shadow with clear boundary. D and E. CT 3-D reconstruction. The lesion is cystlike with a clear boundary and visible separation (insert shows tumor clearly visible after staining). F. CT-reconstructed sagittal and transverse (left insert) image of bone lesion showing ovate, low-density lesion with uneven, visible septation and marginal bone sclerosis. SPECT/CT showing sparse distribution of the nuclide in lesions, with marginal sclerotic region without obvious metabolic activity and concentrated nuclide-flanking lesion (right insert).

Table 1. Antibodies used and their pretreatments

Antibody	Clone	Pretreatment
Vimentin	V9	Citric acid
p63	4A4	Citric acid
CD34	QBEnd/10	Citric acid
Catenin-β	17c2	Citric acid
CD10	56C6	EDTA
S-100 protein	4C4.9	Citric acid
SMA	1A4	No pretreatment
MSA	HHF35	No pretreatment
Desmin	D33	No pretreatment
CD117	YR145	EDTA
CD68	KP1	Trypsin digestion
CD123	BR4MS	EDTA
CD163	10D6	Citric acid
ALK	5A4	Citric acid
p53	DO-7	Citric acid
p16	6H12	Citric acid
EMA	E29	No pretreatment
Ki-67	MIB-1	Citric acid

days. According to the patient's medical history, it was confirmed that he was healthy and without any history of trauma or other organ tumor. Physical examination demonstrated swelling of the left knee joint and tenderness of the lateral femoral condyle. His patellar grind test was positive, but negative for the rotary extrusion test, anterior and posterior drawer test, and lateral force test. No other abnormality was observed.

Auxiliary examination

Magnetic resonance imaging (MRI; i_Open0.5T, China Resources Wandong Medical Equipment Co, Beijing, China) of the left knee joint was carried out at the local hospital, in which the weighted image of T1 and proton density (PD) showed osteolytic bone destruction with a clear boundary and a hybrid image of relatively low and slightly higher signal (**Figure 1A**, **1B**), indicating cystic damage of the left lateral condyle of the femur and medial condyle bone marrow edema. Computed tomography (CT) (Philips Brilliance 256-iCT, Amsterdam, The *Netherlands*) examination conducted in our hospital showed cystic damage (4.0 × 2.5 × 1.9 cm) of the lateral condyle of the left femur, with a clear border (**Figure 1C-F**). A single-photon emission computed tomography (SPECT)/CT (Optima NM/CT 640, GE Healthcare, Milwaukee, Wisc) image, taken 3 hours after intravenous injection of 99 mTc MDP 25 mCi, clearly showed the
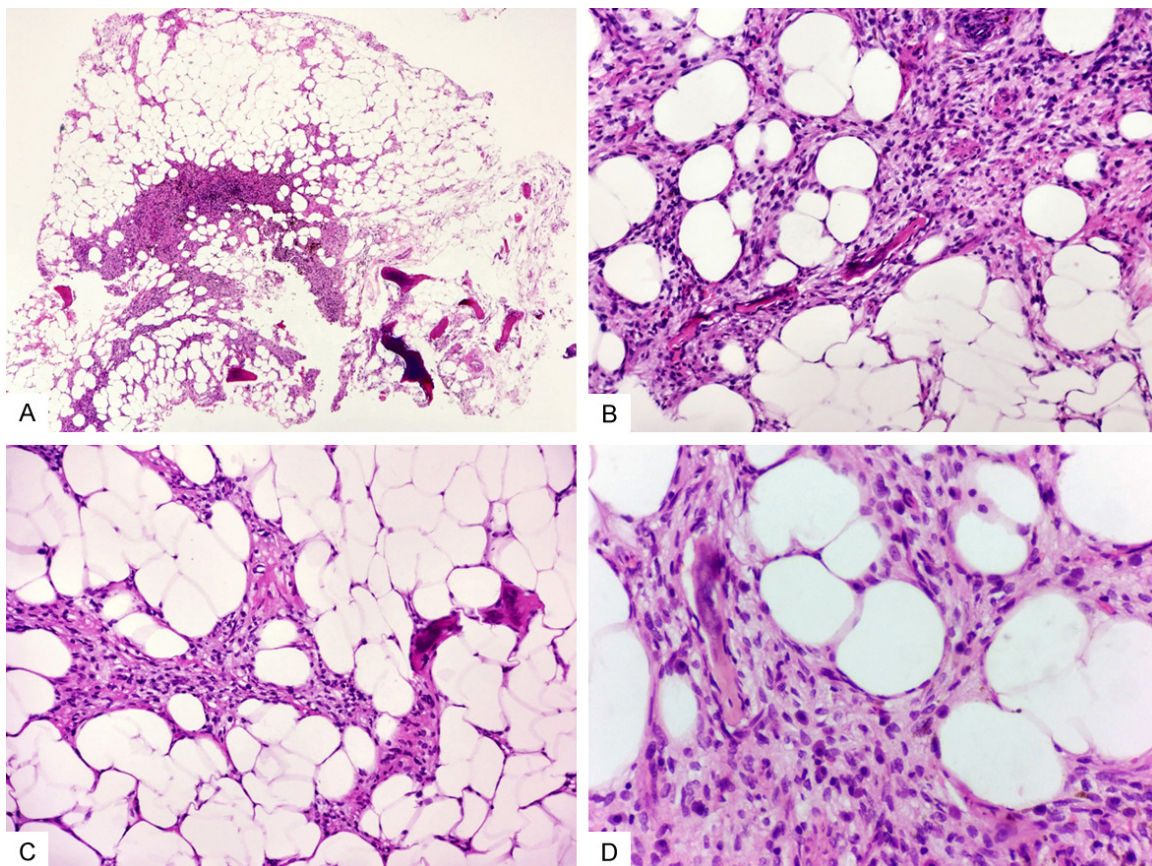
Figure 2. Primary HFLT in bone. (A-D) Lesions were composed mainly of mature adipocytes and fibroblast-like spindle cells, with locally visible residual trabecular bone. (H&E staining; ×40 [A], ×200 [B, C], and ×400 [D]).

bones of the entire body including oval, low-density areas on the left side of the lateral femoral condyle with marginal bone sclerosis. Sparse nuclide distribution was observed in the lesion area with no obvious active metabolism, along with nuclide concentrated in the left medial femoral condyle above the lesions and the left medial tibial condyle (**Figure 1F**). Concentrated or sparse nuclide distribution was not observed in any other bone area. Normal imaging of both kidneys was observed. SPECT/CT diagnosis was of a benign cystic lesion of the left lateral femoral condyle, with active bone metabolism observed on the upper surface of the left lateral femoral condyle, left medial femoral condyle, and left medial tibial condyle. Laboratory tests showed that alkaline phosphatase and other indicators of the test results were in the normal range.

Treatment and follow-up

Initial clinical diagnosis was left knee arthritis and cyst of the left lateral femoral condyle, on

which surgery was carried out. Intraoperative arthroscopy showed hyperemia of the left suprapatellar bursa and synovial membrane of the medial knee with slight hyperplasia, cord-like synovial plicae anterior to the medial femoral condyle, normal tension of the anterior and posterior cruciate ligaments, and basically normal inner and outer meniscus, with no special treatment conducted. Then the lateral femoral condyle of the left knee was exposed. A bone knife was used to chisel a 1 × 0.5-cm opening on the cyst wall, the inner tissue of the cyst thoroughly removed by curetting, and a bone graft carried out after immersion in anhydrous ethanol. The scraped tissue was saved as a pathological specimen. Follow-up at 14 months post-operation suggested that the patient recovered well.

Materials and methods

The tumor specimens were fixed in 10% neutral formalin, then conventional paraffin sectioning and hematoxylin and eosin (H&E) staining were
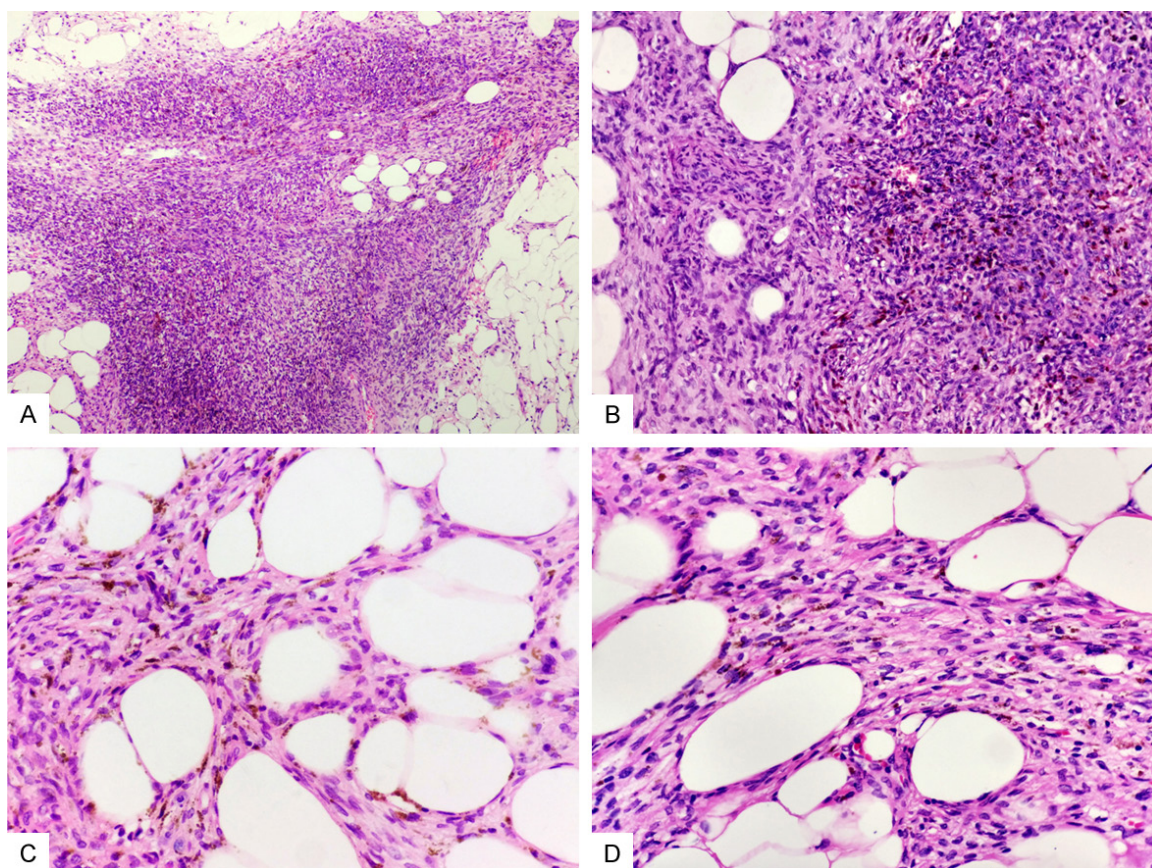
Figure 3. Primary HFLT in bone. (A) Rich spindled cells. (B) Uneven distribution of hemosiderin deposition. (C, D) Spindle cells arranged in bundles with nuclei in fatty, fusiform, fine chromatin, and eosinophilic cytoplasm, note also the scattered pigment deposition. (H&E staining; ×100 [A], ×200 [B], and ×400 [C, D]).

performed. The morphology of tumor tissue was observed under a light microscope. Immunohistochemical staining was performed using the EliVision two-step method, and the surgical steps were carried out according to the instructions. Antigen repair was performed at high temperature and high pressure using potassium ethylenediaminetetraacetic acid (EDTA, 1 mmol/L pH 9.0)/citric acid (0.01 M, pH 6.0) antigen repair fluid, or protease digestion. The primary antibodies and their pretreatment methods are listed in **Table 1**. The primary antibodies and EliVision kit were provided by Maixin Biotech (catalog No. KIT-5930, Fuzhou, China).

Results

Pathological examination

The obtained tissue was pale grey, white, brown, and broken, about 3 × 2.5 × 0.5 cm in size, with an uneven texture. Microscopic exam-

ination showed that the lesion consisted of unevenly distributed mature adipocytes and fibroblast-like spindle cells containing hemosiderin deposits. The spindle cells had round or fatty, spindly nuclei, fine chromatin, slightly acidic cytoplasm, and no obvious nuclear fission. The spindle cells were arranged in sheets, bundles, or whirlpools. Fibrous septa between fat lobules contained short spindle cells, which were arranged either in fascicles or interspersed among the adipocytes. Some of the tissue was pure adipose. Uneven hemosiderin distribution was observed in the spindle-cell areas, with macrophages engulfing hemosiderin seen in a focal or scattered pattern, as well as multinucleated giant cells observed in some areas (**Figures 2**-**4**). Different degrees of reactive inflammatory cells were seen in the tumor tissue, including mast cells, lymphocytes, plasma cells, and eosinophils. There was only a small amount of residual bone fragments in the lesion, and no hematopoietic tissue was
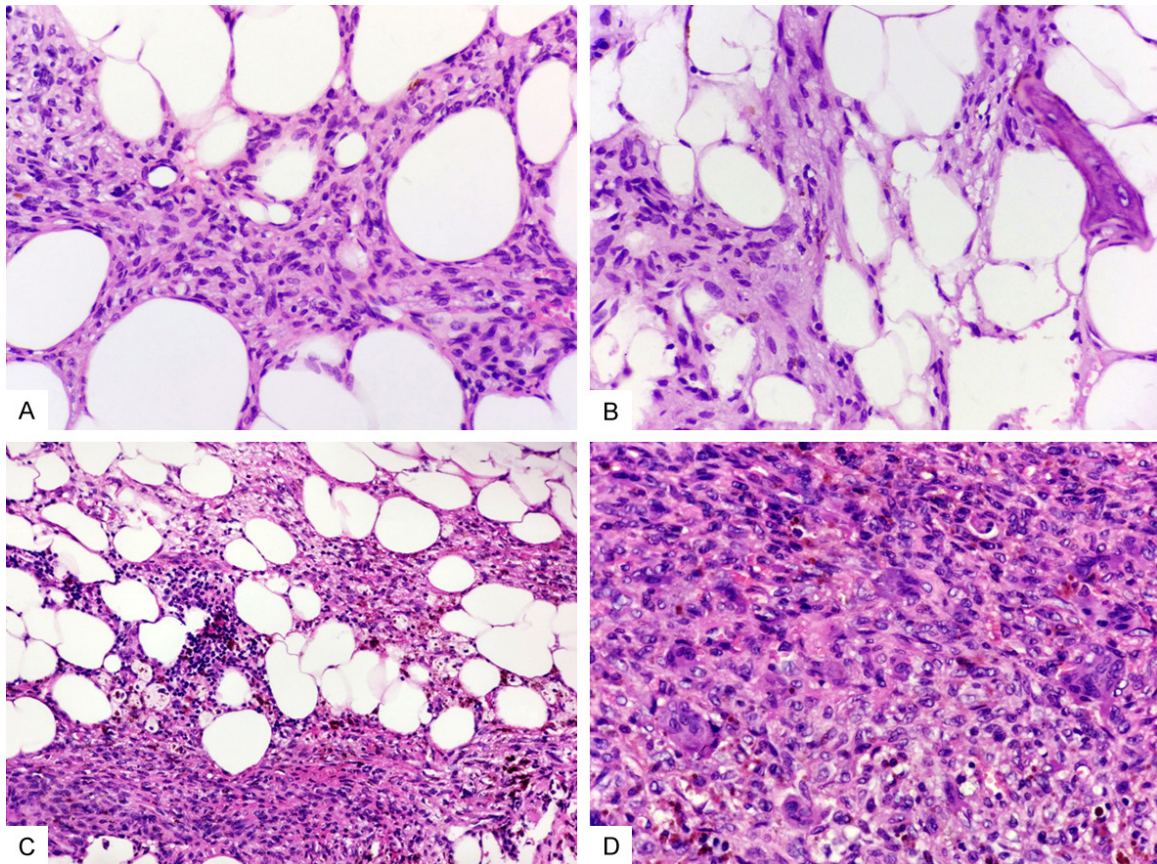
Figure 4. Primary HFLT in bone. (A) Spindle cells grew around individual adipocytes. (B) Spindle cells interspersed among the adipocytes, with remnant trabecular bone seen in tumor tissue. (C) Locally visible foam cells and focal lymphocytic infiltration. (D) Locally visible multinuclear giant cells. (H&E staining; ×400 [A, B, D], and ×200 [C]).
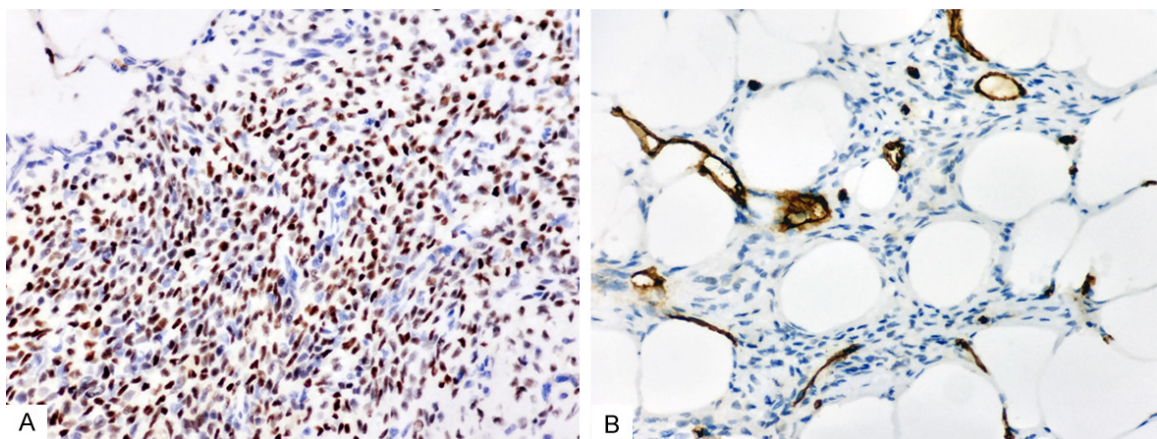

Figure 5. Primary HFLT in bone. (A) p63 positive expression rate of spindle cells in immunohistochemistry was about 60%. (B) Immunohistochemistry showing that spindle cells were CD34 negative. (Immunohistochemical staining; ×200 [A], and ×400 [B]).

observed. In the HFLT, there were no small aggregates of damaged capillaries or small blood vessels with thrombosis and perivascular hyalinization, nor were there myxoid stromata.

Immunophenotype findings

Immunohistochemistry revealed spindle cells expressing vimentin, p63 (the proportion of

Table 2. Reported lesion site, expression of CD34, and TGFBR3/ MGEA5 status or chromosome t (1;10) of HFLT

Study	No. of patients	Soft Tissue/ Bone	CD34 Positive	TGFBR3 and/or MGEA5 Rearrangement	T (1;10)
Marshall et al. [1]	10	10/0	3/3	-	-
Kazakov et al. [2]	2	2/0	2/2	-	-
Browne et al. [3]	13	13/0	7/9	-	-
Luzar et al. [4]	1	1/0	1/1	-	-
West et al. [5]	1	1/0	1/1	-	-
De Vreeze et al. [6]	1	1/0	1/1	-	-
Wettach et al. [7]	1	1/0	1/1	-	1/1
Hallor et al. [8]	1	1/0	-	1/1	-
Moretti et al. [9]	1	1/0	-	-	-
Ramalho et al. [10]	1	1/0	1/1	-	-
Antonescu et al. [11]	14	14/0	-	12/14	-
Carter et al. [12]	7	7/0	-	2/7	-
O'Driscoll et al. [13]	5	5/0	-	-	-
Zreik et al. [14]	1	1/0	-	1/1	-
Current study	1	0/1	0/1	-	-

-: Not available or not test.

positive expression was about 60%-70%) (**Figure 5A**) but not CD34 (**Figure 5B**), calponin, β-catenin, CD10, S-100 protein, alpha smooth muscle actin, actin, desmin, CD117, CD68, CD123, CD163, lysozyme, anaplastic lymphoma kinase, p53, p16, nor epithelial membrane antigen, with a Ki-67 proliferation index of <4%.

The final pathological diagnosis was femoral HFLT.

Discussion

In this report, we reviewed all 60 published documented cases of HFLT, attempt to looking for seemingly reproducible clinicopathological and Cytogenetics features [1-14] (**Table 2**). We aimed to investigate the clinical, imaging, and histopathologic features of primary HFLT in bone.

Our review suggests that HFLT predominately occurs during the middle-aged women (median age, 50 years; range: 0.7-78 years), the ratio of male to female was 1:2.8 (or 16:44) [1-14] with close to half (46%) the cases having a history of trauma or vascular disease [3]. HFLT occurs in the shallow soft tissue of limb extremities, which is most common in the foot/ankle (66%) [1-10, 12-14], but also involves the hands, fore-arms, and legs [6, 10-13], and occasionally the cheek [1].

However, HFLT in bone has never been reported in the literature. The course of HFLT often lasts up to several years before the appearance of obvious symptoms [1, 3, 9, 15]. In the current case, HFLT occurred in the patient's lateral femoral condyle, which might have been overlooked were it not for the knee joint pain and dysfunction. Morphological features of the current case were similar to that of soft tissue HFLT. It has been reported that most cases (89.4%) of HFLT are characterized by CD34 expression in spindle cells [1-7, 10]. However, the current case tested negative for CD34 expression. In addition, high expression of p63 was observed in the current case, indicating that p63 markers might help distinguish HFLT, which has never been reported in the literature of HFLT cases.

The imaging change of bone in primary HFLT shows characteristics of a tumor with a clear boundary. The internal structure of the tumor varied because of the different proportions of fibrous tissue, adipose tissue, and hemosiderin in various regions, demonstrating varied images. Through CT value determination and fat suppression, CT and MRI can explicitly demonstrate which part of the tumor is in the nature of adipose tissue [6, 16-19], while another part showed hybrid adipose and fiber signal image [5]; the content of hemosiderin can vary [5, 9], demonstrating low signals from both T1WI and T2WI and high signals from *short tau inversion recovery* sequences [20, 21]. PECT metabolism was not active. Due to the limited imaging description of HFLT [6, 9], there is no diagnostic experience in the imaging of bone HFLT. Therefore, it is easy to be misdiagnosed as a bone cyst.

The differential diagnosis of bone tumors is generally based on clinical, imaging, and histo-

pathological features, sometimes in combination with immunohistochemical or molecular genetic characteristics. In this case, in addition to the clinical characteristics of age, lesion location, and insidious onset, the imaging showed a single-bone focus with a clear boundary and induration, suggesting a slowly progressing lesion. From a pathological perspective, this case should be differentiated from lesions of similar histomorphology: (1) Pigmented villonodular synovitis/diffusive giant cell tumor of the tendon sheath, which is a kind of fibrous-tissue-cell tumor usually originating from a joint, tendon sheath, or slippery bursa synovial tissue, showing infiltrating growth of synovial tissue, with a tumor containing hemosiderin deposition and relatively unified tumor cells, mostly round or ovate. In rare cases, the tumor cells in the lesions can have a short fusiform shape and they may infiltrate adipose tissue, similar to HFLT. However, nuclear fission is common in a large number of multinucleated giant cells scattered within the tumor. Immunohistochemical expression of tissue-cell markers are demonstrated, which can be easily identified; (2) Giant cell tumor of the bone, is composed of tumorous, ovoid mononuclear cells and uniformly distributed osteoclast-like giant cells. In rare cases, the mononuclear cells in the giant cell tumor are fusiform with a small number of giant cells that are accompanied by hemorrhage and hemosiderotic deposition with p63 expression [22], which is similar to HFLT and need to be differentiated; (3) Adipose-derived tumor, usually a spindle-shaped-cell lipoma and lipofibromatosis, both of which contain adipocytes and spindle-shaped, fibroblast-like cells, ropelike collagen, and a lack of hemosiderin-containing features of HFLT. Immunohistochemistry shows that both diseases demonstrate different levels of expression of MSA and SMA, but not HFLT [3, 9, 15, 23, 24]; (4) The marginal region of a pleomorphic hyalinizing angiectatic tumor (PHAT), and myxoinflammatory fibroblastic sarcoma (MIFS) demonstrates histological features similar to those of HFLT, with relatively mild spindle-cell infiltration of adipose tissue and deposition of hemosiderin. However, PHAT shows obvious plexiform expansion of thin-walled vessels with fibrin-like material deposition, and cytoplasmic pseudo inclusion bodies seen in the nuclei of tumor cells. MIFS lesions contain high mucus-but low adipose-content, while usually little or no mucus is produced in HFLT. In addition, CD34

can be expressed in all three diseases [12, 25], with a similar cytogenetic phenotype, behave as a clonal reciprocal translocation between chromosomes 1 and 10, or TGFBR3 and/or MGEA5 gene rearrangements. Therefore, it is theorized that HFLT may be a precursor lesion of PHAT and MIFS [4, 8, 11, 12, 25-27].

Carter et al. [12] found TGFBR3 and/or MGEA5 rearrangements in 28.6% of classical HFLT, a very lower percentage than in prior studies (88.2%, 15/17) [7, 11, 14, 27]. This may partly reflect previous studies with cases known as t (1;10) enriched cytogenetic [8, 11, 12], or perhaps merely represent statistical variation [12]. The number of cases studied so far is very small, and the TGFBR3 and MGEA5 Rearrangements are Much More Common in "Hybrid" HFLT-MIFS [11, 12, 14, 25], so, cytogenetics of HFLT should be studied further.

HFLT has the biological behavior of locally invasive growth, which can easily relapse (30%-50%) [1, 3, 9, 15, 24], but rarely metastasizes [23]. The effective treatment is to remove the tumor as a whole and completely scrape away the tumor tissue (for those occurring in bone), with inactivation treatment for any tumor cells that might have survived to reduce the chance of recurrence. Of course, treatment should improve in the future.

In conclusion, primary bone HFLT, which demonstrates morphological features similar to those occurring outside the bone, is very rare. Preoperative imaging diagnosis and confirmative diagnosis by biopsy using coarse needle aspiration has important, guiding significance for clinical choice of suitable treatment. The epidemiological characteristics and prognosis of bone primary HFLT should be studied further.

Disclosure of conflict of interest

None.

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