REVIEW ARTICLE

Report of an Unusual Case of Hemosiderotic Fibrohistiocytic Lipomatous Tumor with Systematic Review of Clinicopathological Characteristics and Differential Diagnosis

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ABSTRACT

The spectrum of lipomatous lesions ranges from benign to highly malignant disease. Differentiation between these mesenchymal lesions is important for pathologist as well as clinician to indicate prognosis and choose the most appropriate treatment. Hemosiderotic firohistiocytic lipomatous tumor (HFLT) is a rare subtype of lipomatous tumor. The diagnosis is usually based on clinical, histological, and immunohistochemical (IHC) information. We reported a case of 56 years old man with a painful mass in the dorsal aspect of the thigh showing an unusal clinical presentation but a characteristic histological and IHC features. In this article we have retrospectively reviewed the 67 cases of HFLT reported in literature so far along with one case reported at our institution. The review focuses on clinicopathological and histomorphological characteristics of HFLT and the related entities. The hallmark of HFLT and its related lesions is complex admixture of mature adipose tissue, spindle tumor cells with striking deposition of hemosiderin pigment. Even though HFLT shows marked predeliction for the distal extremeties especially the foot/ ankle with a female preponderance, they can occur at uncommon site such as thigh and also in males as seen in our case.

KEY WORDS: Pleomorphic hyalinizing angiectatic tumor, Hemosiderotic fibrolipomatous tumor, Myxoinflammatory Fibroblastic Sarcoma, Hemosiderin, Lipoma.

Introduction

Hemosiderotic Fibrohistiocytic Lipomatous Tumor (HFLT), Pleomorphic Hyalinizing Angiectatic Tumor (PHAT), and Myxoinflammatory Fibroblastic Sarcoma (MIFS) are rare mesenchymal neoplasms with a tendency for the distal lower extremities. Although each of these entities have been described independently in literature, various histological and genetic observations over the past two decades have led to speculation that these tumors may be interrelated. This hypothesis is based on both histomorphological and genetic features, but the exact relationship between these three entities remains a topic of controversy and debate for the scholars. In this article, we have analyzed the key histomorphologic and immunohistochemical (IHC) features of a case of HFLT which showed an unusual clinical presentation and a discussion about the closest differentials which easily confuses the pathologist and lead to chances of misdiagnosis. Since the available literature over these entities are limited, we hereby will evaluate the relationship between these tumors.

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The spectrum of lipomatous lesions ranges from

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benign to highly malignant disease. Differentiation between these lesions is important to indicate prognosis and choose the most appropriate treatment.

Case presentation

A 63-year-old male presented to surgery department of our institution with a painless swelling over upper one third of right thigh. The patient had noticed the lesion one and a half year before, which has gradually progressed to the present size (24×12 cm). There was no significant medical history or history of trauma. Family history was noncontributory. On physical examination, swelling was 24x12 cm with ill-defined margins, which was non tender, with no local rise of temperature. On further examination, patient had difficulty in flexion and external rotation of thigh and a resistance involving half the anterior medial side of the thigh was present. MR imaging revealed lipomatous lesion of the right thigh measuring 28× 13 × 10 cm with irregular boundaries. The lesion showed multiple far-reaching intramuscular and subfascial extensions. The assessment of internal structures showed a homogeneous, lobulated lesion suspicious of liposarcoma.

Complete tumor resection was performed with free margins. After resection the specimen was subjected to histopathological evaluation.

The specimen was fixed in 10% neutral formalin, then conventional paraffin sectioning and hematoxylin and eosin (H&E) staining were performed. The morphology of tumor tissue was observed under a light microscope.

On gross examination, lipomatous lesion measured 28×13×10cm. It was darker yellow than the normal surrounding fat. External surface was well circumscribed, congested and showed blood vessels. Cut surface showed collated appearance. Cystic areas were filled with necrotic debris and hemorrhagic areas were made out (Figure 1).

Microscopically, ten representative samples throughout the whole tumor were reviewed. Histopathological examination revealed a neoplastic lesion composed of spindle cells infiltrating into adipocytic component in a honey comb pattern . These spindle cells had elongated, vesicular nuclei, inconspicuous nucleoli and scanty cytoplasm. The adipocytic component was mature without atypia and no lipoblasts were seen. There were numerous small to large ectatic blood vessels with a number of them

Figure 1: Cut section of the tumor showing solid and cystic areas. Areas of necrosis noted

showing organising thrombi, aggregates of histiocytes containing hemosiderin pigment (Figure 2). No evidence of increased mitotic activity was noted. On IHC staining of CD34, a notable diffuse staining primarily of the spindle cells, fibrocytes and vascular endothelium was seen (Figure 3). On staining with CD68 we found out positive staining for macrophage lineage such as tissue histiocytes. (Figure 4)

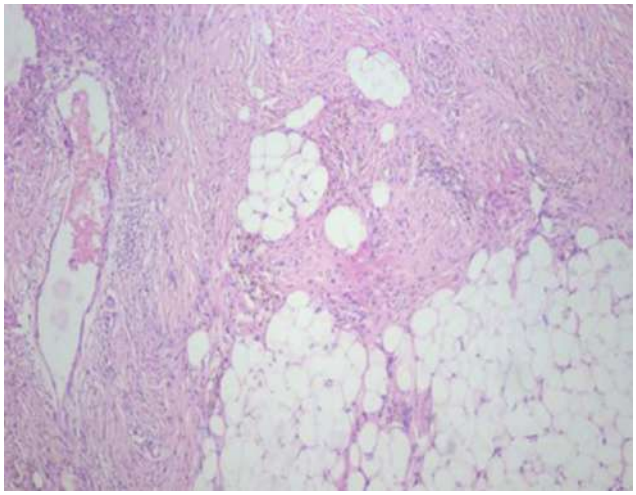

Figure 2: Photomicrograph showing varying proportions of bland spindle cells, mature adipose tissue, ectatic blood vessels and hemosiderin pigment. The spindle cells are seen in the fascicular and whorled arrangement dissecting the adipocyte component in honey comb pattern (H&E, 10x)

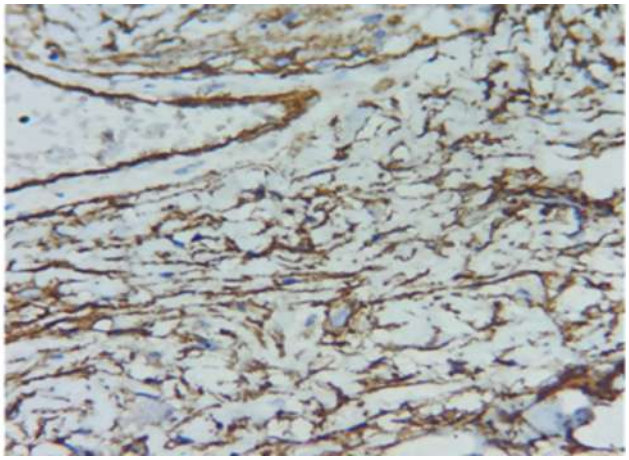

Figure 3: Photomicrograph showing CD34 immunostaining showing diffuse positivity of capillary endothelium and spindle cell component (40x)

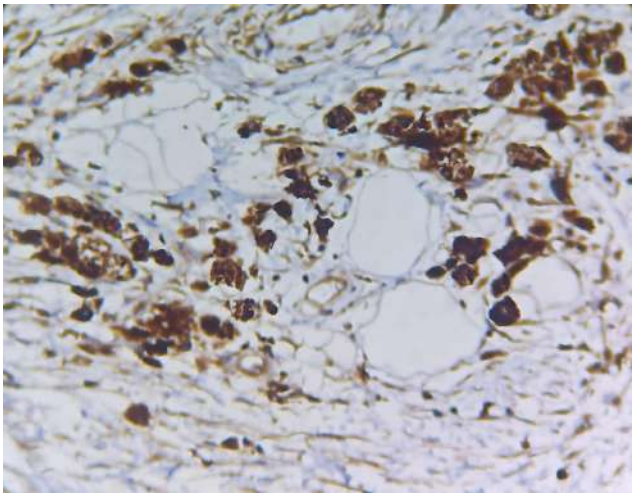

Figure 4: Photomicrograph showing CD68immunostaining showing diffuse positivity for macrophages (40x)

By combining histology and IHC features of resected specimen with clinical information, the diagnosis of HFLT was established. There were no operative or post-operative complications noted. Eighteen months after the excision, the patient continued to show no signs of recurrence.

Methods

We reviewed 67 cases of HFLT from the literature, published in English and Portuguese language which were available at Pubmed data base (Table 1).

Case reports, articles that diagnosed HFLT with adequate evidence supported by gross examination, histology, biopsy and previous recurrrences were included. Demographic data such as age at diagnosis, gender, location and size were recorded. An attempt to look for clinico-pathologic features of HFLT along with IHC features was done. All the 67 cases were studied using descriptive statistics.

Table 1: Data collection

Data base	Results
Pubmed	8 Original articles 3 Letter to editor 1 Updating article 3 Case series 7 Case reports 4 Review articles 1 Research article 1 Short communication 1 Scientific article

Results

The demographic characteristics of all HFLT included were studied and tabulated (Table 2). Our review of the literature suggests that HFLT predominately presents in middle-aged women (median age being 50 years and mean age being 51 years). Age group ranged from 7 months to 78 years, the ratio of male to female was 1: 2.6 with close to half (46%) the cases having a history of trauma or vascular disease.

HFLT occurs within the soft tissue of limb extremities, with foot/ankle accounts for 77%, but also involves the hands,[1–3] forearm,[4,5] wrist[6] and one case involving cheek and finger.[7]

It has been reported that majority cases of HFLT are characterized by CD34 expression in spindle cells and vascular endothelium.

It was noted that HFLT needs to be pathologically distinguished from related adipocytic lesions such as PHAT and MIFS which share similar location and morphologic characteristics. Summary of key morphological and genetic features of adipocytic lesions are tabulated in Table 3.

Discussion

HFLT is a rare benign fibrolipomatous lesion first described as an entity in 2000 by Marshall - Taylor

Table 2: Demographicand morphological characteristics of cases from reviewed studies

Study	Year	Number of patients	Gender	Average age in years	Localisation	Size
Marshall *et al.* [7]	2000	10	2 - Male 8- Female	50.6	8 - Foot 1 - Cheek, 1- Finger	Range 2.5 -17cm
Kazakov *et al.* [8]	2005	2	2 - Female	54	1- Foot 1- Foot	6x5x4 cm
Browne *et al.* [1]	2005	13	6 - Male 7 - Female	49	12- Ankle/foot 1 - Hand	Range 1- 13cm
Luzar *et al.* [9]	2006	1	Female	47	Ankle	1.9x1.2 cm
West *et al.* [10]	2007	1	Female	38	Foot	NA
de Vreeze *et al.* [11]	2008	1	Male	66	Thigh	19x8x4 cm
Wettach *et al.* [12]	2008	1	Female	35	Foot	NA
Hallor *et al.* [13]	2008	1	Female	40	Ankle	NA
Ramalho *et al.* [14]	2009	1	Female	33	Knee	10x8x6 cm
Moretti *et al.* [15]	2010	1	Female	56	Foot	7x5x2 cm
Antonescu *et al.* [2]	2011	14	2 - Male 12 - Female	45	13 - Foot 1 - Hand	NA
Sawalha Setal. [3]	2011	1	Female	55	Hand	3x1 cm
Carter et al. [4]	2014	7	3 - Male 4 - Female	53	4 - Foot 3 - Fore-arm	NA
O'Driscoll et al. [5]	2014	5	3 - Male 2 - Female	60	4 - Foot 1 - Fore-arm	18 cm
Marusic Z et al. [16]	2014	1	Female	57	Ankle	15x5 cm
Zreik *et al.* [17]	2016	1	Female	77	Foot	NA
Morency *et al.* [18]	2016	1	Female	55	Foot	3x1 cm
Wilk *et al.* [19]	2016	1	Female	45	Foot	14x6 cm
Etchebehere *et al.* [20]	2016	1	Female	38	Thigh	22x18x11cm
Hou *et al.* [21]	2018	1	Male	50	Knee joint	4x2.5x1.9cm
Bourhroum N et al. [22]	2019	1	Female	50	Ankle	7 cm
Pang CY et al. [6]	2021	1	Female	45	Wrist	NA
Current study	2022	1	Male	63	Thigh	28x13x10cm

NA - Not available

and Fanburg - Smith. It accounts for 0.2% of benign lipomatous lesion. [7]

HFLT generally affects the ankle and the dorsum of the foot, although it may appear in other locations such as cheeks and hands. It typically affects adults, more commonly females, in the 5th and 6th decades of life. The distinct feature about our case is its huge size, site and occurrence in male. Thigh is not the usual site of presentation. Our case and only two other cases in literature (de Vreeze *et al.* [11] and Etchebehere *et al.* [20])have reportedthigh as the location.

Histologically, it is characterized by a lipomatous lesion composed of three elements occurring in varying proportions. These elements include mature adipocytes, spindle cells and hemosiderin pigment, which is present predominantly in macrophages within the spindle cell areas, whose original deposit is unclear. The mature adipose tissue is infiltrated by strands of fibrous tissue featuring fibroblastic spindle cells and hemosiderin deposits.

Scattered areas with atypical pleomorphic cells may be present. Focal clusters of ectatic blood vessels as seen in PHAT are not uncommon. Chronic inflammatory cells are usually seen in the background. Mitosis or necrosis are usually not seen. CD34 positivity clearly differentiates the fibroblastic differentiation while CD68 positivity shows diffuse staining for the macrophages. [1]

Adipocytic lesions with overlapping clinical and histopathological features

There is an ongoing debate about the resemblance of early PHAT and HFLT; some consider HFLT a precursor lesion of PHAT, implicating HFLT to be a neoplastic lesion,[8,23]others consider HFLT an individual more reactive lesion.[1,9]

HFLT and PHAT

The hypothesis that PHATis related to HFLT was first suggested by Folpe and Weiss[24] in their 2004 study on 41 PHAT cases. These investigators noted that in nearly 50% of their cases, there was the presence of areas which were morphologically indistinguishable from HFLT at the periphery.

These HFLT-like areas were labeled "early PHAT," and were felt to represent the precursor lesion to classic PHAT[24].PHAT and HFLT both shares recurrent t(1;10) (p22;q24) rearrangement involving the TGFBR3 and MGEA5 genes.[2,13]

Same as HFLT, PHAT also has usually middle-aged adults preponderance and a proclivity for the lower extremities, though a few cases has occurred at the sites such as the arm, thigh, buttocks, or trunk with a median size of approximately 6cm. Becauseangiectatic vessels is a prominent feature, PHAT quite a few times is clinically mistaken for a hematoma or vascular neoplasm. PHAT is a vaguely circumscribed mass composed of spindled or pleomorphic cells surrounding clusters of thin-walled, ectatic vessels with sub-endothelial and intraluminal fibrin deposits and perivascular hyalinization.

Although PHAT could appear circumscribed at low power, the margin is typically infiltrative. The lesional cells range from spindled to strikingly pleomorphic and shows frequent intranuclear inclusions. Mitotic activity in PHAT is very low (<1/50 HPF). Hemosiderin deposits can be seen in macrophages or in the cytoplasm of the lesional cells. Scattered inflammatory cells are usually present.[25]

Myxoid stroma is focally present and usually there is a prominent inflammatory component. Cytologically, HFLT is consists of bland fibroblasts without significant mitotic activity and may contain scattered osteoclast-type giant cells. Small ectatic vessels with mural hyalinization or fibrinous thrombi may be present.[1,24]HFLT-like areas can be found at the periphery or admixed with otherwise typical examples of PHAT. This observation led to a hypothesis that HFLT may well be a precursor lesion to PHAT.[24]

In few rare cases it is seen that, PHAT and HFLT has progressed to a sarcoma of variable histologic grade, more often with in the setting of recurrences.[2,4,13,17] The sarcomas in such cases have myxoid stroma and a prominent inflammatory infiltrate and shows morphologic resemblance to MIFS. Solid, undifferentiated spindle cell sarcoma-like morphology has also been reported.[17]

Most PHATs and HFLTs are both positive for CD34 and negative for S100, SMA, and desmin.[4,7,23,24]

HFLT and MIFS

MIFS also referred as "inflammatory myxohyaline tumor of the distal extremities,"[26] "acralMIFS,"[27] and "inflammatory myxoid tumor of the soft parts with bizarre giant cells,"[28] is a locally aggressive, rarely metastasizing, fibroblastic tumor of borderline malignancy that typically involves the distal extremities of middle-aged adults.

The marginal region of a PHAT, and MIFS demonstrates overlapping histomorphogy with HFLT. There is seen 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 with 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

Literature suggests that there does not seem to be a direct morphologic link between HFLT and MIFS, and the available molecular genetic data within the literature are contradictory, likely attributable to the use of different morphologic criteria for the diagnosis of MIFS by different investigators. Although cases are described as representing "hybrid HFLT-PHAT," the preponderance of evidence suggests that such lesions are way more closely associated with HFLT and PHAT representing a sort of morphologic progression to high grade myxoid sarcoma.

Conclusion

Ambiguity existed about reactive or neoplastic origin of HFLT. It is now well-established on the basis of histomorphology and molecular genetic evidence that HFLT and PHAT represent different manifestations of a single entity, with HFLT representing

Table 3: Summary of key morphologic and genetic features of adipocytic lesions

Diagnosis	Morphologic Features	Association with HFLT	Molecular alteration
HFLT	Mature adipose tissue, myxoid stroma CD34-positive spindled cells with intracytoplasmic hemosiderin deposition CD68 -positive macrophagesseen Small aggregates of variable sized blood vessels Areas resembling "miniature" PHATs	Not applicable	Frequent
PHAT	Clusters of thin-walled, ectatic blood vessels, containing organizing thrombi and surrounded by amorphous eosinophilic material Pleomorphism seen, CD34-positive tumor cells with intranuclear pseudoinclusions and intracytoplasmic hemosiderin deposition Low-mitotic activity Chronic inflammatory cell infiltrate Peripheral areas identical to HFLT	Yes	Frequent
MIFS	Multinodular and poorly circumscribed hyalinized zones, typically containing bizarreappearing cells with prominent macronucleoli Areas of dense chronic inflammation myxoid nodules, often containing multivacuolated ("lipoblast-like") fibroblastic cells Mitotic activity is low Necrosis not seen Arborizing, thick-walled vessels as seen in myxofifibrosarcoma is usually absent here CD34 positive	No	Infrequent
HFLT with progression to myxoid srcoma ("hybrid HFLT-MIFS)	Areas of typical HFLT Myxoid sarcoma showing a well-developed, thick-walled vasculature Pseudolipoblasts may be seen Absence of hyalinized zones Absence of "Reed-Sternberg-like" or "virocytelike" cells	Yes	Frequent

Adapted from: Boland & Folpe [25]

the precursor or "early" lesion of classic PHAT. The hallmark of these lesions is complex admixture of mature adipose tissue, spindle tumor cells with striking deposition of hemosiderin pigment. Even though HFLT shows marked prediliction for the distal extremeties especially the foot/ ankle and female gender, they can occur at uncommon site such as thigh and in a male patient as seen in our case.

Abbreviations

HFLT: Hemosiderotic Fibrohistiocytic Lipomatous Tumor; **PHAT**: Pleomorphic Hyalinizing Angiectatic Tumor, **MIFS**: Myxoinflammatory Fibroblastic Sarcoma; **TGFBR3**: Transforming Growth Factor Beta Receptor 3; **MGEA5**: Meningioma Expressed Antigen 5; **IHC**: Immunohistochemical

Conflict of interest

Nil

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