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Case report

Lipoblastoma-like tumor of the inguinal region: a close mimicker of myxoid liposarcoma

Manuel Mazzucchelli[1], Giuseppe Angelico[2], Lucia Salvatorelli[1], Giada Maria Vecchio[1], Chiara Romano[1], Paolo Vigneri[3,4], Maria Paola Mariani[5], Gerardo Ferrara[6], Gaetano Giuseppe Magro[1]

[1] Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Anatomic Pathology, University of Catania, Catania, Italy; [2] Department of Medicine and Surgery, Kore University of Enna, Enna, Italy; [3] Medical Oncology Unit, Humanitas Istituto Clinico Catanese, Catania, Italy; [4] Department of Clinical and Experimental Medicine, Center of Experimental Oncology and Hematology, University of Catania, Catania, Italy; [5] Anatomic Pathology Unit, Macerata General Hospital, Macerata, Italy; [6] Department of Anatomic Pathology and Cytopathology, G. Pascale National Cancer Institute Foundation (IRCCS) Naples, Italy

Summary

Lipoblastoma-like tumor is a rare mesenchymal neoplasm, typically arising in the vulvar region of young women. Although it is considered a benign tumor, rare local recurrences and exceptionally distant metastases have been reported. Histological examination reveals a well-circumscribed tumor with lobulated pattern, composed of a mixture of mature adipocytes, spindle cells and lipoblasts set in abundant myxoid stroma with numerous thin-walled capillary-like vessels. Due to the rarity of this neoplasm and its morphological resemblance with other benign and malignant lipomatous tumors, the diagnosis of *lipoblastoma-like tumor* is often challenging. Herein, we present a case occurring in the inguinal region of a 28-year-old woman. Histological examination showed a mixture of mature adipocytes, bland-looking spindle cells with fibrillary cytoplasm, and numerous univacuolated lipoblasts set in a prominent myxoid matrix containing numerous thin-walled branching vessels. Immunohistochemically, neoplastic cells showed diffuse immunostaining for CD34 and negativity for α-smooth muscle actin, desmin, Rb1, MDM2 and STAT6. The main differential diagnoses included myxoid liposarcoma, spindle cell lipoma and cellular angiofibroma. FISH was negative for *DDIT3*; moreover, no evidence of regional gain or loss of *RB1* was identified by FISH. Based on morphological, immunohistochemical and cytogenetic/molecular findings, a final diagnosis of "*lipoblastoma-like tumor"* of the inguinal region was rendered.

Key words: lipoblastoma-like tumor, soft tissue tumors, myxoid liposarcoma, spindle cell lipoma, RB1

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Correspondence
Giuseppe Angelico
E-mail: giuangel86@hotmail.it

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Introduction

Lipoblastoma-like tumor (LLT) is a rare benign lipomatous neoplasm, typically arising in the vulva, most commonly in young adults[1-4], although in recent years a small number of single case reports have been described in unusual anatomical sites, including the spermatic cord and gluteal region[5-7]. It is typically a well-circumscribed and lobulated mass, variably

composed of adipocytes, spindle cells and lipoblasts[1,2]. Myxoid stroma containing a prominent network of thin-walled vessels is an additional characteristic feature[1,2]. To date, only a few cases have been reported in the literature, mostly as single case reports or small series[1-11]. Currently available follow-up data suggest that LLT is clinically indolent, with a subset of lesions which may locally recur, especially if incompletely excised; metastasis and dedifferentiation into high grade sarcomas have not been reported so far[10,11].

The diagnosis of LLT is often challenging not only due to its rarity but also for its close morphologic overlap with other lipomatous tumors such as lipoblastoma, spindle cell lipoma, myxoid liposarcoma (MLPS) and atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLPS)[2-4]. Molecular and/or immunohistochemical (IHC) analysis are not useful for diagnosis, but their application is helpful in excluding other lipomatous tumors. Although a subset of LLT have shown the loss of nuclear Rb1 staining by means of immunohistochemistry, deletions or other alterations involving *RB1* (or its locus on chromosome 13q) by FISH have not been identified[10].

Herein, we present a rare case of LLT in a 28-year-old woman presenting with an inguinal mass, clinically suspicious for being an enlarged lymph node.

Materials and methods

The surgical specimen was originally submitted for histological examination in neutral-buffered 10% formalin, dehydrated using standard techniques, embedded in paraffin, cut to 5 µm and stained with hematoxylin and eosin (H&E). Immunohistochemical studies were performed with the labeled streptavidin-biotin peroxidase detection system using the Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ). The antibodies tested were vimentin (dilution 1:100), α-SMA (dilution 1:200), desmin (D33 clone; dilution 1:100), CD34 (dilution 1:50), pancytokeratins (AE1/AE3 clone; dilution 1:50), Rb1 (G3-245 clone; dilution 1:50), MDM2 (IF2 clone; dilution 1:100) and STAT6 (s20-S621 clone; dilution of 1:200). Status of *DDIT3* (12q13) and *RB1* (13q14) was evaluated by FISH using break apart probe sets for *DDIT3* (Abbott Molecular, Abbott Park, IL) and *FOX01* (Vysis-Abbott).

Results

A 28-year-old woman presented with a 6 cm left inguinal mass, clinically suspicious for being an enlarged lymph node (clinical suspicion for lymphoma). The patient underwent surgery and the sample was sent for histological examination.

Gross examination revealed a 6-cm nodular, multi-lob-

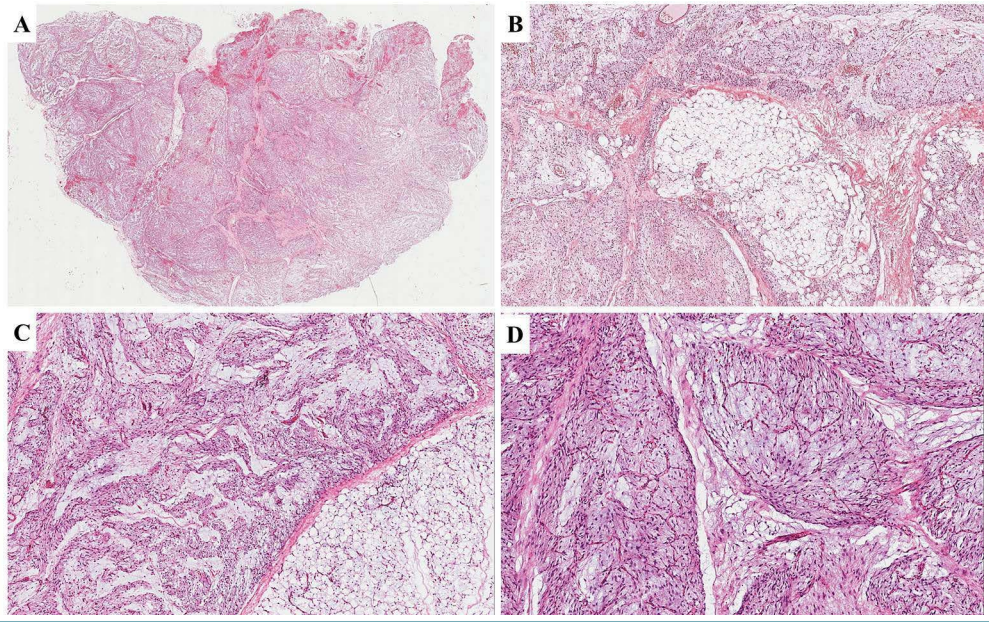

Figure 1. (A) Well-circumscribed neoplasm with lobulated growth pattern. (B) Variable proportions of mature adipocytes were observed within the tumor. (C) Prominent fibrous septa were within the tumor. (D) The tumor showed a prominent myxoid matrix with prominent capillary-like branching vessels.

ulated mass, grayish in color, with a fleshy appearance. Hematoxylin and eosin (H&E) stained sections showed a mesenchymal neoplasm with well-delineated large lobules separated by variably-sized fibrous septa (Fig. 1 A-C). The tumor showed moderate cellularity and was composed of a mixture of mature adipocytes, bland-looking spindle cells with ovoid nuclei containing finely granular chromatin (Fig. 2 A) and numerous univacuolated lipoblasts (Fig. 2 B-C) lacking nuclear enlargement and hyperchromasia; moreover, neither mitoses nor necrosis were found. The cells were set in a prominent myxoid stroma with a rich vas-

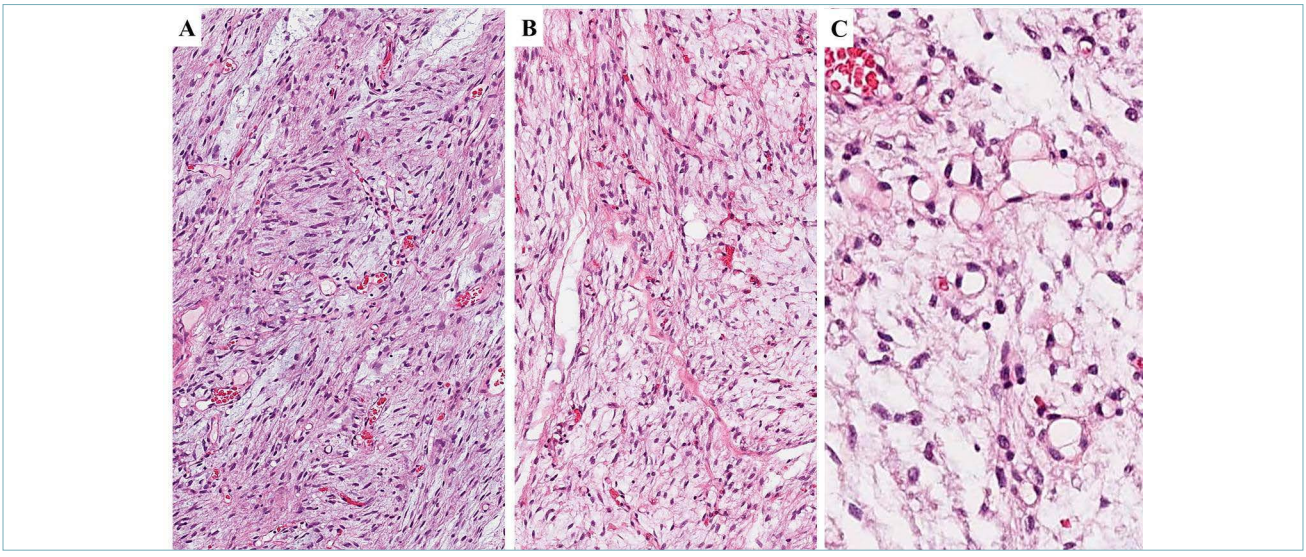

Figure 2. (A) Moderately cellular neoplastic component consisting of bland-looking spindle cells with ovoid nuclei set in a myxoid stroma. (B) Interspersed with bland-looking spindle cells, numerous vacuolated cells were observed. (C) At higher magnification these cells showed morphological features consistent with uni- or multivacuolated lipoblasts.

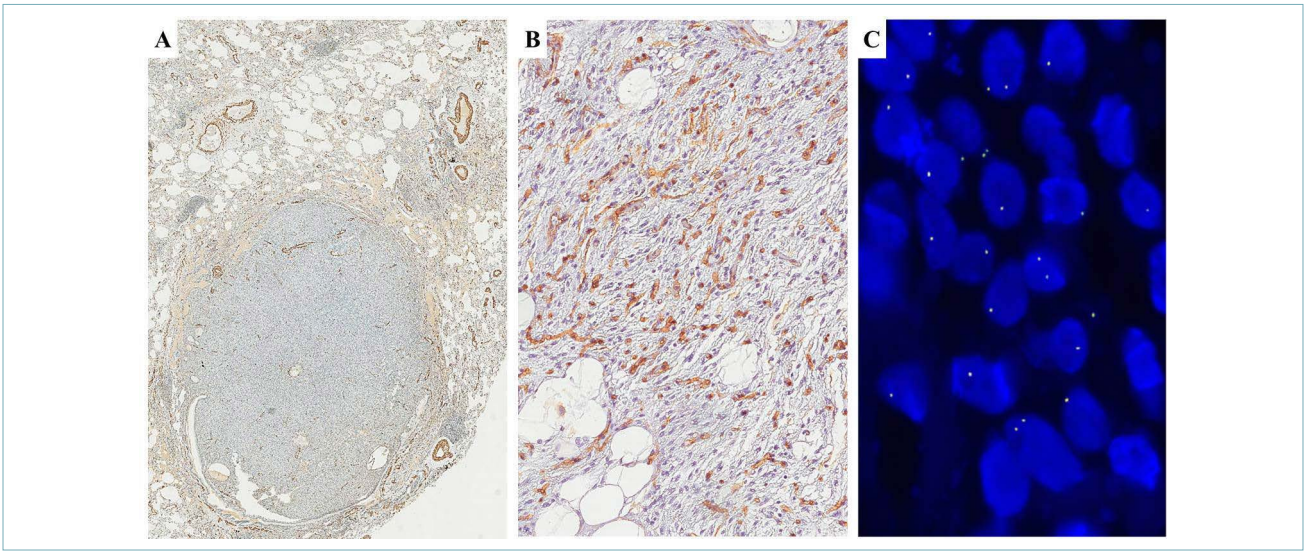

Figure 3. (A) By immunohistochemistry, neoplastic cells were negative for smooth muscle actin. (B) Diffuse immunohistochemical staining for CD34 was observed. (C) FISH analysis for the detection of structural alteration of 13q14 locus was performed; however, no evidence of regional gain or loss of RB1 was identified.

cular component consisting of numerous thin-walled, capillary-like branching vessels (Fig.1 C). A variable degree of stromal collagenization was present, either as dense aggregates or wispy fibers; rare floret-like cells were identified in the fibrous septa.
The lesion showed focal infiltration of perilesional mature adipose tissue; however, resection margins were tumor-free.
Immunohistochemical analyses showed diffuse reactivity for CD34 and vimentin and negativity for RB1, α-smooth muscle actin, desmin, pan-cytokeratin (AE1/AE3) MDM2 and STAT6 (Fig. 3 A-B).
Based on the morphological and immunohistochemical features, the main differential diagnosis revolved around spindle cell lipoma (myxoid variant) and myxoid liposarcoma.
Given the negative immunostaining for RB1, FISH analysis for the detection of structural alteration of 13q14 locus was performed; however, no evidence of regional gain or loss of RB1 was identified (Fig. 3C). Moreover, given the close morphological resemblance to myxoid liposarcoma, the tumor was also tested for DDIT3-associated gene fusions; however, FISH analysis failed to detect 12q13 rearrangements.
Based on the abovementioned morphological, immunohistochemical and cytogenetic findings, a final diagnosis of "*lipoblastoma-like tumor of the inguinal region"* was rendered. After six years of follow-up the patient is alive with no evidence of local recurrences or distant metastases.

Discussion

LLT is an uncommon benign mesenchymal tumor with less than 100 cases reported so far[10,11].
LLT occurs mainly in young women, and usually presents as a well-circumscribed mass in the vulvar region. Inguinal region represents a rare site of occurrence with only a few reported cases[5,6]. LLT was originally believed to be restricted to females; however, recent reports described its occurrence also in the spermatic cord of male patients[5-7]. Moreover, two recent papers expanded the spectrum of lipoblastoma-like tumor of the vulva by reporting additional cases occurring in the male genital region as well as extragenital cases[5,11] (Tab. I).
Histologically, LLT is closely reminiscent of lipoblastoma, being composed of a lobulated tumor containing variable proportions of mature adipocytes, uni/bivacuolated lipoblasts, and bland-looking spindle cells set in a myxoid matrix with prominent thin-walled branching vessels[1,2]. Nuclear atypia, pleomorphism and tumor necrosis are absent; only rarely mitotic figures can be found. LLT exhibits a benign clinical behavior with local recurrences (mainly due to incomplete surgical resection) documented only in rare cases[1,2]. Exceptionally one patient with distant metastases has been reported in association with concurrent pathogenic *PIK3CA* and *MTOR* activating mutations, both in the primary and in the lung/pleural metastasis[11]. The morphological features of LLT show a partial overlap with other benign and malignant lipomatous tumors, including lipoblastoma, atypical spindle cell/pleomorphic lipomatous tumor (ASPLT), spindle cell lipoma and myxoid liposarcoma[1-11].
Although morphologically similar, lipoblastoma is usually restricted to pediatric patients and predominantly affects deep soft tissues of the limbs. Molecular studies have also demonstrated *PLAG1* gene rearrangement as a distinct molecular signature of lipoblastoma, which is not observed in LLT[12].
Atypical spindle cell/pleomorphic lipomatous tumor (ASPLT) is a recently described, morphologically low-grade and clinically indolent adipocytic tumor, which has been included in the 5th edition of the WHO Classification of Soft tissue and Bone tumors[13]. Histologically, it is composed of atypical spindle cells, adipocytes, lipoblasts and pleomorphic (multinucleated) cells, set in an extracellular matrix which may vary from purely myxoid to predominantly collagenous[13]. Most cases (50-70%) show loss of nuclear RB1 expression, and FISH analyses have shown deletions/losses in 13q14 in a significant subset of cases[13]. Our case showed some morphologic overlap with ASPLT, but the abundance of lipoblasts and the lack of structural alterations of the 13q14 at FISH analysis prompted us to rule out a diagnosis of ASPLT.

Table I. Reported cases of LLTs outside the vulva.

Reference	Tumor site	Age, sex
Schoolmeester et al.[3]	Groin	32, F
Hirose et al.	Groin	/
Droop et al.[5]	Spermatic cord	20, M
Gambarotti et al.[6]	Spermatic cord	17, M
Anderson et al.	Spermatic cord	/
	Inguinal region	/
	Pelvis	/
	Scrotum	/
	Limbs	/
	Retroperitonum	/
Gross et al.	Flank	/
	Shoulder	/
	Foot	/
	Forearm	/
	Chest wall	/
Yergin et al.[8]	Gluteal region	58, M

Other tumors to take into consideration for the differential diagnosis are cellular angiofibroma and SCL, which share the same molecular alteration (loss of 13q14 region)[14]. Cellular angiofibroma is a rare mesenchymal tumor which typically arises in the genital and inguinal areas of both female and male patients. It is usually a moderately to highly cellular neoplasm composed of uniform, short spindle cells in an edematous to fibrous stroma containing numerous small to medium-sized thick-walled blood vessels with rounded or branching lumina. Small aggregates or individual adipocytes are observed in about 50% of cases[14]. Immunohistochemically, it generally exhibits loss of RB1 protein, as a result of structural alterations in 13q14 region which may be detected by FISH analysis[14]. Based on these data, our case shared only few features with cellular angiofibroma (the anatomical location and RB1 negativity on immunohistochemistry), but the morphological and molecular features made us rule out a diagnosis of cellular angiofibroma.

From a morphological point of view, the tumor we have dealt with was much more similar to SCL. In fact, the present case shared the following morphological features with SCL: i) adipocytic differentiation; ii) bland-looking spindle cells, iii) myxoid matrix, iv) stromal collagen; v) lipoblasts; vi) CD34 immunoreactivity; vii) lipoblasts (these cells can be occasionally found)[15]. Unlikely SCL, LLT exhibits a lobular configuration (i.e. tumor lobules delineated by variably-sized fibrous septa) as well as a diffuse plexiform, capillary-like vascular network. In addition, SCL lacks nuclear RB1 staining in association with the 13q14 deletion (by FISH analysis)[15]. This molecular hallmark was lacking in our case, arguing against a diagnosis of SCL.

Once SCL was ruled out, myxoid liposarcoma represented the main diagnostic concern. In this regard, our case showed several morphological similarities with MLS including: i) adipocytic differentiation; ii) myxoid matrix; iii) plexiform capillary network; iv) multinodular growth pattern; v) lipoblasts.

However, from a clinical point of view, MLS generally arises in the lower limbs of young adults[16]. Unlikely LLT, MLS usually lacks striking lobulation and both the adipocytes and the stromal cells of the fibrous septa show nuclear atypia. From a molecular point of view, MLS is characterized by 12q13 rearrangement which often results in *DDIT3-FUS* gene fusion[16]. In our case, FISH analysis failed to detect *DDIT3-FUS* rearrangement. Therefore, based on the clinicopathological and cytogenetic findings, a diagnosis of MLS was ruled out.

Conclusions

We emphasize that the diagnosis of LLT may be challenging not only due to its rarity, but also for the possibility that this tumor may arise at extra-vulvar sites. Pathologists must be aware of the existence of this rare neoplasm in order to avoid confusion with other benign and malignant adipocytic tumors showing morphological overlap, especially lipoblastoma and MLS. Awareness of the existence of LLT is – in our opinion – the "*conditio sine qua non*" for its diagnosis (surgical pathologists recognize only what they know).

Conflicts of interest statement

Authors declare no conflict of interest.

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None.

Authors' contributions

All listed authors contributed to the production of this manuscript and are listed in the appropriate order.

Ethical consideration

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethic Committee Catania 2, A.R.N.A.S. Garibaldi-Nesima of Catania, Palermo Street 636, 5-95122, Catania (protocol code: 3647/DSA; 30 December 2020).

The non-interventional and retrospective nature of our study did not require any informed consent, even if written informed consent had been obtained from each patient before surgical procedures. The clinical information was retrieved from the patients' medical records and pathology reports. Patients' initials or other personal identifiers did not appear in any image.

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