

## Case Report

# Primary endometrial endometrioid carcinoma with signet ring cells: an unexpected morphology of a common tumor

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**Abstract:** The presence of signet ring cells within a uterine malignancy is believed by many standard gynecological pathology references to be a strong evidence of a metastatic adenocarcinoma. Primary endometrial carcinomas associated with signet ring cells are an extremely rare finding with only 4 reported cases in literature. Herein we report a case of primary endometrial endometrioid carcinoma with a significant component of signet ring cells, afterwards, a historical overview and discussion of the major differential diagnoses in such context is provided.

**Keywords:** Endometrial cancer, endometrioid carcinoma, signet ring cell carcinoma

## Case report

An 80 years old woman presented to Gynecologic clinic complaining of post-menopausal bleeding in August 2010. An Endometrial biopsy was performed and the results returned as endometrioid adenocarcinoma, most probably of endometrial source, FIGO grade 2. One month later, the patient underwent laparoscopic assisted vaginal hysterectomy and bilateral salpingo-oophorectomy along with lymph node dissection and omental samplings. Pelvic washings were negative for malignancy. The patient was doing well without evident recurrences until the writing of this report.

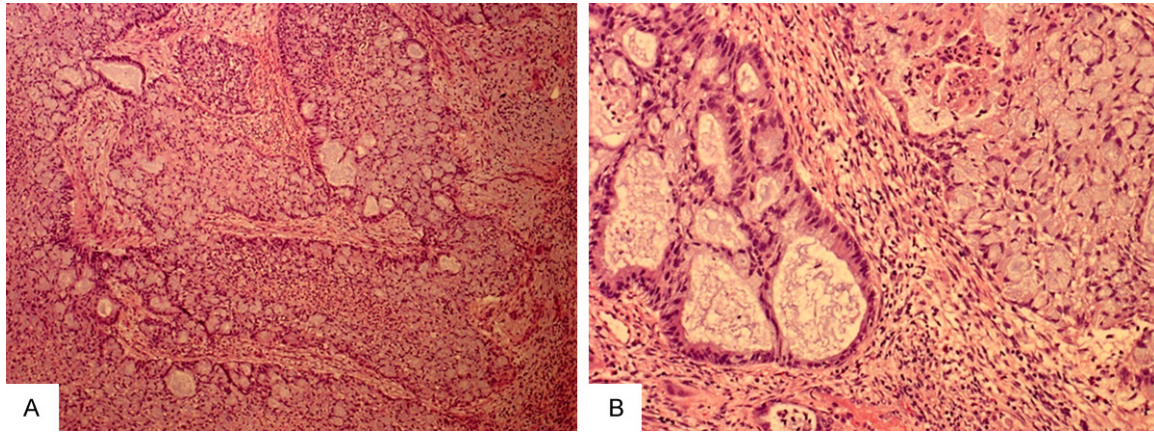
## Pathologic features

The surgical specimens were received for intra-operative frozen section consultation. The hysterectomy specimen consisted of auterus and cervix measuring 7.7×5.3×2.5 cm with attached bilateral adnexae. The uterus weighed 63.8 gm. The serosa was intact and smooth with one small 0.7 cm subserosal leiomyoma. The anterior endometrium contained a tan-white polypoid mass measuring 2.2 cm in maximal dimension. Examination of transverse sections of the

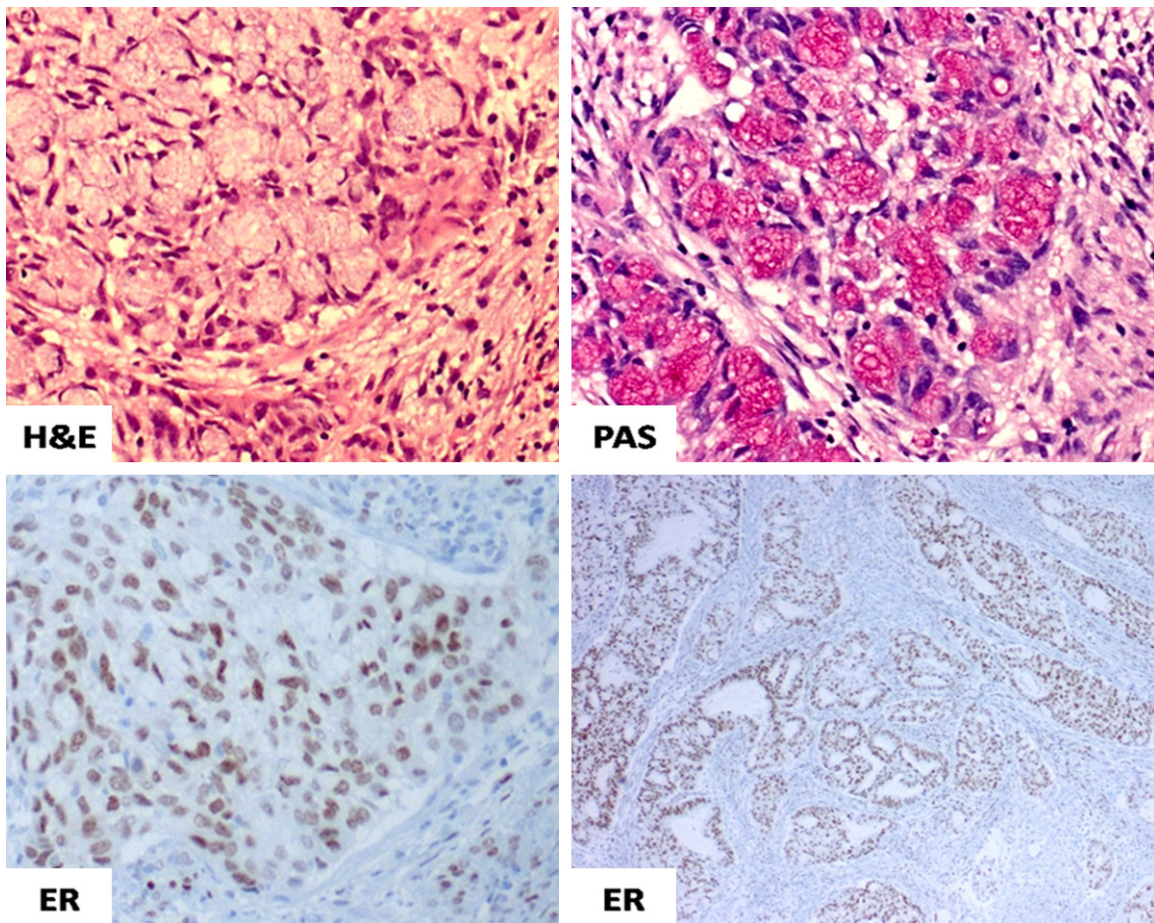
rest of the uterine wall showed a 2 mm endometrial thickness, while the myometrial thickness averaged 1.0 cm. Grossly, invasion of the inner third of the myometrium by the polypoid mass was anticipated. Frozen section examination was interpreted as endometrioid carcinoma, FIGO grade 2 with invasion of the inner half of myometrial thickness. The lower uterine segment, cervix, uterine serosa and parametrial tissues were grossly uninvolved. Examination of the adnexal specimens revealed a grossly unremarkable normal sized bilateral ovaries and fallopian tubes. For permanent microscopic examination, the tumor was submitted entirely along with representative sections from the endomyometrium, lower uterine segment, and cervix. Bilateral ovaries and fallopian tubes were entirely submitted. Multiple specimens representative of lymph node dissection were then received, including bilateral external iliac, pelvic and periaortic lymph nodes. A total of 22 lymph nodes were identified and submitted for microscopic examination. Peritoneal samples from cul-de-sac were submitted entirely for microscopic evaluation.

Microscopic examination of the endometrium demonstrated adenocarcinoma with classic

## Primary endometrial endometrioid carcinoma with signet ring cells



**Figure 1.** Microscopic view of the tumor showing a mixture of classic endometrioid histologic type and signet ring cells (A). Higher magnification in (B) shows classic endometrioid component (left) and adjacent signet ring component (right) within the myometrium (H&E stain, original magnifications 40× and 100×).



**Figure 2.** Signet ring cells. H&E stain (upper left), and PAS stain highlighting the cytoplasmic mucin (upper right). Immunohistochemical positivity for Estrogen Receptor (ER) in signet ring cells (lower left) and the classic endometrioid component (lower right). (200× and 100×).

endometrioid and a focal mucinous component. The nuclear grade was intermediate, and the architecture was analogous of FIGO grade 2

(**Figure 1**). The maximum myometrial invasion was measured as 25% of greatest myometrial thickness. Maximal tumor dimension mea-



sured 2.2 cm. The non-cancerous endometrium was weakly proliferative. Additional findings in the myometrium were adenomyosis and a subserosal leiomyoma. One interesting finding within the tumor was the presence of signet ring cells (constituting about 30% of the total tumor volume) admixed with the classic endometrioid carcinoma (**Figure 1B**); a Periodic-Acid Schiff (PAS) stain for mucin was performed on the tumor sections and highlighted these mucin-containing signet ring cells (**Figure 2**). These cells were also detected as single as well in small clusters within the myometrium and lymphovascular spaces. Although the myometrial invasion only measured 25%, there was an extensive and deep lymphovascular space invasion within the myometrium, reaching as far as 2 mm from the uterine serosa. Microscopically, the lower uterine segment, cervix, uterine serosa and parametrial tissues were uninvolved. No significant pathological changes were detected in the fallopian tubes. The ovaries were unremarkable except for endosalpingiosis. No malignancy was identified in the 22 identified lymph nodes or in the peritoneal samples.

Immunohistochemical stains were performed on the tumor sections and showed that both the classic endometrioid carcinoma and the signet ring cell components are equally positive for estrogen receptor (ER) (**Figure 2**) and progesterone receptors (PR), CK7, pancytokeratin, and EMA, while only the stromal cells were positive for CD10. The tumor cells were negative for CDX2, CK20, p53 and GATA3. The immunohistochemical staining results are summarized in **Table 1**. Clinical investigations to rule out a metastatic source of the signet ring cell adenocarcinoma were performed, including physical and radiological examination of the breast, gastrointestinal tract, and others. The final pathologic diagnosis is therefore a primary endometrioid carcinoma with a signet ring cell component.

### Discussion

Most metastatic cancers involving the uterus are originating in other organs of the female genital tract (e.g. ovary and cervix). The endometrium is a rare site for metastasis from non-gynecological malignancies. The first reported case of a metastatic tumor in the uterus by an extrapelvic primary was by Legg in 1878 [1], as part of the patient's disseminated metastases.

The following century witnessed many consecutive reports and case series of metastatic malignancy to the uterus, among most of these series, the most common primary sites are the breast (42%-55%), colon (18%), and stomach (11-25%) [2-4]. Kumar et al [2] found that uterine metastases were the presenting picture in about one fourth of their 63 studied cases. Most of the patients complained of abnormal vaginal bleeding, and almost 2 thirds had concurrent ovarian metastases. The major histological features shared by the different series were a predominant infiltration of the myometrium, sparing of benign endometrial tissue, absence of premalignant lesions of the endometrium (e.g. endometrial hyperplasia), and a signet ring cell morphology [5]. The frequent consecutive series describing these metastases and the sharing of a signet ring pattern, along with the absence of any reports of a primary uterine carcinoma with such a pattern, made it rational for standard pathology textbooks to emphasize the presence of signet ring cells in the endometrium as a strong evocative sign of metastatic carcinoma [5, 6].

Primary signet ring carcinomas of the female genital tract are generally rare. Most of the cases belong to cervical signet ring carcinoma, accounting for less than 5% of all cervical adenocarcinomas [7, 8]. Primary ovarian signet ring cell carcinomas are even rarer with only a few reported cases [7]. Signet ring cells, however, had been occasionally detected in non-epithelial ovarian tumors, including signet ring stromal cell tumor [9] and teratomas [10] and signet ring morphology had been also seen in potentially benign ovarian stromal tumors, like signet ring stromal tumor and sclerosing stromal tumor of the ovary.

In 1997, Mooney et al reported the first case of primary endometrial carcinoma with signet ring cells [11]. In that case, a component of typical Endometrioid carcinoma was present and negative results of the extensive clinical search for extrauterine primary provided good evidence that the tumor was a primary uterine adenocarcinoma. Other supportive evidences for that conclusion were the absence of systemic metastases, the lack of deep myometrial invasion, and a negative immunohistochemical staining for BRST-2 (a breast carcinoma marker), although these were by no means conclusive. A few recently published papers [12-14] identified additional cases, one of signet ring-rich

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**Table 1.** Summary of immunohistochemical reaction in classic endometrioid and signet ring components

IHC Stain	ER	PR	panCK	EMA	CDX2	CK20	GATA3	p53
Endometrioid component	+	+	+	+	-	-	-	-
Signet ring	+	+	+	+	-	-	-	-

mucinous endometrial carcinoma with extensive stromal decidualization and adenomyotic foci involved by the tumor, the signet ring cells were reactive for Ber EP-4, CK7, CA125 and ER. Staining with CDX2 was negative. The second case was of endometrioid carcinoma involving an endometrial polyp. The signet ring cells were reactive for AE1/3, CK7 and ER, but not for GCDFP-15 or CK20. No information regarding extrauterine disease or investigational work up to rule out metastatic origin were provided [12]. In the third case [13], the endometrial tumor was staged FIGO IVB primary signet-ring cell carcinoma of the endometrium with a minor component of endometrioid adenocarcinoma. The tumor cells showed positivity for panCK, CK7, and EMA, and focally for p53; while CK 20, chromogranin, synaptophysin, p16, a-fetoprotein, carcinoembryonic antigen (mono and polyclonal), and thyroid transcription factor-1 (TTF-1) were all negative. Another recent report [14] showed one interesting finding, the tumor positivity to HPV 11 by PCR, in addition, the signet ring cells were also positive for p16 and vimentin, while negative for CEA, ER and PR. All reported cases had mucin-detecting special stains (either PAS or Alcian blue) positivity as evidence of mucinous differentiation in the signet ring cells.

Based on several facts, we believe our case is a primary endometrial endometrioid carcinoma with a signet ring component and a minor mucinous component. First, the absence of an identifiable extra-uterine primary and systemic disease despite thorough clinical investigations; which is almost always the case for uterine metastases [2]. Second, the presence of a component of classic endometrioid carcinoma intermingled with the signet ring cells. Third, the signet ring cells showed a similar immunophenotype profile to the endometrioid component (Table 1). Fourth, the tumor was mainly involving the endometrium, with only partial involvement of the inner myometrium. Fifth, the presence of a primary in other organs of the female genital tract was excluded by our extensive histopathological examination of these

organs. The fact that our case showed extensive lymphovascular space invasion, may raise the question whether endometrioid carcinomas with signet ring cells may perhaps behave worse clinically than expected

for grade and stage-matched endometrioid carcinoma, the question remains clarified.

A point worth of discussion is the differential diagnosis of cells with signet ring morphology within the endometrium. Beside the most common source, which is metastatic adenocarcinoma, and the few above-described primary adenocarcinoma cases, consideration of a non-epithelial origin of these cells should be kept in mind by practicing pathologists to prevent the misinterpretation of an otherwise reactive endometrial condition as a malignant lesion [15]. Examples must include adenomatoid tumors with focal signet ring morphology partially represented in endometrial curettings. This potentially benign tumor is of mesothelial origin and consequently will show positivity to conventional mesothelial markers such as calretinin and not for epithelial markers like BerEP4. Decidualized endometrial stromal cells can also be a source of confusion due to their polygonal outline and clear cytoplasm. A helpful strategy is the lack of staining with epithelial markers as well as mucin special stains. Another differential is histiocytic proliferations within the endometrium, for which a positive reaction for CD68 assists in confirmation of their histiocytic nature. Occasionally, endometrial reparative changes following endometrial cauterization might include the appearance of signet ring stromal cells, again immunoreactivity to stromal markers and absence of positivity to epithelial markers is of paramount help to the pathologist.

### Summary

The presence of signet ring cells is an unusual finding in the endometrium; nevertheless it is a source of confusion for many practicing pathologists. Whether as a sole finding or as a component of an ordinary adenocarcinoma, the first differential diagnosis that should come to mind is a metastatic carcinoma, for which a clinic-radiological correlation with the histo-immunochemical examination is mandatory. A diagnosis of primary signet ring carcinoma of the

endometrium, should only be given following exclusion of possible metastases, absence of similar findings in other gynecological organs, and a supportive immunohistochemical panel indicating an endometrial origin of the tumor. Several non-neoplastic conditions of the endometrium may be associated with signet ring morphology. In all cases, an objective panel of immunohistochemical stains should be helpful.

## Disclosure of conflict of interest

None.

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