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Review

Primary endometrial carcinoma with signet-ring cells. A case report and review of the literature

Javier Navarro Sierra[1], Andrea Espiau Romera[1], Marta Narváez Salazar[1], María Jesús Puente Luján[1], Beatriz Eizaguirre Zarza[2], Laura Baquedano Mainar[1]

[1] *Department of Obstetrics & Gynecology of Miguel Servet University Hospital, 50009, Zaragoza, Spain*

[2] *Department of Anatomic Pathology of Miguel Servet University Hospital, 50009, Zaragoza, Spain*

Summary

Endometrial adenocarcinoma with signet-ring cells is an infrequent histological type of carcinoma that usually corresponds to a metastasis of a primary carcinoma of another origin, mainly from the gastrointestinal tract or the breast. For this reason, in view of this histological finding, it is essential to carry out a thorough evaluation including mammography, gastroscopy, colonoscopy and thoracoabdominopelvic CT. To date, only six cases of primary endometrial carcinoma with signet-ring cells have been reported in the English literature. A 73-year-old patient was referred to the Gynecology Department with a 3-day history of postmenopausal bleeding. She was diagnosed with primary endometrial adenocarcinoma with signet-ring cells. The anatomopathological special features of the surgical specimen are presented, as well as the evolution of the patient, who remained asymptomatic and free of disease 28 months after surgery. A review of the literature is performed, emphasizing the peculiarities of this rare histological subtype. Despite the fact that primary endometrial carcinoma with signet-ring cells is an infrequent tumor, it must be considered in the differential diagnosis of malignant tumors of aforesaid origin. It is essential to carry out a correct and an extensive investigative study as well as an immunohistochemical analysis of the samples obtained for its confirmation diagnosis.

Key words: Endometrial adenocarcinoma; Signet-ring cells; Immunohistochemical analysis.

Introduction

Endometrial adenocarcinoma with signet-ring cells is a type of carcinoma that owes its peculiar appearance to the presence of a large mucin-filled vacuole within its cells that displaces the nucleus to the periphery [1]. When this infrequent histological subtype appears in the endometrium, it usually corresponds to a metastasis of a primary carcinoma of another origin, mainly from the gastrointestinal tract or the breast [1].

The World Health Organization Classification of tumors considers signet-ring cell carcinoma as a rare histological variant of cervical carcinoma of the uterus, although it does not include it among the histological variants of endometrial carcinoma [2]. To date, only six cases of primary endometrial carcinoma with signet-ring cells have been published in the English literature [1, 3-6].

The objective of this work is to present the case of a patient diagnosed with primary endometrial carcinoma with signet-ring cells, performing a review of the literature on this rare pathology.

The publication of this case report was approved by Aragon Ethics Committee in Zaragoza, Spain, and complied with the declaration of Helsinki for Human Research of 1974 (last modified in 2000).

Case Report

A case of a 73-year-old patient, without toxic habits (non-smoker, non-drinker of alcohol), with a body mass index of 32 kg/m^2, hypertension and DM-2 undergoing treatment with a surgical history of colpoperineoplasty in 2008 and endometrial polypectomy by hysteroscopy in 2011, is presented. She was referred to the Gynecology Department in November 2017 due to a postmenopausal bleeding of 3 days of evolution without other associated symptoms.

Gynecological examination revealed normal external genitals, old blood remained in the vagina without active bleeding, slightly prominent atrophic cervix, with normal examination on bimanual palpation. The transvaginal ultrasound revealed a uterus with multiple myomas, with a dominant 28mm intramural myoma on the left lateral face, and a thickened and heterogeneous endometrium of 35 $\times$ 30 $\times$ 17 mm without a visible subendometrial halo. An aspiration biopsy was taken with a pathological diagnosis of mucinous adenocarcinoma with signet-ring cells (Figure 1). In the immunohistochemical study (IHC) it was found: Estrogen Receptors (ER) positive (90%), Progesterone Receptors (PR) positive (80%), Vimentin positive, p16 negative, Carcinoembryonic Antigen (CEA) positive, Cytokeratin 7 (CK7) positive, Cytokeratin 20 (CK20) negative, GATA3 negative and PAX8 positive. The immunohistochemical overexpression of the hormonal receptors and vimentin, in

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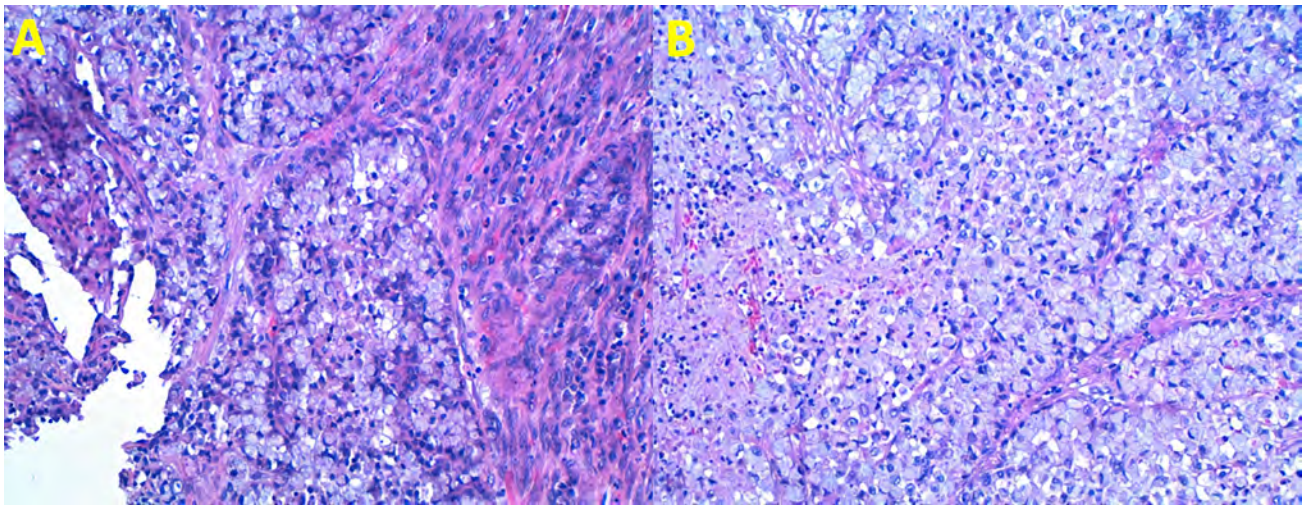

Figure 1. — Endometrial mucosa with diffuse infiltration by signet-ring cells. (A) Endometrial mucosa with diffuse infiltration by signet-ring cells. Normal endometrial gland is seen within the tumor. Hematoxylin-eosin (H&E) 10×. (B) Diffuse proliferation of signet-ring cells: basophilic, mucinous cytoplasm and nucleus rejected to the periphery. H&E 20×.

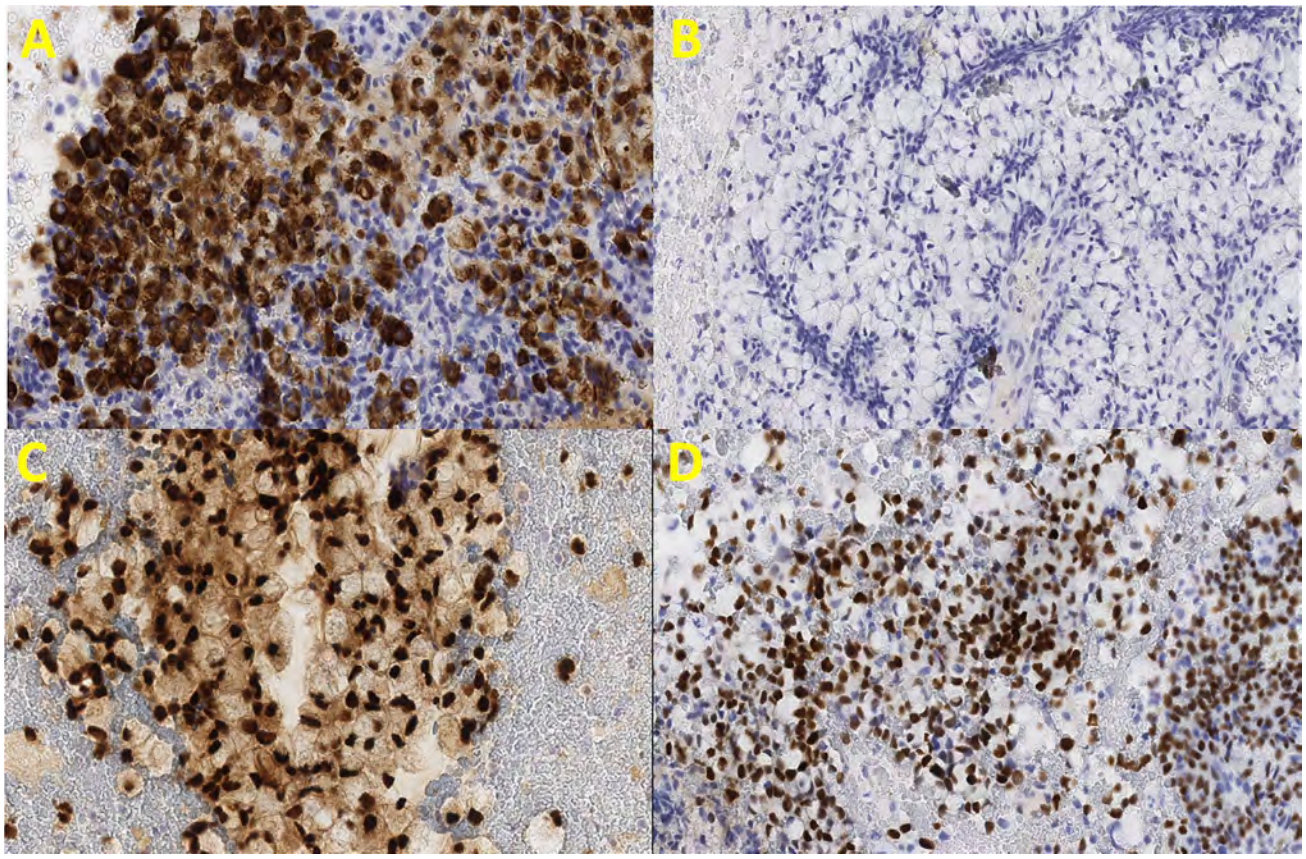

Figure 2. — Immunohistochemical analysis. (A) Endometrial mucosa with diffuse infiltration by signet-ring cells. Cytokeratin 7 + 35, 7×. (B) Signet-ring cells: mucinous cytoplasm and nucleus pushed to the periphery. Cytokeratin 20-25, 4×. (C) Signet-ring cells PAX8 + 35, 7×. (D) Signet-ring cells progesterone receptors (PR) + 32×.

addition to the negativity of p16, suggest endometrial origin versus endocervical origin. Besides, negativity for GATA3 and CK20 seems to rule out a primary origin in the breast and colon, respectively (Figure 2).

Magnetic resonance imaging (MRI) revealed an endometrium occupied by a 40 × 28 × 35 mm lobulated, poorly defined and heterogeneous mass, with post-contrast enhancement and significant restriction in the diffusion se

Table 1. — *Published cases of Endometrial Adenocarcinoma with signet-ring cells: review of the literature.*

AUTOR	AGE	SYMPTOMS	IHQ	FIGO STAGE	SURGICAL TREATMENT	ADJUVANCE	PATIENT FOLLOW-UP
Mooney *et al.* 1997 [3]	65	Asymptomatic	Vimentin-/BRST-2-/CEA+	-	HT+DA+BPL+ Omentectomía	-	Free of disease 6 months after surgery
Chebib *et al.* 2010 [4]	51	Trousseau Syndrome + ascites + weight loss	CK7+/CK20-/p16-/CEA-	IVB	HT+DA+BPL	QT (6 cycles with Carboplatin + Taxol)	Death of metastasic disease 6 months after surgery
Boyd *et al.* 2010 [5]	46	Heavy menstrual bleeding	ER+/CK7+/CEA+	-	Subtotal HT	-	-
Boyd *et al.* 2010 [5]	59	Postmenopausal bleeding	ER+/CK7+/CK20-	-	HT	-	-
Pusiol *et al.* 2014 [6]	53	Heavy menstrual bleeding	ER-/PR-/Vimentin+/p16+/ CEA-	IB	HT+DA+BPL+PL	-	Free of disease 22 months after surgery
Akkalp *et al.* 2015 [1]	77	Postmenopausal bleeding	ER+/Vimentin+/CK7+/CK20- /CEA-	IA	HT+DA+BPL	RT	Free of disease 14 months after surgery
Case presented	73	Postmenopausal bleeding	ER+/PR+/Vimentin+/p16- /CK7+/CK20- /CEA+/GATA3-/PAX8+	IIIA	HT+DA+BPL+PL +Omentectomía	QT (6 cycles with Carboplatin + Taxol) + RT	Free of disease 28 months after surgery

HT: Hysterectomy, DA: Double Anexectomy, BPL: bilateral pelvic lymphadenectomy, PL: Paraortic lymphadenectomy, QT: chemotherapy, RT: radiotherapy, CK7: Cytokeratin 7, CK20: Cytokeratin 20, ER: Estrogen receptors, PR: progesterone receptors, CEA: carcinoembryonic antigen.

quence. Besides, the mass invaded more than one-half of the myometrium, predominantly on the anterior side. The cervix appeared not to be invaded. Thoracoabdominopelvic CT ruled out the existence of lymphadenopathy and neoplastic involvement at a distance. In the preoperative analytical study tumor markers were requested, with CA-125 values of 15.77 U/ml and HE-4 of 152 pmol/L. The remainder of the evaluation, which included mammography, chest X-ray, colonoscopy and gastroscopy, was normal.

In December 2017, complete staging surgery for endometrial cancer was performed via abdominal, including peritoneal lavages, simple total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymphadenectomy, and omentectomy. The patient postoperative course was uneventful and she was discharged on the fifth day after the intervention.

The definitive pathology diagnosis in the surgical specimen, made by two expert gynecologic oncology pathologists, was FIGO IIIA undifferentiated endometrial adenocarcinoma with signet-ring cells (pT3a (uterine serosa involvement), pN0 (0/29)). In a multidisciplinary tumor board, due to the definitive diagnosis and the advanced FIGO stage of the tumor, it was decided to administer adjuvant treatment with chemotherapy (carboplatin + paclitaxel 6 cycles), followed by adjuvant external radiotherapy (46 Gy divided in 23 doses) and brachytherapy to the vaginal cuff, which ended in August 2018.

In April 2020, 28 months after surgery, the patient was asymptomatic and without evidence of recurrence.

Discussion

Signet-ring cell adenocarcinoma is an infrequent primary tumor subtype in the endometrium. To date, only six cases have been described in the literature, which are summarized in Table 1.

The diagnosis of this type of adenocarcinoma is one of exclusion, as in the presence of signet-ring cells in an endometrial tumor, the first diagnosis to rule out is a metastasis of a primary carcinoma of another origin, mainly from the gastrointestinal tract or the breast. For this reason, it is essential to carry out a thorough evaluation to include mammography, gastroscopy, colonoscopy and thoracoabdominopelvic CT [1].

Likewise, in view of this histological finding, the IHC analysis of the surgical specimen is essential and is quite helpful to guide us towards the primary origin of the tumor. In this sense, it has been described that primary endometrial carcinoma is usually positive for cytokeratin 7 and negative for cytokeratin 20, while metastatic adenocarcinoma of the colon is usually the opposite [1, 4, 5]. Furthermore, negativity for GATA3, a marker not used in the previous published cases, rules out the primary origin in the breast because of its high sensitivity when there is a primary tumor of the aforesaid origin [7]. Moreover, PAX8 is a novel tumor marker whose positivity suggests a tumor origin in the epithelium of the Müllerian ducts rather than a gastrointestinal or breast carcinoma [8]. In relation to CEA, a tumor marker associated mainly with tumors of the gastrointestinal tract, the cases published to date have not been consistent in their results, since three cases were CEA negative [1, 4, 6], while three others were CEA positives [3, 5]. Therefore, this marker has a limited value both to confirm or to rule out a gastrointestinal origin of the primary tumor.

On the other hand, it is also important to make a differential diagnosis between an endometrial or cervical origin of the tumor. The presence or absence of certain risk factors, the findings of the physical examination and imaging tests and the determination of the human papillomavirus (HPV) status will help established the diagnosis, as well as the IHC studies since the positivity of the hormonal receptors and vimentin, and the negativity of p16, together with the absence of HPV infection, suggest an endometrial origin of the lesion [1, 4, 5], while contrary results are associated with a cervical origin, as published by *Giordano et al*. [9]Only the case published by *Pusiol et al.* [6] had negative hormonal receptors and positive p16 as well as infection by HPV genotype 11, despite the endometrium being its primary origin.

Furthermore, it is important to bear in mind that sometimes we can find signet-ring cells in the endometrium whose origin is not neoplastic; this occurs occasionally during the decidualization process of the endometrium [10] or reactively after cervical cauterization [11].

Four of the published cases have appeared in postmenopausal women [1, 3, 4, 5], in which the most described symptom, as in the patient presented in this work, has been bleeding [1, 5] In relation to the other two cases, one had a late presentation with a clinical history of ascites, weight loss, and bilateral deep vein thrombosis [4] while the other turned up by chance in a screening cytology [3]. In contrast, the two cases published in premenopausal women presented with heavy menstrual bleeding of several months of evolution [5, 6].

Regarding the therapeutic management of this infrequent subtype of carcinoma, there is no standardized treatment protocol and the cases published to date differ in the schemes used. In relation to the surgical act, the majority of cases include hysterectomy (HT) + double adnexectomy (DA) + bilateral pelvic lymphadenectomy (BPL) in their schemes [1, 3, 4, 6], while in the two cases by *Boyd et al.* [5] only HT was performed. The FIGO stage and subsequent disease-free survival of the patients are unknown. Only this case and the one by *Pusiol et al.* [6] include the performance of a para-aortic lymphadenectomy. Moreover, an omentectomy has only been carried out in two cases, this case and the one by *Mooney et al.* [3]. Furthermore, in relation to adjuvant treatment, only two of the cases published to date received it. The patient reported by *Chebib et al.* [4] received chemotherapy, while the patient reported presented by *Akkalp et al.* [1] was treated with radiotherapy.

Despite this great discrepancy in the management schemes used, these tumors tend to be considered as high-

grade carcinomas and with a high risk of recurrence, so we consider that the therapeutic attitude should be similar to other high-risk endometrial carcinomas, performing complete staging surgery followed by adjuvant treatment with chemotherapy and radiotherapy [12, 13]. Only in this case this scheme has been followed in its entirety, and due to the good evolution the patient has had, being the one with the longest isease-free interval to date (28 months), this scheme could be considered the most appropriate therapeutic management option for this type of tumor.

Currently, it is very difficult to assess the long-term prognosis of this kind of neoplasia because of the few cases described in the literature to date and the short follow-up period reported in most of them.

Conclusions

Despite the fact that primary endometrial carcinoma with signet-ring cells is an infrequent tumor, it must be taken into account in the differential diagnosis of malignant tumors of the aforesaid origin. It is essential to carry out a correct and extensive clinical evaluation, as well as an immunohistochemical analysis of the samples obtained for confirmation of the diagnosis.

Ethics approval and consent to participate

The publication of this case report was approved by Aragon Ethics Committee (CEICA), in act number 19/2016, in Zaragoza, Spain. Besides, this work complied with the declaration of Helsinki for Human Research of 1974 (last modified in 2000).

Authors' contributions

Javier Navarro Sierra and Laura Baquedano Mainar established the suspicion of an endometrial cancer in the patient. Javier Navarro Sierra performed the review of the literature. Andrea Espiau Romera and Marta Narváez Salazar performed the staging surgery for endometrial cancer. BE carried out the pathological and immunohistochemical study of the samples. Javier Navarro Sierra, María Jesús Puente Luján and Laura Baquedano Mainar wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no competing interests.

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Corresponding Author:
LAURA BAQUEDANO MAINAR, M.D., Ph.D.
Hospital Universitario Miguel Servet, Obstetrics & Gynecology Department, Paseo Isabel La Católica 1-3, 50009, Zaragoza, Spain
e-mail: lbaquedanome@hotmail.com