Unusual Variants of Endometrial Stromal Sarcoma

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Context

- Endometrial stromal sarcoma (ESS) is a diverse and relatively rare group of malignant mesenchymal tumors originating in the uterus.
- ESS are subdivided into low-grade (LGESS) and high-grade (HGESS) according to the most recent WHO classification based on their morphologic features, immunohistochemical (IHC) profile, and underlying genetic alterations.
- We aimed to describe cases of "presumed" LGESS that display rare histologic, IHC, and/or molecular findings.

Methods

- We performed a retrospective review of ESS reports diagnosed from 2019-2024 in one institution, to detect cases with highly unusual pathologic features. Clinical information, H&E and IHC slides were evaluated, and only cases with performed next-generation sequencing (NGS) were included.

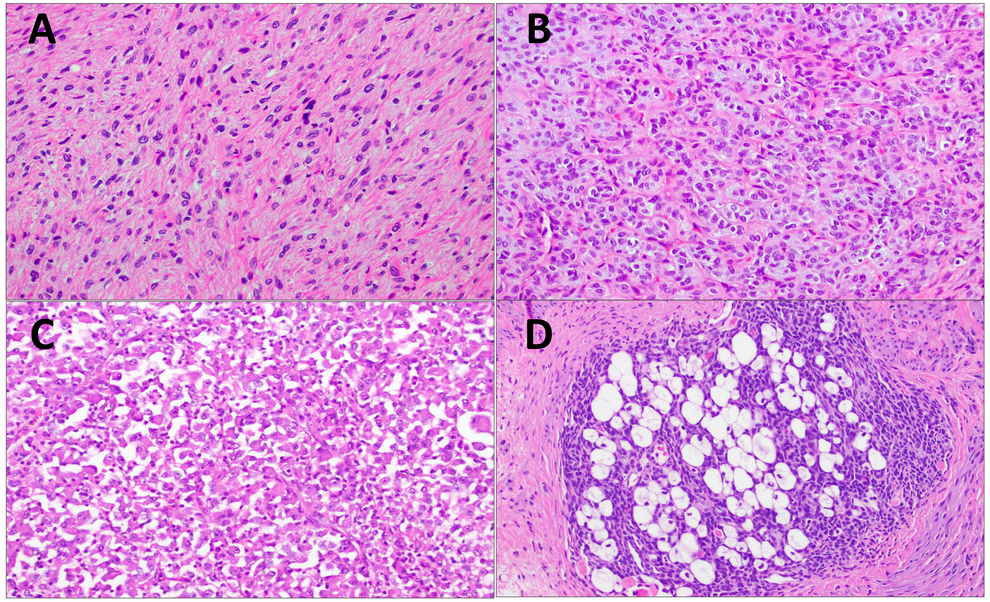

Figure 1 A-D. Case 1-4, respectively. H&E 200x.

Case #	Cytological features	Growth pattern	Necrosis	Mitotic index (per 10 HPF)	Relevant IHC	Gene fusion	Additional molecular alterations	Disease status
1	Ovoid-to-spindled	Fascicular	Present	25	Desmin+, SMA+, cyclin-D1+ (focal), CD10-, ER-	*EPC2::PHF1*	Amplification of *MDM2, CDK4,* and *HMGA 2*	Lost to followup
2	"Sex cord-like"	Sheets and nests	Absent	1	SF1+, CD10+, desmin+, ER+ (weak), cyclin-D1+ (focal), Calretinin +, WT1-, ALK-	*EPC1::EZH2*	*ALK* (VUS)	AWD (145 mo)
3	Rhabdoid	Alveolar	Present	> 30	AE1/AE3+ (focal), CD10+ (focal), WT1+ (focal) cyclin-D1+ (focal), ER/PR-, SMA-, desmin-, myogenin-	*JAZF1::SUZ12*	*NF2* (pathogenic mutation), *BRCA2* (VUS)	NED (14 mo)
4	Spindled admixed with brown fat	Nested	Absent	0	CD10+, WT1+, ER/PR+, desmin-	N/A	N/A	NED (45 mo)

Table 1. Summary of morphologic, immunohistochemical, molecular, and clinical characteristics.

Results

➢ **Case 1**

- The tumor consisted of spindled-to-ovoid cells with eosinophilic cytoplasm and vesicular nuclei, set in a fibromatous/fibromyxoid background (Figure 1A). There was brisk mitotic activity and coagulative necrosis. IHC was positive for desmin, SMA and cyclin-D1 (focally), and negative for CD10 and ER. NGS identified an EPC2::PHF1 fusion, previously reported in a single case of LGESS. Additionally, amplifications of MDM2, CDK4, and HMGA2 were detected.

➢ **Case 2**

- The tumor was composed of spindled and epithelioid cells with monomorphic nuclei, fine chromatin, and inconspicuous nucleoli, reminiscent of sex cord-stromal tumors (Figure 1B). IHC was positive for desmin, CD10, and SF1, and patchy positive for ER, cyclin-D1, EMA, and calretinin. NGS detected an EPC1::EZH2 fusion, previously described in a single case of ESS.

➢ **Case 3**

- The tumor was made of cells with striking rhabdoid appearance, arranged in an alveolar growth pattern, exhibiting necrosis and high mitotic activity (Figure 1C). Immunohistochemistry showed focal positivity for keratin AE1/AE3, CD10, WT1, cyclin-D1, and negativity for ER and PR. NGS identified a JAZF1::SUZ12 fusion, a finding commonly associated with conventional LGESS, despite the lack of any morphologic resemblance in this case.

➢ **Case 4**

- The tumor showed a peculiar adipocytic (brown fat) differentiation in an otherwise typical LGESS (Figure 1D). IHC was positive for CD10, WT1, and ER/PR, and negative for desmin. Molecular studies were not performed.

Conclusions

- These cases broaden the spectrum of morphologic, immunohistochemical, and molecular features seen in ESS, underscoring the need for a comprehensive diagnostic approach. In some instances, tumors with genetic fusions typically associated with LGESS may contain high-grade features, leaving their clinical behavior uncertain.

References

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