

# Histogenesis of lipomatous component in uterine lipoleiomyomas

## Uterus lipoleiomyomlarının lipomatöz içeriğinin histogenezi

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### ABSTRACT

Uterine neoplasms composed of an admixture of smooth muscle and adipose tissue are rare and have been designated as lipoleiomyomas. The origin of this tumor is still controversial and it has not been sufficiently studied. The aim of our study was to investigate the immunohistochemical phenotype of fat cells in uterine lipoleiomyomas so as to clarify their origin. Archived tissue samples of 10 uterine lipoleiomyomas were selected and analyzed immunohistochemically for vimentin, desmin, and HMB-45 expression. The patients ranged from 31 to 63 years of age (mean age 53.5±9.9). Seven tumors which affected the uterine corpus, showed intramural location; while two cases were subserosal, and one was in the cervix. All tumors were constituted by irregular bundles of smooth cells and mature large adipose cells. The amount of adipose component varied from 5 to 95% of the tumor mass. Cytological atypia and necrosis were not seen. Immunohistochemical investigations revealed obvious reactivity to vimentin and desmin in perivascular immature mesenchymal cells and tumoral smooth muscle cells. Adipose cells in the tumors demonstrated uniform vimentin expression and inconsistent desmin immunoreactivity. All adipose cells were negative for HMB-45 antigen. However, HMB-45 antigen was weakly positive in spindle shaped tumor cells of two cases. In our study, the immunohistochemical findings suggest a complex histogenesis for these tumors, which may arise from perivascular immature mesenchymal cells or direct transformation of smooth muscle cells into adipocytes by means of progressive intracellular storage of lipids.

**Key words:** Female genital tract, histogenesis, lipoleiomyoma

### ÖZET

Düz kas ve yağ dokusundan oluşan uterus tümörleri lipoleiomyom olarak adlandırılır ve nadiren görülürler. Bu tümörlerin kökeni hala tam olarak anlaşılamamıştır. Bu konuda az sayıda açıklayıcı çalışma vardır. Bu çalışmanın amacı uterus lipoleiomyomlarındaki yağ hücrelerinin fenotiplerini immünhistokimyasal olarak belirlemek ve kökenlerini tanımlamaktır. Arşivimizde bulunan 10 uterus lipoleiomyomuna ait doku örneği çalışmaya alındı ve vimentin, desmin ve HMB-45 ekspresyonu açısından immünhistokimyasal olarak incelendi. Çalışmaya alınan hastaların yaşları 31-63 yaş arasında idi (Yaş ortalaması: 53,5±9,9 yıl). Tümörlerin yedisi uterus korpusunda ve intramural yerleşimli idi. İki olgu subserozal ve bir olgu servikal yerleşim göstermekteydi. İncelemeye alınan tüm tümör örnekleri düzensiz düz kas lifleri ve büyük matür yağ hücreleri içermekteydi. Tümörlerdeki matür yağ dokusu oranı %5-95 arasında değişmekteydi. Örneklerde sitolojik atipi ve nekroz izlenmedi. Çalışmamızda yaptığımız immünhistokimyasal incelemede; vimentin ve desmin ile tümör düz kas hücrelerinde ve damarlar çevresindeki immatür mezenkimal hücrelerde belirgin pozitif boyanma saptandı. Tümör örneklerindeki yağ hücrelerinde aynı düzeyde vimentin ekspresyonu, ve zayıf ve değişen oranda desmin reaktivitesi saptandı. Tüm yağ doku hücrelerinde HMB-45 antijeni negatif olarak bulundu. Bununla birlikte, iki olguda içi tümör hücreleri HMB-45 ile zayıf pozitif boyanma gösterdi. Damarlar çevresi immatür mezenkimal hücrelerden köken alan ve/veya düz kas hücrelerinin progressif intrasellüler lipid depolaması sonucunda direkt matür yağ dokuya dönüşümü sonucu gelişebilen bu tümörlerin histogenezi immünhistokimyasal bulgulara göre de kompleks yapıdadır.

**Anahtar sözcükler:** Kadın genital sistemi, histogenez, lipoleiomyom

### INTRODUCTION

Uterine lipoleiomyoma is a rare mesenchy-

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hmal neoplasm and mostly described as a variant of uterine leiomyoma. They constitute less than 0.2% of benign uterine tumors (1-6).

The other nomenclatures for this tumor are fibrolipoleiomyoma, benign mixed mesodermal tumor, lipomatous tumor, and so on (3). Since most cases are not referred due to their benign behaviour and also in most circumstances the fat component represents a more or less abundant cell population in the context of common leiomyomas of the uterus their precise incidence is unknown (1,4). These tumors usually occur in postmenopausal women between 50 and 75 years of age. Many of these patients are asymptomatic, but in some patients symptoms are similar to those of uterine leiomyomas, such as pelvic discomfort, heaviness, and pressure, or vaginal bleeding (1,4,7).

Lipoleiomyoma is composed of variable mixture of smooth muscle and mature adipose tissue. Sometimes this tumor is accompanied by anomalous blood vessels surrounded by smooth muscle cells, and it is termed angiomyolipoma, eg. renal angiomyolipoma (RAML) (8). Although the histogenesis of RAML is uncertain, it is believed to arise from a pluripotent cell that differentiates into adipocytes and smooth muscle cells, as suggested for lipoleiomyoma (2,8). Several reports in the literature have documented positive reactivity of HMB-45 for smooth-muscle cells in angiomyolipoma (8). Furthermore, HMB-45 antigen positivity was described in uterine lipoleiomyoma by Aung et al (2).

The origin of the lipomatous lesions of the uterus has been the subject of much speculation, including misplaced embryonic fat cells, metaplasia of muscle or connective tissue cells into fat cells, lipocytic differentiation of a specific primitive connective tissue cell, perivascular fat cells accompanying the blood vessels into the uterine wall during surgery, or fatty infiltration or degeneration of connective tissue (9).

The aim of the study is to investigate presumptive histogenesis of uterine lipomatous lesions and to present their histological features,

and to discuss the possible origin of this lesion.

## **MATERIALS and METHODS**

We reevaluated 10 cases diagnosed as uterine lipoleiomyomas in Department of Pathology, Adana Baskent University, between 1999 and 2007. We recorded the following parameters: estimated percentage of tumor area involved by adipocytes, presence and degree of atypia of smooth muscle and adipocytes, mitotic rate, and tumor borders (circumscribed versus infiltrative).

The surgical specimens were fixed in 10% neutral-buffered formalin and paraffin embedded. For immunohistochemistry, serial sections of 5- $\mu$ m-thickness were cut from the paraffin blocks. The sections were deparaffinized with xylene and rehydrated with ethanol. Nonenzymatic antigen retrieval was performed on each slide and washed by phosphate-buffered saline. Immunohistochemical staining was performed manually using the standard avidin-biotin-peroxidase complex technique with DAKO (LSAB kit; DAKO, Glostrup, Denmark). The slides were exposed to primary antibodies for vimentin Ab-2 (cloned V9, NeoMarkers, Fremont CA, USA) desmin Ab-1 (Clone D33, dilution 1:50, NeoMarkers, Fremont CA, USA) and HMB-45 (code N1545, LSAB kit; DAKO, Glostrup, Denmark).

Immunoperoxidase staining of smooth muscle cells, adipocytes and perivascular mesenchymal cells are scored as negative and positive.

## **RESULTS**

During the study period, 707 patients with uterine leiomyomas were identified, and 10 lipoleiomyomas were found. Thus, lipoleiomyomas were found in 1.4% of patients with uterine leiomyomas.

The patients ranged from 31 to 63 years of age (mean age  $53.5 \pm 9.9$ ). Five cases were post-

menopausal, two were perimenopausal and three cases were in reproductive period. Nine patients sought medical attention for symptomatic leiomyomas (pelvic pain, enlarged uterus, and/or dysmenorrhea). One patient presented for treatment of a gynecological malignancy (endometrial carcinoma).

### Gross Pathology

Eight women underwent hysterectomy and bilateral salphingoophorectomy, two myomectomy for a pre-operative diagnosis of leiomyoma. One patient underwent hysterectomy and bilateral salphingoophorectomy and pelvic para-aortic lymph node dissection for endometrial carcinoma. The size of the lipoleiomyomas ranged from 1.5 cm to 19 cm, with a median of 4.75 cm.

Seven tumors affected the uterine corpus, and they were located intramurally; two cases were subserosal, and one was in the cervix. The gross appearance depended on the amount of fatty component. With microscopic foci of adipose differentiation, the cut surface resembled the usual leiomyoma. In cases with a large amount of fat, the cut surface was yellow and occasionally lobulated (Figure 1).



Figure 1. Gross appearance of lipoleiomyoma with high adipocyte component, showing a yellowish lobulated cut surface.

### Histopathological Findings

All lipoleiomyoma cases consisted histo-

logically of smooth muscle tissue admixed with a varying amount of mature adipose tissue. The amount of adipose component varied from 5% to 95% of the tumor mass. In two cases, the tumors consisted largely of mature adipose tissue (95%), and also islands composed of bundles of smooth muscle fibers and fibrous connective tissue were seen among the adipose tissue (Figure 2). In three cases hyaline degeneration was detected. Blood vessels in the stroma were not prominent and showed the usual, thin walled appearance. Cytological atypia (in smooth muscle cells or adipocytes), necrosis, and calcification were not seen. The mitotic rate was zero in all cases. In cases with malignancy no gross or microscopic contiguity between the lipoleiomyoma and the malignancy was observed. None of the tumors had infiltrative margins.

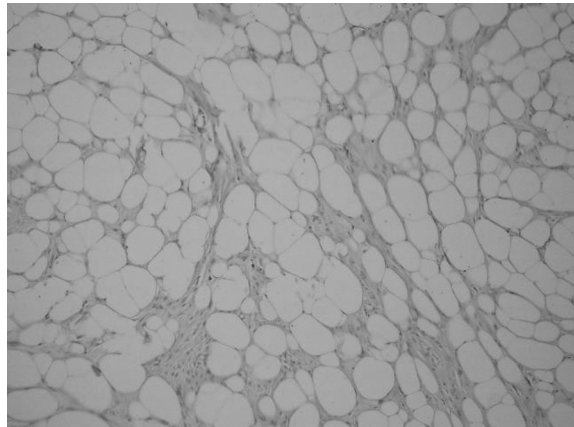
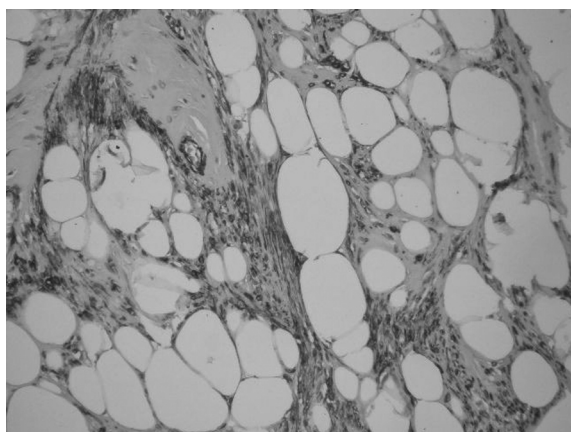


Figure 2. Numerous mature lipocytes between smooth muscle cells in a lipoleiomyoma (HE x100).

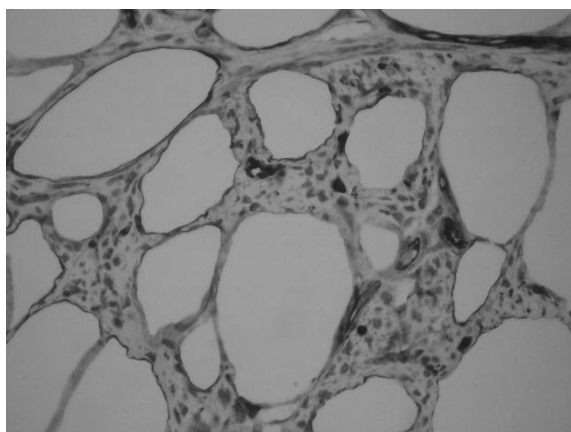
### Immunohistochemistry

Vimentin and desmin were widely expressed in smooth muscle cells, pericytes, and endothelial cells (Figure 3). Varying degrees of immunoreactivity for vimentin were uniformly detected in fat cell components of all tumors (Figure 4).

Tumor cells with adipose feature also demonstrated inconsistent desmin immunoreactivity. The number of desmin-positive tumor cells was variable in various tumors and within different areas of the same tumor.



**Figure 3.** Smooth muscle cells in a lipoleiomyoma showing strong vimentin immunoreactivity (x200).



**Figure 4.** Intense vimentin immunoreactivity in mature lipocytes of lipoleiomyoma (x400).

All adipose cells were negative for HMB-45 antigen. However, HMB-45 antigen was weakly positive in spindle shaped tumor cells of two cases.

## DISCUSSION

Uterine lipoleiomyoma is a rare benign mesenchymal neoplasm and mostly described as a variant of uterine leiomyoma (1-7). The reported incidence varies from 0.03% to 0.2% (10). Lipoleiomyomas can occur anywhere in the uterus or the uterine cervix. They can be subserosal, intramural or submucosal (1,4). In our cases, seven tumors were in the uterine corpus, and intramural; two cases were subserosal and

one of them was in the cervix.

Histopathologically, three types of uterine tumors with lipomatous component are seen (2,9): a) Pure lipoma consisting of adipocytes and very few scattered smooth muscle cells, b) Lipoleiomyoma with a variable amount and distribution of adipocytes and smooth muscle cells, c) Angiomyolipoma with prominent vascular structures admixed with adipocytes and smooth muscle cells.

The diagnosis of uterine lipomatous tumors is based on the recognition of mature adipocytes. Lipoblast (11) and atypical smooth muscle cells (12) have been reported anecdotally in uterine lipoleiomyomas. The differential diagnosis of similar uterine tumors with adipose tissue and spindle cells include; spindle cell lipoma, angiolioma, angiomyolipoma, myelolipomas, atypical lipoma, and well-differentiated liposarcomas. In our cases, all lipoleiomyomas were comprised of mature adipocytes and smooth muscle cells. There was neither lipoblastic component, atypia nor necrosis and mitotic activity in adipocytes or smooth muscle cells.

The origin of lipomatous tumors is controversial. Sieinski (5) summarized the different proposed theories in: 1) Misplaced embryonal mesodermal rests with a potential for lipoblastic differentiation, 2) Lipoblast or pluripotential cells migrating along uterine arteries and nerves, 3) Adipose metaplasia of stromal or smooth muscle cells in a leiomyoma.

There are many controversies in the pathogenesis and origin of tumor cells in uterine lipoleiomyoma and angiomyolipomas (5,6,9-11,13).

Our immunohistochemical studies have revealed reactivity of adipocytes for vimentin and desmin confirming the hypothesis of their direct transformation from smooth muscle cells into adipose cells. Furthermore, in our series the presence of vimentin positivity in mesenchymal cells around the vessels strengthen the neometaplasia of pericapillary pluripotential mesenchymal cells as Seinski and Resta et al. have sug-

gested (4,5). In all cases, variable degrees of vimentin and desmin positivity in mature adipocytes might suggest a direct transformation of muscle cells into adipose cells.

Moreover, in our cases neither angimyolipoma like vessels, nor HMB-45 antibody positivity was seen. Just in two cases weak HMB-45 positivity in spindle cells was seen. Yaegashi et al. described a uterine angimyolipoma, where smooth muscle cells from a tumor area were spindle shaped and negative for HMB-45 antigen (13). As in literature we found out that uterine and renal angimyolipomas were different clinical entities, having similarity only in histologic pattern (10).

In conclusion, our study revealed that the histological and immunohistochemical findings suggest a complex histogenesis for these tumors, in that they might arise from mesenchymal immature cells or from direct transformation of smooth muscle cells into adipocytes by means of progressive intracellular storage of lipids.

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