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PGR Gene Fusions Identify a Molecular Subset of Uterine Epithelioid Leiomyosarcoma with Rhabdoid Features

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Abstract

Genetic aberrations among uterine epithelioid leiomyosarcomas are unknown. Following identification of an index case with *NR4A3-PGR* fusion demonstrating monomorphic morphologic features, we interrogated additional uterine tumors demonstrating similar histology and sought to describe the morphologic and immunohistochemical characteristics of *PGR*-rearranged sarcomas. Targeted next-generation RNA sequencing was performed on RNA extracted from formalin-fixed paraffin-embedded tissue of the index case. Fluorescence in situ hybridization (FISH) using custom probes flanking *PGR* and *NR4A3* genes was applied to 17 epithelioid leiomyosarcomas, 6 endometrial stromal tumors, and 3 perivascular epithelioid cell tumors. *NR4A3-PGR* fusion (n=4) and *PGR* rearrangement (n=2) were detected in six (35%) epithelioid leiomyosarcomas. Median patient age was 45 years, and all presented with FIGO stage I or II tumors, two being alive with disease at 75 and 180 months. All tumors were centered in the cervical stroma or myometrium and consisted of cells with abundant eosinophilic cytoplasm (epithelioid) including many displaying dense intracytoplasmic inclusions (rhabdoid). Myxoid matrix and hydropic change imparted a microcystic growth pattern in four tumors. Five also showed a minor spindle cell component which was low-grade in three, consisting of bland spindle cells with low mitotic activity. High-grade spindle cell morphology was seen in two tumors, exhibiting a storiform pattern of atypical spindle cells associated with brisk mitotic activity. Desmin, ER and PR were positive in all six tumors, while CD10 and HMB45 were negative. *PGR* rearrangements define a genetic subset of epithelioid leiomyosarcomas with often biphasic morphology consisting of epithelioid and rhabdoid as well as spindle cell components.

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Keywords

Epithelioid leiomyosarcoma; endometrial stromal sarcoma; PEComa; uterine sarcoma; rhabdoid; *NR4A3*; *PGR*

INTRODUCTION

Recurrent chromosomal translocations resulting in gene fusions have been well documented among uterine sarcomas, particularly those of endometrial stromal derivation. *JAZF1-SUZ12* fusion represents the most common genetic aberration described among low-grade endometrial stromal sarcomas, followed by less frequent *JAZF1-PHF1* (1), *EPC1-PHF1* (1), *MEAF6-PHF1* (2), *MBTD1-CXorf67* (3), and *EPC2-PHF1* fusions (4). *YWHAЕ-NUTM2* (5, 6), *ZC3H7B-BCOR* (7) (8, 9), *EPC1-SUZ12* (10), and *EPC1-BCOR* (10) gene fusions have also been identified among high-grade endometrial stromal sarcomas with distinctive morphologic and immunophenotypic features. Endometrial stromal sarcoma associated fusions have also been reported in undifferentiated uterine sarcomas, which in retrospect likely represent misdiagnosed or underrecognized high-grade endometrial stromal sarcomas or high-grade endometrial stromal sarcomas that arose from low-grade tumors (11).

Fusions have also been identified in less common uterine mesenchymal tumors. These include inflammatory myofibroblastic tumors which often harbor *ALK1* rearrangements (12–15) and fibrosarcoma-like uterine sarcomas underpinned by *NTRK* fusions (16). Patients with *ALK1*-rearranged tumors who develop recurrent disease may benefit from treatment with ALK directed therapies such as crizotinib or alectinib (17) (18) and those with *NTRK* fusion may benefit from larotrectinib and repotrectinib (19, 20). Patients may not need access to these drugs by clinical trial after an anticipated FDA approval of larotrectinib in October 2018. *TFE3* and *RAD51B* rearrangements have also been described in a subset of uterine perivascular epithelioid cell tumors (PEComas) (21–24).

Genetic aberrations among uterine epithelioid leiomyosarcomas are unknown likely due to the rarity of such tumors; whether gene fusions are involved in the pathogenesis of epithelioid smooth muscle tumors has yet to be elucidated. We recently encountered a group of uterine epithelioid leiomyosarcoma that harbors novel *PGR* gene rearrangements. In this study, we characterized the fusion partner gene by targeted next-generation RNA sequencing (RNAseq) and confirmed *PGR* rearrangement by fluorescence in situ hybridization (FISH). We also sought to describe the morphologic and immunohistochemical features of this distinctive clinicopathologic entity.

MATERIALS AND METHODS

Case Selection

The index case was previously diagnosed as an epithelioid leiomyosarcoma with nuclear isomorphism and a distinctive rhabdoid component that was found to harbor a *NR4A3-PGR* gene fusion by RNASeq. Retrospective archival searches of the surgical pathology files at Memorial Sloan Kettering Cancer Center (New York, NY, USA), Massachusetts General Hospital (Boston, MA, USA), and King Edward Memorial Hospital (Perth, Australia), as

well as the consult files of three of the authors (E.O., C.R.A., C.J.R.S.) were conducted for uterine epithelioid leiomyosarcomas, endometrial stromal sarcomas with epithelioid change, and uterine PEComas (Table 1). These entities were selected based on the distinctive monotonous morphology of the index case that may lead to classification as epithelioid leiomyosarcoma, PEComa, or endometrial stromal sarcoma with epithelioid features. All available hematoxylin-and-eosin (H&E) and immunohistochemical stained slides as well as pathology reports were reviewed by two pathologists (S.C., C.R.A.). Inclusion in the study required rhabdoid and epithelioid morphology with only mild to moderate nuclear pleomorphism; tumors with marked nuclear pleomorphism were excluded. Gross, morphologic, and immunophenotypic features were recorded. Clinical data, including age, stage, and outcome, was obtained through the electronic medical records and pathology reports at Memorial Sloan Kettering Cancer Center, Massachusetts General Hospital, and King Edward Memorial Hospital. This study received institutional research board approval.

Immunohistochemistry

Staining was performed on four µm formalin-fixed paraffin-embedded tissue sections for desmin, CD10, estrogen receptor (ER), progesterone receptor (PR), and HMB45 (Supplementary Table 1). Appropriate on-slide positive controls were used. Immunohistochemical stains were evaluated using a semi-quantitative scoring method based on the percentage of positive tumor cells as follows: negative (0), 1–25% (1), 26–50% (2), 51–75% (3), and 76–100% (4).

Next-generation targeted RNA sequencing

RNA was extracted from formalin-fixed paraffin-embedded tissue cut onto positively charged glass slides (four µm section, 7–10 per case) using the ExpressArt FFPE Clear RNA Ready kit (Amsbio, Cambridge, MA). RNAseq libraries were prepared using 20–100 ng total RNA with the TruSight RNA Fusion Panel (Illumina, San Diego, CA), an enrichment-based assay that targets 507 known fusion-associated genes. The sample was sequenced with 76 base-pair paired-end reads on an Illumina MiSeq. Results were analyzed using the STAR aligner and Manta fusion caller as well as the JAFFA fusion caller utilizing BOWTIE2 aligner (25, 26). mRNA expression level of *NR4A3* was evaluated in the index case and compared to >100 sarcoma types available on the same RNAseq platform. The expression of *PGR* could not be evaluated since this gene was not represented on the targeted RNAseq gene list.

Fluorescence in situ hybridization

As previously described, FISH was performed on interphase nuclei from formalin-fixed paraffin-embedded four µm tissue sections using custom bacterial artificial chromosomes (BAC) flanking *NR4A3* and *PGR* (Supplementary Table 2). Briefly, BAC clones were chosen according to the UCSC genome browser (<http://genome.ucsc.edu>) and obtained from BACPAC sources of Children's Hospital of Oakland Research Institute (Oakland, CA; <http://bacpac.chori.org>). BAC DNA was isolated, labeled with fluorochromes by nick translation, denatured, and hybridized to de-paraffinized pre-treated slides. Slides were incubated overnight, washed, and mounted with DAPI using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany) and Isis 5 software (Metasystems). Gene rearrangement

was confirmed when at least 20% of 200 successive tumor nuclei showed a break apart signal.

RESULTS

Clinical features

The entire cohort consisted of 26 tumors, including 17 epithelioid leiomyosarcomas, 6 endometrial stromal tumors with epithelioid features (1 low-grade endometrial stromal sarcoma, 4 high-grade endometrial stromal sarcomas, 1 endometrial stromal nodule), and 3 PEComas identified from institutional pathology and consultation archives (Table 1). The six patients with *PGR* fusion-positive tumors classified as epithelioid leiomyosarcoma had a median age of 45 (range, 41 to 56) years (Table 2). Four patients presented with a uterine or pelvic mass associated with painful menses or abdominal pain in two of them. Two other patients presented with symptomatic fibroids. All patients were treated with total hysterectomy and bilateral salpingo-oophorectomy and found to have either FIGO stage I or II disease. Only one patient received post-operative chemoradiation. Two patients with FIGO stage II tumors were alive with disease 75 and 180 months after initial presentation. Three patients with FIGO stage I or II tumors had no evidence of disease at last follow-up, 96, 9, and 1 month after initial presentation, respectively. One patient with FIGO stage I disease was lost to follow up.

Limited clinical data was also available in 14 of the remaining 20 patients with *PGR* fusion-negative uterine tumors (Supplementary Table 3). Eleven patients presented with a uterine or pelvic mass, two of whom also had abdominal pain. Three patients had abnormal vaginal bleeding. The median age was 56 (range, 27 to 71) years. All were treated surgically, with three patients also receiving chemotherapy and one receiving chemoradiation. Among the 12 patients with available staging and follow-up data, 4, 2, 3, and 3 patients presented with stage I, II, III, and IV disease, respectively. One died of disease 4 months after initial presentation, and three recurred 3 to 29 months later. Two patients had no evidence of disease 5 and 60 months from presentation. The remaining six patients were lost to follow-up.

Pathologic features

PGR fusion-positive sarcomas ranged from 3 to 27 (median, 9) cm in size (Table 3). Three were centered in the cervix, one of which extended into the corpus and another into the ovary. Two tumors were limited to the corpus. One tumor arose in the corpus and extended into the vaginal wall. Tumors displayed a variably brown, red, yellow-tan to white, friable, hemorrhagic cut surface. One was multi-cystic, while another was predominately necrotic with an adjacent firm, tan whorled rim. Myometrial invasion was pushing in four tumors (Figure 1A) and irregular and tongue-like in two (Figure 1B). No involvement of the endometrium was seen.

All six tumors were composed of an epithelioid and rhabdoid component consisting of uniformly cellular sheets of cells with abundant eosinophilic granular cytoplasm and centrally or eccentrically located nuclei with irregular membranes, occasional grooves,

vesicular chromatin, and mostly one to two prominent nucleoli (Figures 2A and 2B, Table 3). Median mitotic index was 10 (range, 4 to 19) per 10 high power fields (HPF). Myxoid matrix and hydropic change were seen in three and one tumors, respectively, imparting a microcystic growth pattern.

Five tumors also exhibited a spindle cell component (Table 3). Three consisted of densely cellular foci of small cells with fusiform nuclei, inconspicuous nucleoli, and scant wavy eosinophilic cytoplasm (Figure 2C) with a mitotic index of <1 per 10 HPF. This component was predominately distinct from foci of epithelioid cells (Figure 3A and 3B). The spindle cell component in the other two tumors consisted of cells with intermediate size ovoid to elongated nuclei with one or two prominent nucleoli, irregular nuclear membranes, and abundant eosinophilic cytoplasm arranged in a storiform pattern (Figure 3C). The mitotic index was 8 per 10 HPF in one of the two tumors (Figure 3D).

Numerous small arterioles without perivascular tumor cell whorling were seen throughout the tumors. Scattered large thick-walled blood vessels were also present. Tumor and infarct necrosis was present in only one tumor, while lymphovascular invasion was seen in two (Table 3).

Among the *PGR* fusion-negative tumors, the median tumor size was 12 (range, 3 to 28) cm (Supplementary Table 4). Rhabdoid morphology was seen in all 20 tumors, 15 of which also showed a spindle cell component. Myxoid stroma was seen in only four tumors, three of which showed both rhabdoid and spindle cell features. Median mitotic index was 9 (range, 1 to 55) per 10 HPF. Lymphovascular invasion and tumor cell necrosis was seen in nine and seven tumors, respectively.

Immunohistochemical features

Desmin was positive in all six *PGR* fusion-positive tumors (Table 3, Figure 4A). Expression was present in both epithelioid and rhabdoid and spindle cell components. In three tumors, immunoreactivity was seen throughout the spindle cell component and only scattered cells in the epithelioid and rhabdoid component (Figure 4B). All six tumors expressed PR and ER (Figures 4C and 4D). HMB45 was performed on four tumors and was negative. Five tumors tested for CD10 were also negative. H-caldesmon was positive in one tumor, but negative in four others; myogenin was negative in three tumors (data not shown).

Among the *PGR* fusion-negative tumors, desmin expression was seen in 11 epithelioid leiomyosarcomas, 2 endometrial stromal tumors, and 3 PEComas (Supplementary Table 4). CD10 was positive in three epithelioid leiomyosarcomas, two endometrial stromal tumors, and two PEComas. ER and PR expression were seen in nine epithelioid leiomyosarcomas, one endometrial stromal tumor, and three PEComas. HMB45 staining was present in 25% of cells in three epithelioid leiomyosarcomas and in >25% of cells in all three PEComas.

Molecular features

Targeted RNA sequencing of the index case (case 1) demonstrated a *PGR-NR4A3* fusion, resulting from a t(9;11)(q22.3;q22.1) translocation (Fig. 5A). The fusion junction reads showed that *PGR* exon 2 was fused in frame to the entire coding sequence of *NR4A3*,

starting with exon 2 (Fig. 5B). Thus, the projected fusion protein would include the progesterone receptor domain of PGR and the entire NR4A3 protein. A marked mRNA upregulation of *NR4A3* was observed compared to other sarcoma types (Fig. 5C). *NR4A3* and *PGR* rearrangements were also confirmed subsequently by FISH. The remaining study group was screened by FISH for abnormalities in both *NR4A3* and *PGR* genes. A *NR4A3-PGR* fusion was detected in three additional tumors previously diagnosed as epithelioid leiomyosarcoma (Figure 6). *PGR* rearrangement with no identifiable fusion partner was observed in two tumors also previously diagnosed as epithelioid leiomyosarcoma. *PGR* and *NR4A3* rearrangements were not detected by FISH in the remaining 11 epithelioid leiomyosarcomas, 5 endometrial stromal tumors, or 3 PEComas.

DISCUSSION

In this study, we identified a molecular subset of uterine epithelioid leiomyosarcoma exhibiting distinctive isomorphic epithelioid and rhabdoid features and harboring *PGR* rearrangements, often in association with an *NR4A3* fusion partner. All six tumors affected pre- or perimenopausal women and arose from either the wall of the uterine corpus or cervix. Most tumors exhibited a biphasic appearance with a high-grade epithelioid and rhabdoid component alongside or intermixed with a low- or high-grade spindle cell component. Myxoid matrix and hydropic change often imparted a microcystic and reticular pattern. Diffuse PR, diffuse or focal ER, and at least focal desmin expression was seen in all tumors, while CD10 and HMB45 were negative in all tumors tested. Two of the six patients developed recurrent disease, confirming the malignant behavior of these tumors.

The progesterone receptor gene (*PGR*) is located on 11q22.1 and encodes a member of the steroid receptor superfamily. Expressed ubiquitously in human tissues, the encoded protein mediates the physiological effects of progesterone involved in the establishment and maintenance of pregnancy. Differential expression of PGR may occur in tumorigenesis; however, *PGR* mutations and polymorphisms are infrequent in cancer. Somatic *PGR* mutations are usually missense and occur in approximately 1% of all cancer types. According to The Cancer Genome Atlas, *PGR* mutations were found in only 2.4% of endometrial carcinomas and were enriched among endometrioid tumors (27); *PGR* mutations comprise only 0.2% of ovarian high-grade serous carcinomas (28). No *PGR* gene fusions have been identified by TCGA studies in various common cancer types, including breast and ovarian malignancies (28, 29). Thus, our findings suggest that this small subset of leiomyosarcomas with distinctive rhabdoid and epithelioid morphology are characterized by novel *PGR* rearrangements, not previously identified in other tumors types.

Fusion of *PGR* with the nuclear receptor subfamily 4, group A, member 3 (*NR4A3*) was seen in two-thirds of our uterine leiomyosarcomas with epithelioid and rhabdoid morphology. *NR4A3* gene located at 9q22 encodes a member of the steroid-thyroid hormone-retinoid receptor superfamily that activates peroxisome proliferator-activated receptor-gamma (PPAR-gamma) (30). *NR4A3* gene fusions, mostly commonly with *EWSR1*, have been detected in extraskeletal myxoid chondrosarcomas (30–32). Other gene fusion partners such as *TAF15*, *TCF12*, *TFG*, *FUS*, and *HSPA8* have also been reported with less frequency among these rare soft tissue neoplasms (31, 33, 34). While our uterine

leiomyosarcomas harboring *NR4A3-PGR* fusions are morphologically distinct from extraskeletal myxoid chondrosarcomas, it is of interest to note that rhabdoid features are characteristic of extraskeletal myxoid chondrosarcomas with non-*EWSR1* *NR4A3* fusions (31). Furthermore, myxoid stroma was seen in three of four *NR4A3-PGR* fusion-positive uterine sarcomas, and not in the remaining two tumors with *PGR* rearrangement only.

These tumors are morphologically distinct from typical uterine epithelioid leiomyosarcomas. In general, epithelioid leiomyosarcomas are defined by round and polygonal cells comprising more than 50% of the overall tumor (35–37). Since epithelioid smooth muscle tumors are rare, criteria predictive of malignant behavior are currently not well established. Based on the largest reported studies, malignancy may be assigned in the setting of any cytologic atypia and five or more mitotic figures per 10 HPF in the absence of tumor necrosis; or five or more mitotic figures per 10 HPF and tumor cell necrosis with any degree of cytologic atypia (35–37). In practice, most epithelioid smooth muscle tumors fulfilling these criteria usually demonstrate marked nuclear pleomorphism, similar to the vast majority of conventional spindle cell leiomyosarcomas. While mild to moderate cytologic atypia was present among our tumors harboring *PGR* rearrangement, overt nuclear pleomorphism was lacking.

The nuclear monomorphism seen in *PGR* fusion-positive leiomyosarcomas resembles that seen in low-grade endometrial stromal sarcomas with epithelioid change (38), high-grade endometrial stromal sarcomas of various genotypes (5, 6, 8, 9, 39, 40), and undifferentiated uterine sarcomas of uniform type (41). The biphasic appearance of *PGR* fusion-positive uterine leiomyosarcomas may be confused with low-grade endometrial stromal sarcomas with epithelioid change (38) and high-grade endometrial stromal sarcomas harboring *YWHAE-NUTM2* fusion (5, 6) or *BCOR* internal tandem duplication (39, 40). However, the complete lack of CD10 expression, typical low-grade endometrial stromal sarcoma morphology, and endometrial involvement in *PGR* fusion-positive sarcomas all argue against endometrial stromal derivation and are helpful features in their distinction from low-grade endometrial stromal sarcomas with epithelioid change and high-grade endometrial stromal sarcomas with *YWHAE* or *BCOR* genetic abnormalities. Undifferentiated uterine sarcoma of either uniform or pleomorphic type remains a diagnosis of exclusion. The presence of desmin expression and *PGR* rearrangement allow distinction of *PGR* fusion-positive sarcomas from undifferentiated uterine sarcoma.

Uterine epithelioid leiomyosarcomas, including *PGR* fusion-positive tumors, share morphologic overlap with lesions classified as uterine PEComas. Both smooth muscle tumors and PEComas may exhibit epithelioid and spindle cell features as well as melanocytic differentiation by immunohistochemistry. Some studies report that the presence of delicate capillaries surrounding tumor cells and nests favors a diagnosis of PEComa over smooth muscle neoplasia (21); in addition, thick-walled blood vessels, perinuclear vacuoles, and diffuse eosinophilic cytoplasm without granularity are more common among smooth muscle tumors rather than PEComas (21, 42). Expression of two or more melanocytic markers, such as HMB45 and Melan A, even if present in 5% of tumor cells, is considered diagnostic of PEComa in the appropriate morphologic context according to another study (22). However, melanocytic marker expression has also been reported in a subset of uterine

smooth muscle tumors (43–45). With the exception of identifying *TSC1/TSC2* mutations (24) and *TFE3* or *RAD51B* rearrangements (21, 23, 24, 46), there is no gold standard in the diagnosis of uterine PEComas at this time. No *PGR* rearrangements were detected by FISH in the three PEComas tested in our cohort, nor in the cases tested by whole transcriptome RNAseq in our prior study (24). In addition, none of our *PGR* fusion-positive sarcomas showed any HMB45 staining, suggesting that these tumors are in fact distinct from tumors classified as uterine PEComas.

While clinical outcome data is limited, the observed survival among these six patients suggests that *PGR* fusion-positive sarcomas share malignant behavior. Multi-institutional studies with larger number of patients and longer follow-up are required to more accurately describe the clinical behavior of these rare lesions. While none of the patients in our cohort received hormonal therapy, PR expression as a result of *PGR* rearrangement suggests hormonal therapy may be a reasonable approach for treatment of advanced/recurrent disease..

In summary, *PGR* gene rearrangements define a novel molecular subset of epithelioid leiomyosarcomas. These tumors exhibit a high-grade but isomorphic rhabdoid and epithelioid component that may be associated with a low- or high-grade spindle cell component. Myogenic differentiation and lack of CD10 and HMB45 expression distinguish these tumors from mimickers such as endometrial stromal sarcoma and PEComa. Further studies are needed to evaluate the relationship between this genetic subset and the remaining group of epithelioid leiomyosarcoma with similar morphology and clinical features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Tumor interface of *PGR*-rearranged sarcomas.
Tumors may exhibit a (A) circumscribed, pushing border or (B) infiltration into adjacent tissues.

Figure 2. Histology of *PGR*-rearranged sarcomas.

(A) Most tumors have a biphasic appearance with a (B) high-grade rhabdoid and epithelioid component that may be associated with myxoid matrix. (C) The spindle cell component when present demonstrates bland fusiform cells that may impart a microcystic pattern.

Figure 3. Distinctive patterns of spindle cell components of *PGR*-rearranged sarcomas. Spindle cells may be (A) admixed with (left and bottom) or (B) form a distinct nodule (right) separate from the high-grade rhabdoid and epithelioid component. (C) The spindle cell component may show increased nuclear pleomorphism.

Figure 4. Immunoprofile of *PGR*-rearranged sarcomas.

Desmin may be (A) diffuse or (B) focal). All tumors are ER-positive and may demonstrate (C) diffuse ER immunoreactivity. (D) All tumors are diffusely and strongly positive for PR.

Figure 5. Fusion structure and molecular correlates.

(A) Diagrammatic representation of the *NR4A3-PGR* gene fusion, resulting from a t(9;11) (q22.3;q22.1) translocation. The gene loci are indicated with vertical red lines on the horizontal chromosomes, while the exonic breakpoints are indicated by a red arrow. Green and orange arrows indicate the direction of transcription of the individual genes. (B) Detailed RNA sequencing fusion junction reads, exon composition of the fusion transcripts and protein domain structures of each protein. (C) Box plot showing high levels of *NR4A3* mRNA expression for the index case compared to other sarcoma types.

Figure 6. *NR4A3-PGR* fusion by FISH fusion assay.

NR4A3 signal (green, telomeric) comes together with *PGR* signal (yellow, telomeric), in keeping with an unbalanced *NR4A3-PGR* fusion; the red centromeric signal of *PGR* being lost (left). In comparison, two normal cells showing red-yellow signals of *PGR*, separate from the green *NR4A3* signal (right).

Table 1.

Summary of Study Cohort

Tumor type	n	<i>PgR</i> rearrangement (n)	<i>NR4A3</i> rearrangement (n)
Epithelioid leiomyosarcoma	17	6	4
Endometrial stromal tumor	6	0	0
Low-grade endometrial stromal sarcoma	1	0	0
High-grade endometrial stromal sarcoma	4	0	0
Endometrial stromal nodule	1	0	0
Perivascular epithelioid cell tumor	3	0	0

Table 2. Clinical features of *PGR* fusion-positive uterine epithelioid leiomyosarcomas

Case	Age, y	Signs and symptoms	Treatment	FIGO stage	Follow-up, mo
1	43	Painful menses, pelvic mass	Surgery, chemoradiation	II	AWD, 180
2	46	Abdominal pain, pelvic mass	Surgery	II	NED, 9
3	56	Symptomatic fibroids	Surgery	I	LTF
4	42	Uterine mass	Surgery	I	NED, 96
5	41	Uterine mass	Surgery	II	AWD, 75
6	55	Symptomatic fibroids	Surgery	II	NED, 1

AWD indicates alive with disease; LTF, lost to follow up; NED, no evidence of disease.

Table 3.

Pathologic features of *PGR* fusion-positive uterine sarcomas

Case	Size, cm	Morphology			Myxoid	MI	LVI	Necrosis	Immunohistochemical profile					Fusion status
		Spindled	Rhabdoid	+					CD10	Desmin	ER	PR	HMB45	
1*	5	+	+	+	+	19	-	-	0	4	4	4	0	<i>NR4A3-PGR</i>
2	12	+	+	+	+	9	-	-	0	2	4	4	NP	<i>NR4A3-PGR</i>
3	3	+	+	+	+	4	-	-	0	4	4	4	0	<i>NR4A3-PGR</i>
4	15	-	+	+	-	12	+	-	0	3	3	4	0	<i>PGR</i> rearrangement only
5	4	+	+	+	-	10	+	-	0	3	4	4	NP	<i>NR4A3-PGR</i>
6	27	+	+	+	-	10	-	+	NP	3	4	4	0	<i>PGR</i> rearrangement only

F indicates focal; HPF, high power field; LVI, lymphovascular invasion; MI, mitotic index (# per 10 high power fields); NP, not performed.

* Index case subjected to RNA sequencing.