Myxoid and Epithelioid Leiomyosarcoma of the Vagina Harboring *CARMN-NR4A3* Gene Fusion

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Introduction

- Leiomyosarcomas (LMS's) of the gynecologic tract are rare and aggressive malignant mesenchymal tumors characterized by a high recurrence rate and poor prognosis (1,2).
- LMS tumorigenesis is driven by a range of genetic alterations.
- Conventional uterine and soft tissue LMS's frequently exhibit disruptions in key tumor suppressor pathways, including those involving *TP53*, *ATRX*, *MED12*, *RB1*, and *PTEN* (3,4).
- However, other specific gene fusions have been identified, such as rearrangements involving *PGR*, *NR4A3*, and *UBR5*, particularly in epithelioid LMS's with rhabdoid morphology (5,6).
- Among the reported uterine epithelioid LMS's with *PGR* rearrangements, *NR4A3* has been the most common fusion partner.
- The *NR4A3* gene, a member of the nuclear receptor subfamily 4 group A, is involved in various biological and neoplastic processes. *NR4A3* is located on chromosome 9q22 and encodes neuron-derived orphan receptor 1 (NOR1) protein. The protein product plays an important role in cell proliferation, apoptosis, and differentiation (7,8).

Case Presentation

- 45-year-old woman with no significant medical history presented with a posterior vaginal wall mass, but no other symptoms.
- Outside biopsy revealed an "atypical spindle and epithelioid neoplasm with myogenic differentiation, favoring leiomyosarcoma" (Figure 1).

Case Presentation (Continued)

- Preoperative imaging: 8.0 × 7.8 cm complex heterogeneous vaginal mass.
- The patient underwent surgical resection.
- Pathology revealed a spindle cell neoplasm arranged in lobules separated by fibrous bands with hemosiderin deposition and focal infiltrative borders at the periphery. Cells are epithelioid and spindled and are arranged in sheets / trabeculae with associated abundant myxoid matrix and hemorrhage. Cytologically, there is mild to moderate atypia with no tumor necrosis or significant mitotic activity (Figure 2).
- IHC results are summarized in the Table 1.
- Surgical margins were negative but lymphovascular space invasion (LVSI) was noted.
- Postoperative recovery was unremarkable.
- Molecular studies identified the presence of a rare *CARMN::NR4A3* gene fusion (Figure 1).

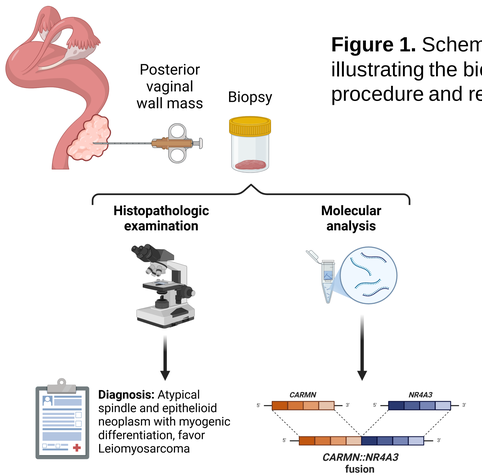

Figure 1. Schematic illustrating the biopsy procedure and results.

Case Presentation (Continued)

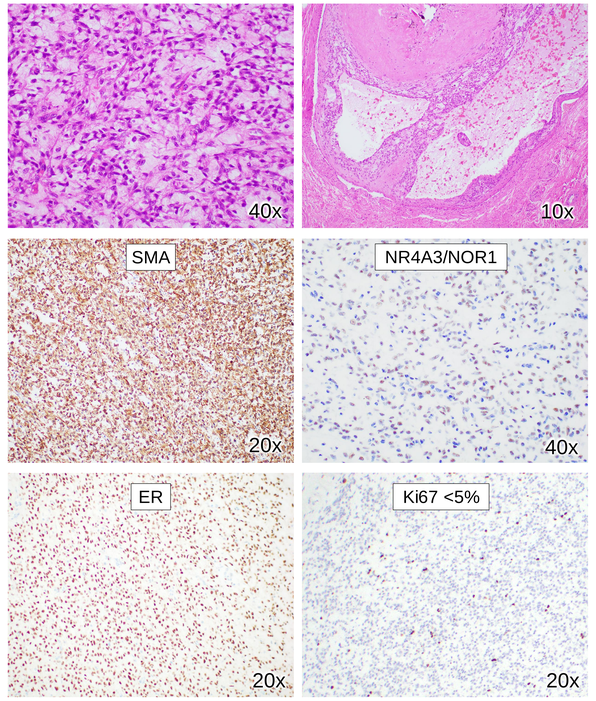

Figure 2. H&E and IHC images.

IHC stain	Result	IHC stain	Result
SMA	**Positive**	PLAG	Negative
Desmin	**Positive**	p16	Negative
H-caldesmon	**Positive**	2SC	Negative
ER	**Positive**	HMB45	Negative
NR4A3 (NOR1)	**Positive**	CD10	Negative
MDM2	Negative	p53	Normal (wt)
Keratin	Negative	ATRX	Retained
CD31	Negative	PTEN	Retained
Calretinin	Negative	RET	Retained
S-100 protein	Negative	MTAP	Retained
		Ki67	**<5%**

Table 1. IHC results.

Discussion

- In the largest and only case series reported to date, 9 gynecologic leiomyosarcomas harboring *NR4A3* gene fusions were described (6).
- All tumors were identified in premenopausal women, involving the uterus, cervix, or pelvis (6).
- All were similarly characterized by lobules of monomorphic epithelioid and/or spindled cells associated with abundant myxoid matrix.
- Myogenic differentiation with frequent estrogen receptor and progesterone receptor staining and no CD10 expression characterized all tumors.
- All cases showed high *NR4A3* RNA expression levels and NOR1 (NR4A3) nuclear staining similar to salivary gland acinic cell carcinomas and a subset of extraskeletal myxoid chondrosarcomas harboring *NR4A3* rearrangements (6).
- To the best of our knowledge, this is the first case of epithelioid and myxoid leiomyosarcoma with *NR4A3* gene fusion arising in the vagina.
- Given the rarity of this tumor variant, our case was reviewed at a multidisciplinary tumor board, which recommended initiation of letrozole 2.5 mg daily as adjuvant hormonal therapy.

References

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