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Pleomorphic Liposarcoma Arising in a Lipoleiomyosarcoma of the Uterus: Report of a Case with Genetic Profiling by a Next Generation Sequencing Panel

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Introduction

Adipocytic tumors are rare in the uterus, likely reflecting the heterotopic or ectopic nature of mature adipocytes in the corpus proper. While mature adipose tissue is considered a normal constituent of cervical stroma(1), the manner by which adipocytes are introduced into the corpus is unclear. A literature review(2) by Fadare and Khabele found a variety of theories over the past century to explain the mechanism or substrate from which adipocytic neoplasms of the uterus might develop — these include adipocytic metaplasia of uterine mesenchymal tissues, misplacement of embryonic adipocytes, adipocytic differentiation of a progenitor connective tissue cell, fatty infiltration by uterine soft tissue and iatrogenic displacement.

One of the more frequent associations of adipocytes in uterine tumors of either the corpus or cervix is with smooth muscle tumors. Lipoleiomyoma or leiomyoma with adipocytic differentiation is a benign neoplasm with an incidence of 0.35–2.1% of patients undergoing treatment for uterine leiomyomata(3). It shows features typical for conventional spindled leiomyoma, but with a widely variable quantity of intermixed mature adipocytes without lipoblasts. Correspondingly, lipoleiomyosarcoma may be considered the malignant counterpart to lipoleiomyoma. It is an uncommon sarcoma composed predominantly of smooth muscle blended with scattered foci of mature adipocytes and lipoblasts(4). Although criteria are not defined for this variant of smooth muscle sarcoma, reported cases of

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lipoleiomyosarcoma have satisfied criteria set forth by the World Health Organization (WHO) for conventional spindled leiomyosarcoma of the uterus(5). Extraordinary cases of uterine liposarcoma of various subtype have been documented to arise in association smooth muscle tumors with or without adipocytic differentiation. To date, myxoid, pleomorphic, round cell and well differentiated liposarcoma have all been described as primary uterine sarcomas, often in association with a lipoleiomyosarcoma, spindled leiomyosarcoma, lipoleiomyoma or spindled leiomyoma(6). Although there are few reports(6) of liposarcoma associated with lipoleiomyosarcoma or solely lipoleiomyosarcoma, tumors with either composition have shown unpredictable behavior. Some patients are without evidence of disease many years after their initial diagnosis. However, if a tumor recurs, it is often early in the disease course and usually within months.

In this report, we present a case of a pleomorphic liposarcoma arising in a lipoleiomyosarcoma of the uterus. Genetic profiling by a next generation sequencing panel of 410 genes was utilized to analyze the molecular genetic alterations of this unusual tumor to provide insight into its pathogenesis and potential targets for therapeutics.

Case Report

A 70 year old woman without significant past medical history presented to her gynecologist with a complaint of dysuria and urinary retention. Her workup included a renal ultrasound which demonstrated a pelvic mass. Further imaging of the chest, abdomen and pelvis by computed tomography showed “an enlarged uterus containing a heterogeneous soft tissue and fatty mass in the corpus that extended to the cervix and displaced the endometrium.” Aside from two small lung nodules measuring 5mm and 1mm, there was no other definitive evidence of distant disease or adenopathy.

The patient underwent exploratory laparotomy, modified radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Gross evaluation described a 9.0 × 8.0 × 7.5 cm mass involving the uterine corpus and cervix that had a tan-yellow and lobulated cut surface with areas of hemorrhage and necrosis.

Histologic sections of the mass showed an infiltrative, destructive neoplasm comprised of two distinct and well-demarcated components (Fig. 1A). The prevailing component (approximately 85%) grew as intersecting fascicles of spindle cells that were intermixed with scattered patches of mature adipocytes and scant typical lipoblasts (Fig. 1B). These spindle cells had eosinophilic-amphophilic cytoplasm and manifested differing degrees of nuclear atypia, but most cells were in the range of moderate to severe atypia. The mature adipocytes in this spindle cell component varied only slightly in size and had small, peripherally located nuclei. Similarly, an occasional typical lipoblast was found among the mature adipocytes and had small, hyperchromatic nuclei and vacuolated cytoplasm. Tumor cell necrosis was present and the mitotic index was from 8 to 10 figures per 10 high power fields (hpf). The minor component (approximately 15%) grew as a lobular proliferation of markedly atypical lipoblasts (Figs. 1C,D) associated with a separate nonlipogenic proliferation of markedly pleomorphic, somewhat epithelioid, cells configured in a nested pattern (Fig.1E). The atypical lipoblasts were pleomorphic with large, hyperchromatic nuclei

characteristically indented by the presence of numerous cytoplasmic vacuoles. The nonlipogenic portion essentially resembled that of an undifferentiated pleomorphic sarcoma. In the pleomorphic lipoblasts, the mitotic index was 0 or 1 figure per 10 hpfs while the nonlipogenic portion was up to 15 figures per 10 hpfs. Lymphovascular invasion was not seen. The endometrium was atrophic.

Immunohistochemical (IHC) stains showed the spindle cell component to be strongly and diffusely positive for desmin, h-caldesmon and smooth muscle actin (Fig. 1F). Smooth muscle makers were negative in the nonlipogenic sarcoma/undifferentiated pleomorphic sarcoma. S100 protein was expressed by mature adipocytes and some typical and pleomorphic lipoblasts. MDM2 was negative.

In addition, the left ovary showed focal infiltration of large, atypical lymphoid cells in a background of small lymphocytes, histiocytes and scattered eosinophils. The atypical lymphoid cells expressed CD2, CD3, CD4, CD5, CD30, TCR beta F1, Granzyme B, were partially positive for CD7 and negative for CD8, CD15, CD20, PAX5, TCR gamma/delta, ALK-1 and TIA-1. Epstein Barr virus in situ hybridization (EBER) showed numerous signals in the large cells.

A validated hybridization capture-based next generation sequencing panel of 410 cancer genes(7) was utilized for deep sequencing of the uterine tumor to detect actionable genetic alterations for potential use of targeted therapy. A formalin-fixed paraffin embedded block containing both sarcoma components was selected for genetic profiling. Five somatic variations were identified (Table 1), 3 of which were mutations and 2 of which were partial or complete gene deletions. Mutations involved *TP53*, *FAT1* and *TERT*. Deletions were seen in *PTEN* and *RBI*. A fold change of less than -2 was used as a cutoff for gene deletion. Mean overall coverage depth was 512X.

The uterine tumor was interpreted as pleomorphic liposarcoma arising in a lipoleiomyosarcoma and individually fulfilled criteria set forth by the WHO Classification of Tumors(8) for pleomorphic liposarcoma of soft tissue and leiomyosarcoma of the uterus. The left ovarian lymphoid infiltrate was interpreted as an EBV positive, CD30 positive T-cell proliferation. The remaining tissues were grossly and microscopically unremarkable.

The mainstay of therapy for uterine sarcoma according to National Comprehensive Cancer Network guidelines(9) is surgical resection with negative margins and usually adjuvant chemotherapy. Agents with activity in uterine sarcoma include gemcitabine and docetaxel, however, their efficacy in rare variants is unknown. The patient sought treatment recommendations from Johns Hopkins Hospital approximately one month after her operation which included six cycles of intravenous gemcitabine and docetaxel. Pre-chemotherapy imaging by computed tomography revealed marked progression of disease. Numerous lung metastases were seen, the largest measured 1.6 cm. Nodules along the small and large intestine were up to 1.2 cm in greatest diameter. A para-aortic lymph node was enlarged at 3.6 cm and radiologically interpreted as consistent with nodal metastasis. The patient received only one cycle of chemotherapy and died suddenly approximately three

months after her diagnosis. An autopsy was not performed. Her cause of death was presumed to be complications of metastatic disease.

Discussion

The morphologic and IHC features of the present case generated a limited differential diagnosis. Chief among the considered diagnostic entities was a malignant mixed Mullerian tumor (MMMT) with overgrown homologous and heterologous elements. Liposarcoma is very rarely a heterologous element of MMMT in contrast to the far more frequent heterologous elements of chondrosarcoma and rhabdomyosarcoma found in up to 50% of MMMTs(5). The present case was extensively sampled and in the absence of an epithelial component, MMMT was effectively excluded. Dedifferentiated leiomyosarcoma(10) is a more recently described variant of leiomyosarcoma and has been reported in the uterus. Analogous to dedifferentiated carcinoma of the gynecologic tract, dedifferentiated leiomyosarcoma is defined as having conventional leiomyosarcoma coupled with a discrete transition to undifferentiated sarcoma lacking both morphologic and immunohistochemical evidence of myogenic differentiation. Heterologous elements are seen in a minority of cases and, to date, have been either osseous/osteosarcomatous or chondro-osseous type. Dedifferentiated leiomyosarcoma was not the preferred diagnosis for several reasons. First, the literature describes only conventional spindled leiomyosarcoma and not lipoleiomyosarcoma as the “well differentiated” component of each report of dedifferentiated leiomyosarcoma. Second, lipomatous or liposarcomatous heterologous elements have not been found in any dedifferentiated leiomyosarcoma. Third, while the present case had a small component of undifferentiated pleomorphic sarcoma that lacked IHC evidence of smooth muscle differentiation, it was contiguous with the pleomorphic lipoblasts and was not identified elsewhere in the tumor. The combination of pleomorphic lipoblasts and high grade, typically pleomorphic, sarcoma is the diagnostic description of pleomorphic liposarcoma according to the current WHO definition. Given the resemblance of the present case to prior reports of pure uterine lipoleiomyosarcoma and cases of liposarcoma arising in smooth muscle tumors with adipocytic differentiation as well as fulfillment of histologic criteria for leiomyosarcoma and pleomorphic liposarcoma, the present case was classified as pleomorphic liposarcoma arising in a lipoleiomyosarcoma.

In morphologic context of the present case, the five somatic alterations involving *TP53*, *PTEN*, *RB1*, *FAT1* and *TERT* identified by next generation sequencing show an overlapping spectrum of genetic changes recorded in leiomyosarcoma as well as pleomorphic liposarcoma. These mutations and deletions are commonly found in many forms of cancer and are not intrinsically diagnostic either in isolation or in combination. Instead, these data offer insight into the genetic underpinnings that may have driven or contributed to tumor development and provide potential targets for pharmacologic therapy.

The well known tumor suppressor gene, *TP53*, positioned at 17p13.1, encodes a variety of p53 isoforms that manage cell cycle, DNA repair and changes in metabolism. *TP53* mutations have been identified in some, but not all, leiomyosarcomas and pleomorphic liposarcomas(11). The present case had a *TP53* nonsense mutation in exon 5 identical to that in a prior report of conventional soft tissue leiomyosarcoma(11). It is believed that soft

tissue leiomyosarcomas bearing inactivating TP53 mutations are more aggressive and such patients have a poorer prognosis.

PTEN is a ubiquitous tumor suppressor gene located at 10q23.31 that can be inactivated in several ways including promoter methylation, mutation or deletion, and is commonly altered in numerous forms of cancer. As many as 50% of endometrioid carcinomas have dysfunctional or entirely ineffective PTEN protein activity(12). The PTEN protein serves as a cell growth inhibitor by antagonizing the PI3K/Akt/mTOR signaling pathway. PTEN's potential to suppress growth and subsequent tumorigenicity is a focus of targeted drug development. *PTEN* deletions similar to the one identified in the present case are seen in a subset of leiomyosarcoma, but not pleomorphic liposarcoma(13).

The retinoblastoma protein (pRB) encoded by the tumor suppressor gene *RB1* at 13q14.2, functions as a cell cycle regulator and is inactivated in a variety of tumors. Dysfunctional pRB also plays a critical role in cervical neoplasia via its interactions with the E7 viral oncoprotein produced in high risk types of human papilloma virus. Deletions of *RB1* have been recorded in pleomorphic liposarcoma and leiomyosarcoma(14, 15).

FAT1 located at 4q35.2, is a member of the fat tumor suppressor gene family of which there are four members. Studies have shown that inactivation of FAT1, a cadherin-like protein that mediates cell-cell adhesion interactions, may contribute to invasion and metastasis of neoplasms. To date, alteration of *FAT1* has not been documented in leiomyosarcoma nor pleomorphic liposarcoma. The mutation in the present case resulted in an amino acid substitution of valine for isoleucine, both of which are hydrophobic branched chain amino acids with similar structural properties. Using sequence homology comparison(SIFT)(16), this substitution is expected to be tolerated in the *FAT1* protein function.

TERT or telomerase reverse transcriptase at 5p15.33 encodes a telomerase responsible for de novo restoration of chromosomal terminal sequences lost during routine DNA replication. Preservation of telomeres is essential to sustain tumor growth due to the inherent need to undergo relentless cell division. *TERT* alterations have not been found in leiomyosarcoma or pleomorphic liposarcoma, but a majority (74%) of myxoid/round cell liposarcomas harbor mutation of the *TERT* promoter region(17). A *TERT* alteration matching that in the present case has been shown to induce an increase up to 4-fold of *TERT* promoter activity(18).

In summary, the clinical and pathologic findings in a case of pleomorphic liposarcoma arising in a uterine lipoleiomyosarcoma were described. The somatic genetic alterations discovered in this unusual tumor show a spectrum of changes found in both leiomyosarcoma and pleomorphic liposarcoma.

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Figure 1.

The uterine tumor showed two well demarcated components: one consisting of spindle cells mixed with patches of mature adipocytes (upper two thirds of image) and the other consisting of lobules of atypical lipoblasts (lower third of image) and nonlipogenic sarcoma (A). The spindle cells had moderate to severe atypia, 8 to 10 mitotic figures per 10 hpfs (B) and tumor cell necrosis. The pleomorphic lipoblasts contained numerous cytoplasmic vacuoles that compressed and indented their prominent and hyperchromatic nuclei (C,D). Associated with the pleomorphic lipoblast component was a markedly atypical nonlipogenic sarcoma that was morphologically distinct from the dominant spindled component and resembled an undifferentiated pleomorphic sarcoma (E). IHC for Desmin (F), h-Caldesmon and SMA was strongly positive in the spindled component and negative in the undifferentiated pleomorphic sarcoma/nonlipogenic sarcoma component of pleomorphic liposarcoma. S100 protein was expressed by typical and atypical lipoblasts as well as mature adipocytes. The overall features were interpreted as a pleomorphic liposarcoma arising in a lipoleiomyosarcoma.

Table 1

Somatic Alterations Identified by Deep Sequencing of 410 Genes

Gene (reference sequence)	Locus/Nucleotide	Amino Acid(s)	Alteration
<i>TP53</i> (NM_000546)	c.493C>T	p.Q165	Nonsense mutation in exon 5
<i>PTEN</i> (NM_000314)	10q23.31	N/A	Deletion
<i>RBI</i> (NM_000321)	13q14.2	N/A	Intragenic deletion
<i>FAT1</i> (NM_005245)	c.2806G>A	p.V936I	Missense mutation in exon 2
<i>TERT</i> (NM_198253)	g.1295228C>T	N/A	Promoter variant