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Primary Signet-ring Cell Carcinoma of the Uterine Corpus: A Case Report and Review of the Literature

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Abstract Pure signet-ring cell carcinomas of the uterine corpus usually raise the suspicion for a metastatic tumor from other primary sites, e.g., breast or the gastrointestinal tract. And if primary in the uterus, it is more commonly of uterine cervical origin with secondary involvement of the corpus. In general, pure mucinous carcinoma of the endometrium is rare and pure signet-ring cell carcinoma, a form of mucinous carcinoma, is even rarer. Only sparse case reports of primary mucinous adenocarcinoma of the uterine corpus with signet-ring cell features have been described in literature. We report here a case of pure mucinous signet-ring cell carcinoma of the uterine corpus in a 63 year-old morbidly obese woman.

Keywords: *signet-ring cell, mucinous carcinoma, endometrial carcinoma, uterus, low grade carcinoma, mucicarmine satin*

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1. Introduction

Pure signet ring cell carcinomas of the endometrium are rare and most often represent metastasis from other primary sites or cervical origin. Only five cases of primary endometrial signet-ring cell carcinoma of the uterine corpus have been reported till date [1,2,3,4]. Of these five, four cases were described in association with endometrioid type endometrial carcinoma and only one with mucinous carcinoma [1]. Presence of focal signet-ring cell differentiation in a rather garden variety endometrial adenocarcinoma is a more commonly encountered event. The current case report is based on a pure form of signet-ring cell carcinoma of the uterine corpus, review the literature, discuss the differential diagnoses, and emphasizing the need for an accurate diagnosis of this entity of this site.

2. Case Repot

2.1. Clinical Features

A 64 year-old wheelchair bound Caucasian woman with debilitating arthritis presented with postmenopausal bleeding. Her past medical history includes morbid obesity, and hypertension. She underwent gastric bypass operation and many (7 or more) hernia repair surgeries in the past. Family history includes a brother with lung cancer and a sister with endometrial carcinoma.

A CT scan of the chest, abdomen, and pelvis revealed a 5 mm nodular opacity near the minor fissure in the right lung, fullness in the lower uterine segment and cervix, and minimum retroperitoneal and external iliac lymph node enlargement. No palpable breast abnormality was documented. Breast imaging studies were also negative.

A pelvic ultrasound showed a 1.7 cm echogenic mass in the endometrium with distended endometrial cavity. A biopsy of the mass was taken and examined.

Subsequently, an upper and lower GI endoscopies were done to exclude a tumor in the gastro-intestinal tract. Both the endoscopic examinations were unremarkable. Biopsies were obtained from the stomach.

A speculum examination of the cervix and vagina revealed somewhat nodular cervix and an unremarkable vagina.

2.2. Microscopy

The endometrial biopsy showed mucinous adenocarcinoma consisting predominantly of signet-ring cells and large areas of necrosis (Figure 1). The tumor was arising in a background of atrophic endometrium. A mucicarmine special stain show diffuse intra-cytoplasmic mucin (Figure 1).

2.3. Immunohistochemistry

By immunohistochemistry the tumor cells was diffuse and strongly reactive to antibodies to PAX8 (M; MRQ-50; Cell Marque), Estrogen Receptor (R; clone EP1; Dako) and Vimentin (M; V9; Dako) (Figure 2). The cytokeratin 7 (CK7) (M; OV-TL 12/30; Dako) staining was strong, but focal. The tumor cells were completely negative to antibodies to cytokeratin 20 (CK20) (M; Ks20.8; Dako), CDX2 (M; DAK-CDX-2; Dako) (Figure 2) and GATA 3 (M; clone L50-823, Cell Marque) (Figure 2). Curiously the p16 (M; E6H4; Ventana) immunohistochemical staining was focally positive. The above mentioned

findings suggest mullerian origin of the tumor and favor an endometrial primary.

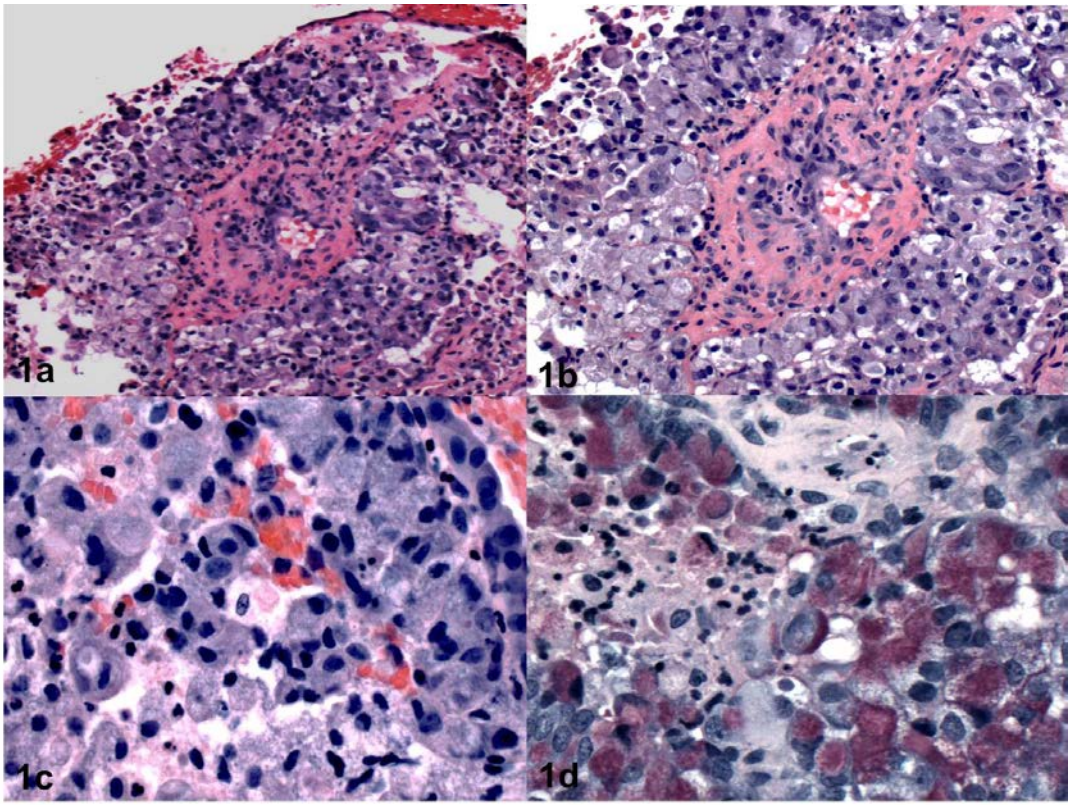

Figure 1. Photomicrograph showing mucinous carcinoma with signet-ring cell features (1a: H&E; 10x); prominent signet-ring cell features (1b: H&E; 20x); signet-ring cell features (1c: H&E; 40x); and signet-rings with intra-cytoplasmic mucin (1d: Mucicarmine; 40x)

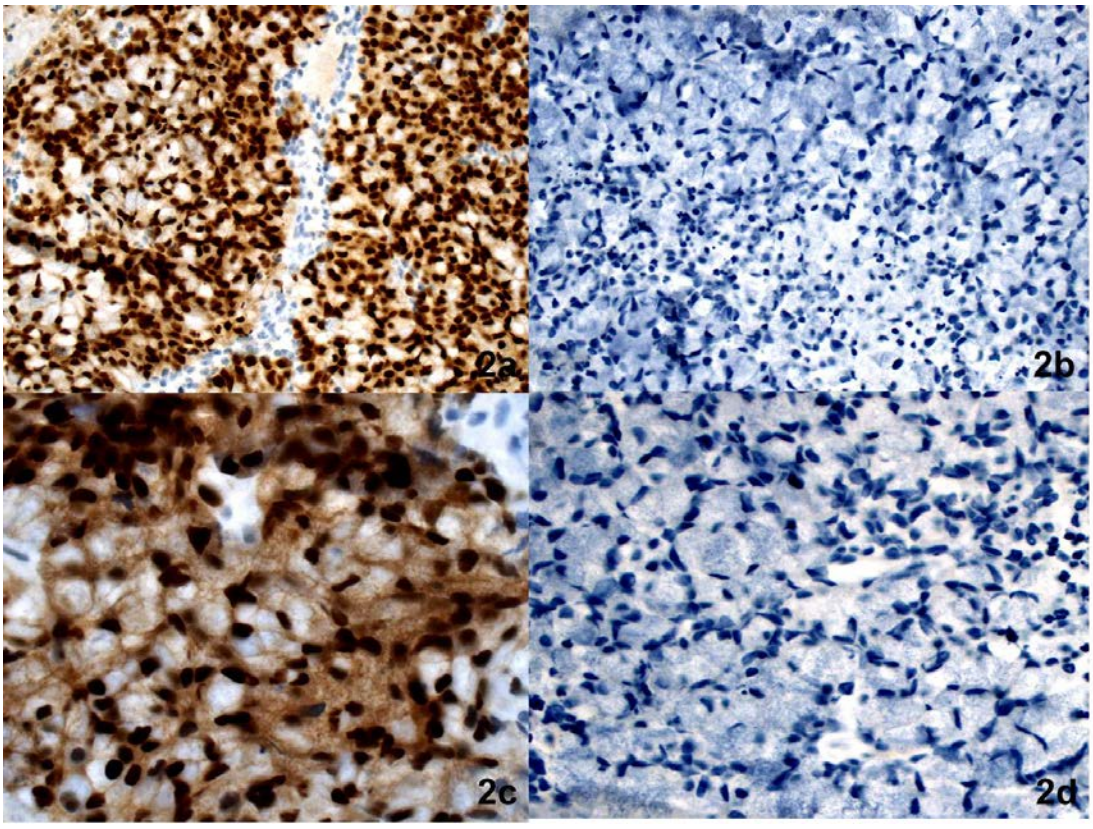

Figure 2. Photomicrograph showing strong and diffuse immunoreactivity to PAX8 (2a: 4x) and (2c: 40x); and complete non-reactivity to CDX2 (2b: 10x) and CK20 (2d: 20x)

The patient was treated by Cisplatin chemosensitization, followed by pelvic radiotherapy. The patient responded to radiotherapy treatment, her bleeding stopped, and she is currently continuing her therapy. She had her last follow-up a month ago, after seven months of her initial diagnosis.

3. Discussion

The 2014 World Health Organization (WHO) classification of the Tumors of the uterine corpus recently has recommended that mucinous carcinoma of the endometrium should be categorized as an independent category instead of a subcategory of endometrioid endometrial carcinoma [5]. An endometrial carcinoma with >50% cells showing mucinous differentiation is now designated as mucinous carcinoma. Molecular testing has shown that mucinous carcinomas often show somatic *KRAS* mutation [6]. These tumors almost always are well differentiated and appear to have relatively good prognosis, although vaginal cuff recurrence has been reported. From these, it appears that mucinous carcinoma has a different biology compared to endometrioid carcinoma and justifies its separate categorization. The signet-ring cell carcinoma is usually referred to a high grade tumor in other organs of the body. The prognosis of primary signet-ring cell carcinoma of the endometrium, possibly a variant of mucinous carcinoma, is unknown. Because of the rarity of the tumor, no big series has been published in English literature. Only rare case reports are available in the literature. It is important to document these individual cases to eventually design a multi-institutional study with sufficient number of cases to help predict the prognosis of this rare entity.

We present here one such rare variant of primary mucinous carcinoma of the endometrium consisting predominantly of signet-ring cells. Because of the comorbidity of the patient, the surgical removal of the primary tumor was not possible. However, extensive clinical and radiologic work-ups were done and no other primary site of tumor was identified.

In general, metastatic carcinoma to endometrium is uncommon and most often found in the context of a disseminated disease [7]. The most notable example of the metastatic tumor is the lobular carcinoma of the breast. It is well known that the invasive lobular carcinoma of the breast can have signet-ring cell morphology. So exclusion of a metastatic invasive lobular carcinoma with signet-ring cell features should top the list of the differential diagnoses in this case. In the absence of a negative mammogram, negative CT scan, and negative GATA 3 immunostain, the possibility of a metastatic lobular carcinoma of the breast has been eliminated. Absent GATA 3 and negative urine cytology also excludes urinary track carcinoma. Signet-ring cell carcinoma is more commonly encountered in uterine cervix as compared to the endometrium; one can favor designating this tumor as primary cervical carcinoma as p16 immunostain was focally reactive. However, a strong ER and Vimentin positivity favors an endometrial origin. Ciliated cells are usually positive for p16 and the reactivity of p16 in this case also represents ciliated cells. This is a pitfall of p16 immunoreactivity and pathologists must be aware of this pitfall.

Many mimickers of signet-ring cell exist and one should be aware of that as well. Among these, signet-ring cells of non-epithelial origin like decidualized or pseudo-decidualized endometrial stromal cells, and histiocytes in endometrial stroma [8,9] are notable. Adenomatoid tumor may also have signet-ring cell features but it is usually present in the myometrium or the uterine serosa and has not been seen in an endometrial biopsy [10].

In summary, we report a rare case of primary mucinous carcinoma of the endometrium with predominant signet-ring cell differentiation. Our report emphasizes that such tumors do not always indicate a metastatic tumor in the endometrium, although a metastatic tumor should always be excluded.

It is highly important to definitely identify the site of origin of this tumor. If the tumor is of cervical origin the surgical approach is different from that of the endometrial tumors. Immunohistochemistry can play an important role in these cases, although the immunostaining patterns may not be uniformly unequivocal. Clinical and/or image analysis may offer additional insight regarding the site of the tumor in the uterus. Table 1 summarizes the comparison of five previously reported cases and the current case.

Table 1. Summary of Five previously reported cases and the current case

Serial No.	Case reports	Age (years)	Final diagnosis	Procedures/ Treatment	Follow-up
1	Mooney et al [4] (1997)	65	Primary signet-ring cell carcinoma of the endometrium	TAH, BSO, and Full Staging	6 month follow up; no recurrence
2	Chebib et al [2] (2010)	51	Primary signet-ring carcinoma of the endometrium	TAH, BSO with lymph node dissection	Died of disease after 6 months
3	Boyd et al [1], (2010)	46	Primary mucinous carcinoma of the endometrium with signet-ring cells arising in adenomyosis	Hysterectomy (part of cervix was removed)	No follow-up available
4	Boyd et al, (2010) [1], 2nd case	59	Endometrioid adenocarcinoma in a polyp with signet-ring cell features	Total Hysterectomy	No follow-up available
5	Pusiol [3] (2014)	53	Primary endometrioid adenocarcinoma of the endometrium with signet-ring cells	Radical hysterectomy, BSO with Lymph node dissection	14 months follow-up; no recurrence
6	Current case (2015)	64	Primary signet- ring cell carcinoma of endometrium	Endometrial Biopsy, followed by chemosensitization and pelvic radiation	7 months follow-up; no recurrence

Note: TAH: Total abdominal hysterectomy; BSO: Bilateral salphingo-phorectomy.

The signet-ring cell carcinoma is usually referred to a high grade tumor in other organs. The biologic behavior of primary signet-ring cell carcinoma, possibly a variant of mucinous carcinoma, is unknown. Because its rarity, no large series has been published. Only rare case report is available in the literature. It is imperative to document these single cases when encountered and eventually designing a multi-institutional study with more cases to study the biologic behavior of this rare entity.

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