UNCLASSIFIED HIGH-GRADE UTERINE SARCOMA WITH ERBB2/ERBB3 MUTATIONS AND S100/SOX10 POSITIVITY: A CASE REPORT DEFINING A NOVEL MOLECULAR ENTITY

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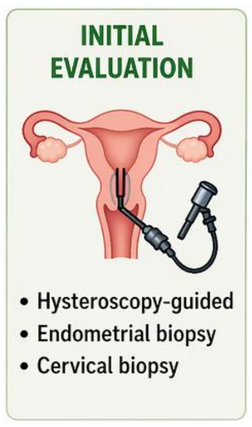
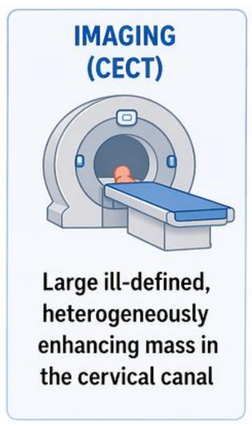
BACKGROUND

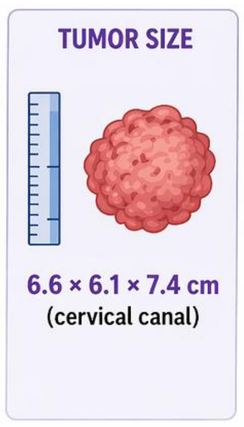
Advances in molecular pathology have significantly refined the classification of high-grade uterine sarcomas (HGUS). Several tumors previously categorized as undifferentiated or high-grade endometrial stromal sarcomas (ESS) have now been redefined as distinct molecular entities, including NTRK-rearranged, SMARCA4-deficient, and COL1A1::PDGFB fusion sarcomas etc[1,2]. Recently, another rare subset of HGUS characterized by diffuse S100 and SOX10 expression with activating ERBB family alterations has been described, recognition of which is crucial, particularly in light of the availability of HER2-targeted therapeutic options[2,3].We report a diagnostically challenging case of this emerging entity, with fewer than ten cases described to date, highlighting the role of readily available molecular surrogate tests.

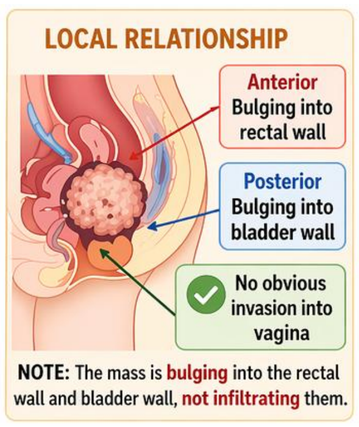
CASE REPORT

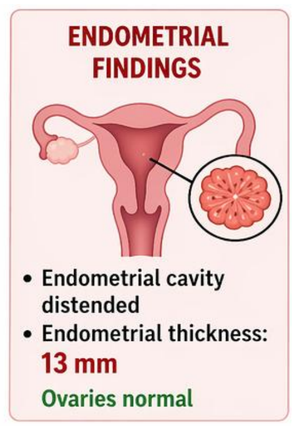
CLINICAL FEATURES



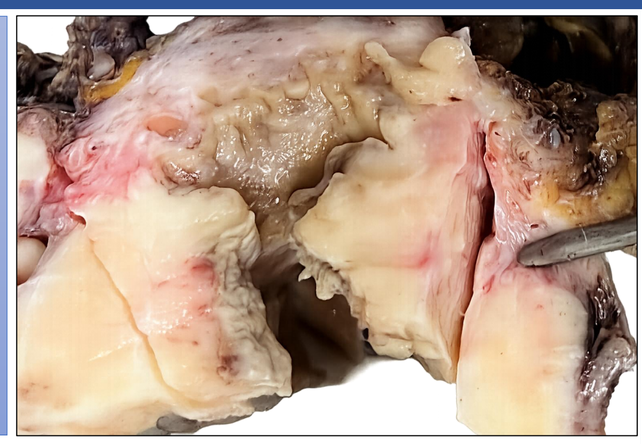




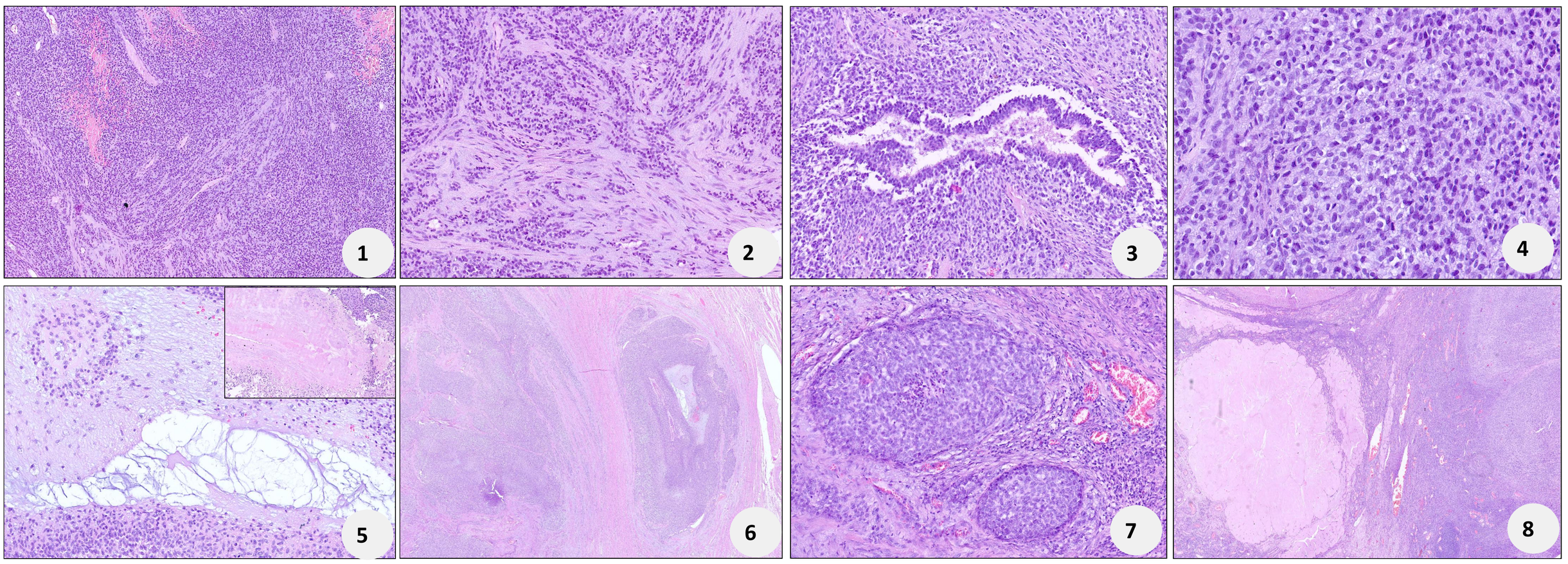




MACROSCOPIC IMAGE

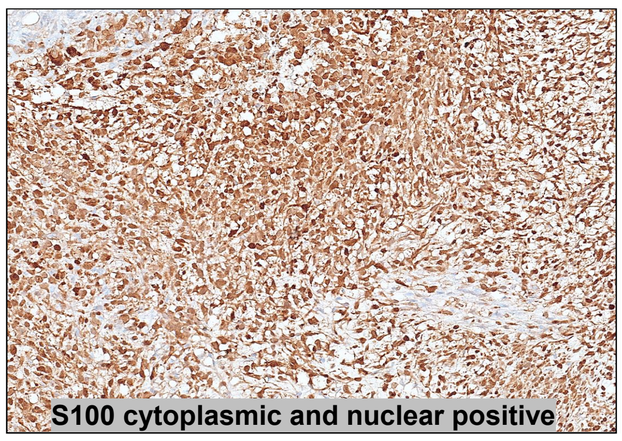


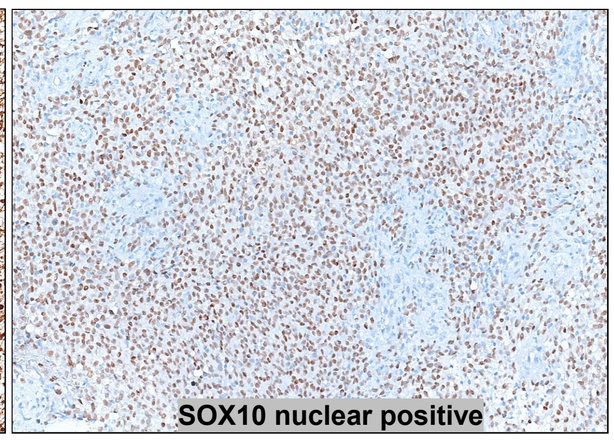
MICROSCOPIC FINDINGS

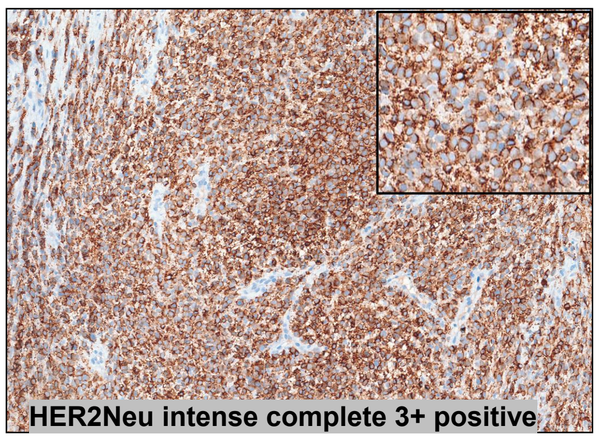


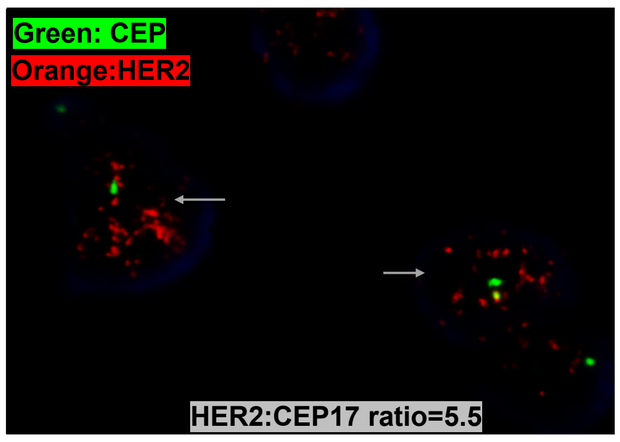
Hematoxylin and Eosin stain at variable magnifications showing tumor cells arranged in: (1) Diffuse dyscohesive sheets (2) cords and (3) Pseudo-glandular architecture. Individual cells are (4) Ovoid to spindle shaped with (5) Edematous and myxoid background (inset: necrosis) (6) Deep myometrial invasion as nodules (7) Lymphovascular involvement (8) Ovarian Deposits

ANCILLARY TESTS









DISCUSSION AND CONCLUSION

CASE	AGE (yrs)	SYMPTOM	SITE and SIZE	EXTENT OF DISEASE	TREATMENT	HISTOLOGY	IHC	FISH	NGS	OUTCOME
Agaimy A et al. 2024 [1] Case 1	53	Abdomino-pelvic mass	Uterus; Size not provided	Metastases to peritoneum, liver, lung, spleen and abdominal wall	TAH+BSO, adjuvant radiotherapy	High-grade infiltrating tumor, medium-sized oval to elongated cells with diffuse non-cohesive sheets. Sparse fibrous stroma.	SOX10 and S100: strong diffuse Cyclin D1: moderate diffuse HER2: strong (3+)	HER2: CEP17 = 2.49	ERBB3mutation:p.Glu928Gly ATRX mutation: p.Tyr264* CDKN2A deletion	Disease related death (systemic metastases) @ 47 months from initial diagnosis
Agaimy A et al. 2024 [1] Case 2	45	Irregular uterine bleeding	Cervical polyp 0.9cm	Uterus confined	Polypectomy	Highly cellular spindle cell tumor, Monomorphic Compact fascicles Fibrosarcoma-like pattern	SOX10 and S100: strong diffuse Cyclin D1: moderate diffuse	Not performed	ERBB2 mutation:p.Val777Leu NRAS mutation: Gln61Lys ATRX mutation CDKN2A deletion CDKN2B deletion	Not available
Shi WJ et al. 2025[2]	57	Abdomino-pelvic mass	Cervix 8 × 7 × 7 cm	Upper vagina	TAH+BSO, adjuvant radiotherapy chemotherapy	Hypercellular spindle cell tumor, arranged in tight fascicles, collagenous to myxoid stroma	SOX10 and S100: strong diffuse HER2: Negative	Not done	ERBB2 mutation: p.Val777Leu ATRX mutation: Frameshift mutation CDKN2A: Deep deletion	Patient disease-free,@ 7 months post-chemotherapy
Current case (2026)	44	Heavy menstrual bleeding	Uterus and Cervix 7.4 x 6.6 x 6.1	Bilateral adnexa with multiple peritoneal deposits	TAH+BSO, adjuvant radiotherapy chemotherapy	Tumor cells arranged in cords and pseudoglandular architecture, myxoid to edematous stroma	SOX10 and S100: strong diffuse Cyclin D1 and ER: focal positive HER2: strong (3+)	HER2: CEP17 ratio = 5.5	Not done	Patient under chemotherapy

This case represents an unclassified HGUS with diffuse S100/SOX10expression and HER2 amplification, supporting the concept of a novel molecularly defined subtype. Recognition is feasible even without sequencing using characteristic morphology, immunophenotype, and HER2 amplification as surrogates, thus bridging a critical gap in molecular biology.

REFERENCES

1. Momeni-Boroujeni A et al. Uterine mesenchymal tumours: recent advances. Histopathology. 2020.
2. Agaimy A et al. ERBB2/ERBB3-mutated S100/SOX10-positive unclassified high-grade uterine sarcoma: first detailed description of a novel entity. Virchows Archiv. 2024.
3. Shi WJ, Fadare O. ERBB2/ERBB3-mutated S100/SOX10-positive uterine sarcoma: something new. Virchows Archiv. 2025 Mar;486(3):605-10.