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Case report

Primary cervical signet ring cell carcinoma: A rare case report and literature review

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ABSTRACT

Introduction: Signet-ring cell carcinoma of the uterine cervix commonly occurs owing to metastasis. Today, the rarity of primary cervical origin is still making it a diagnostic challenge. This review aims to raise awareness to maintain early diagnosis and appropriate management.

Case Presentation: A 37-year-old patient presented with postcoital vaginal bleeding with a history revealing a negative Papanicolaou smear 2 years prior. Pelvic examination revealed a cervical mass and the biopsy was interpreted as a signet ring cell pattern. Detailed extrapelvic evaluation was made to rule out a possible extragenital primary tumor. The patient underwent a type-2 radical hysterectomy, pelvic and paraaortic lymphadenectomy. Following the histopatologic evaluation, the case was diagnosed and managed as primary cervical signet ring cell carcinoma (PCSRCC) with International Federation of Gynecology and Obstetrics 2018 stage IIIC. The patient received adjuvant chemoradiotherapy and is currently disease-free 24 months following surgery.

Discussion: The small number of cases causes difficulty with an accurate diagnosis. Imaging and immunohistochemical (IHC) studies should be performed to distinguish possible primary sites. IHC studies are not yet close to refusing or confirming the diagnosis. Due to the lack of data, there is no consensus on the proper therapeutic strategy. Prognosis and survival appear to depend upon the stage of disease at diagnosis. Therefore, the awareness of such a histopathological kind of cervical cancer is crucial.

1. Introduction

The 2014 World Health Organization (WHO) Classification of Tumors of Female Reproductive Organs classifies gastric, intestinal and signet ring cell type carcinomas as subtypes of mucinous adenocarcinoma (AC) (Karamurzin, 2015). Endocervical ACs display different cellular types and patterns with varying immunohistochemical (IHC) profiles, leading to diversity in differential diagnosis. Currently, the WHO system categorizes endocervical ACs based primarily on morphological features. It is crucial to recognize these subtypes by taking their distinctive features into consideration (Stolnicu et al., 2019).

ACs only account for around 10 %-20 % of all cervical cancer cases. Primary cervical signet ring cell carcinoma (PCSRCC) is an extremely rare histopathologic subtype and has recently been included in the WHO classification (Wilbur et al., 2014). Signet ring cell adenocarcinomas are generally metastases of cancers originating from the stomach, breast, gall bladder, colon, or ovaries. To date, a total of 32 cases of PCSRCC have been reported in the literature, making it a diagnostic challenge due to its rarity. In this report, we present a patient diagnosed with PCSRCC. Additionally, 32 previously reported cases were analyzed (Table 1) to further understand the disease entity.

2. Case presentation

A 37-year-old woman, gravida 2, abortus 2, with regular menstrual periods, presented to our gynecological clinic with postcoital vaginal bleeding. Pelvic examination revealed an approximately 3 cm cervical mass on the endocervical canal. Medical history revealed a negative Papanicolaou smear 2 years prior to hospitalization and a sleeve gastrectomy 7 years before. Her family history was unremarkable.

Cervical mass biopsy was performed, and pathology revealed adenocarcinoma with a signet ring cell pattern. Immunohistochemistry showed positivity for vimentin, pankeratin, monoclonal CEA, and PAX8,

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Table 1
Summary of previously reported cases of PCSRCC.

Authors	Number	Age	Menopausal Status	Presenting Symptom	FIGO Stage	Metastasis	HPV	ER/ PR	IHC Studies	PET	Treatment	Outcome
Moll (1990)[2]	1	50	NA	Postcoital Beeding	III	NA	NA	NA	NA	NA	Sx, RT	DOD 10 M
Mayorga (1997)	1	68	Postmenopaus	Postmenopausal Beeding	IB2	NA	NA	NA	Positive for CEA, CK22	NA	NACT, Sx	NED 35 M
	2	74	Postmenopaus	Postmenopausal Bleeding	IB1	NA	NA	NA	Positive for CEA, CK22	NA	Sx	NED 25 M
Haswani (1998) (2002)	1	33	Premenopaus	Abnormal Vaginal Bleeding	IIIB	Multiple intraabdominal, peritoneal and pelvic nodules	18+	ER- PR-	Positive for CEA	NA	Palliative CRT	DOD 18 M
	2	38	NA	Postcoital beeding	IB	Pelvic lymph nodes	18+	ER- PR-	Positive for CEA, p53	NA	Sx, RT	NED 9 M
Cardosi (1999)[6]	1	53	Perimenopaus	Abnormal Vaginal Bleeding	IIIC	Pelvic and paraaortic lymph nodes	NA	ER+ PR+	Positive for cytokeratin, CEA, chromogranine, ACTH	NA	Sx,RT,CT	NED 6 M
Moritani (2004)[4]	1	29	Premenopaus	Abnormal Vaginal Bleeding	IIIB	Regional lymph nodes	–	ER- PR-	Positive for CK, MUC5AC, Negative for vimentin, MUC2,MUC6	NA	Sx, CT	NED 6 M
Suarez (2007)	1	80	Postmenopaus	Postmenopausal Bleeding	IIIB	Median third of the vagina and left parametrium	NA	ER- PR-	Positive for CK, AE1-AE3, CK20,CEA, Chromogranin A, Synaptophysin. Negative for Vimentin, S-100 Protein, HMB-45, GCDFP 15	Cx	CT, CCRT	DOD 19 M
Insabato (2007)	1	46	Premenopaus	Abnormal Vaginal Bleeding	IB1	NA	NA	NA	NA	NA	Sx, CT, RT	NED 8Y
McCluggage (2007)	1	NA	NA	NA	NA	NA	NA	NA	Positive for CK7, CK16	NA	NA	NA
	2	NA	NA	NA	NA	NA	NA	NA	Negative for CK20 and CDX2	NA	NA	NA
Veras (2009)[5]	1	36	NA	Thromboembolic Events	IV	Multiple Distant Metastasis	+	ER- PR-	Positive for P16 and CK7. Negative for CK20, CDX2, Dpc4	NA	CT	DOD 7 W
	2	43	NA	Metastases of Lung and LN	IV	Multiple Distant Metastasis	+	ER- PR-	Positive for P16 and CK7. Negative for CK20, CDX2, MMG	NA	CT	DOD 2 M
Lowery (2009)[10]	1	60	Postmenopaus	Postmenopausal Bleeding	IB1	–	NA	NA	NA	NA	RT, Sx	NED>10Y
Balci (2010)	1	53	Postmenopaus	Postmenopausal Bleeding	IIB	–	18+	ER- PR-	Positive for P16, CK7, CEA, MUC1, MUC5. Negative for CK20, MUC2, Chromogranine, vSynaptophysin, CD56,Vimentin, CDX2, TTF-1, MMG	NA	Sx	NA
Yoon (2011)	1	47	Premenopaus	Postcoital Beeding	IB1	–	16+ 18+	NA	Positive for p53 and Rb	CX	Sx	DOD 6 M
Giordano (2012)	1	45	Premenopaus	Abnormal Vaginal Bleeding	IIB	Sigmoid, Right ovary	18+	NA	Positive for CK7,CA-125, CEA and p16. Negative for vimentin	NA	Sx	NA
Kaidar-person (2013)	1	37	Premenopaus	Postcoital Beeding	IIB2	Left parametria	NA	NA	Negative for chromogranin, Synaptosin, CEA	Cx + PN	CCRT, Sx	NED 4 M
Washimi (2015)	1	31	Premenopaus	Abnormal Vaginal Bleeding	IB1	–	18+	ER- PR-	Positive for MUC2,CDX2, CEA, CK7. Negative for MUC1, MUC5AC, MUC6,P53, CK20, TTF-1, GCDFP-1, Mammaglobin, Chromogranin-1, p16,HIK1083	Cx	Sx, CT	NED 41 M
Cracchiolo (2016)	1	64	Postmenopaus	Abdominal fullness	IVB	Supraclavicular adenopathy	NA	ER- PR-	Positive for CK7, CEA, P16. Negative for S-100 protein, Synaptophysin, CDX2, CK20	Cx	Palliative	DOD 3 M
Sal (2016)[8]	1	48	NA	Postcoital Beeding	IB1	–	18+	ER- PR-	Positive for p16, CDX2, MUC1,MUC2, MUC5AC. Negative for Synaptophysin, Chromogranin A, CK20	Cx	Sx	NED 18 M
Doghri (2017)	1	48	Premenopaus	Abnormal Vaginal Bleeding	IV	Liver, Lombo-aortic adenopathy	18+	ER- PR-	Positive for p16, CK7, CEA. Negative for Synaptophysin, Chromogranin A, CK20, Vimentin	NA	Palliative CT	DOD 3 M

(*continued on next page*)

Table 1 (*continued*)

Authors	Number	Age	Menopausal Status	Presenting Symptom	FIGO Stage	Metastasis	HPV	ER/ PR	IHC Studies	PET	Treatment	Outcome
Wang (2018)[7]	1	48	Postmenopaus	Postmenopausal Bleeding	IVB	Bilateral lower lung, Paraaortic lymph nodes, bilateral external iliac lymph nodes, peritoneal seeding	NA	NA	Positive for CK20, P16. Negative for CK7, MUC6, CD56, Synaptophysin, Chromogranin A.	NA	Sx, CT	No Progression 8 M
Hamada (2019)	1	40	Premenopaus	Abnormal Vaginal Bleeding	IB2	–	NA	NA	NA	Cx	Sx, CT	Recurrent 29 M
	2	44	NA	NA	IB1	–	NA	NA	NA	Cx	Sx	NED 15 M
Kawai (2019)	1	40	NA	Abnormal Cervical Cytology	NA	NA	16+	NA	Positive for p16, CA125, CK7, MUC5AC. Negative for p53, TTF1, CDX2, CK20, E-cadherin, beta-catenin, 5, MUC2, MUC6	NA	NA	NA
Li (2021)	1	35	NA	Postcoital Beeding	IB2	Bilateral Ovaries	18+	ER- PR-	Positive for CK7, P16, CEA,D2-40,Ki-67, CK20,CDX2,MUC2,MUC6. Negative for AFP, p53,CK17,Inhibin A, Vimentin		Sx, CT, RT	NED 16 M
Kim (2021)	1	43	Premenopaus	Abnormal Vaginal Bleeding	IIIC1	Pelvic lypmh nodes	18+	ER-	Positive for p16, CEA, CK7, MUC1,5,6	Cx, PN	CT, RT	DOD 15 M
Culminas Riezyl B. (2021)[3]	1	44	Premenopaus	Abnormal Vaginal Bleeding	IB2	–	NA	NA	NA	NA	Sx, CT,RT	NED 24 M
Salmen (2021)	1	50	Perimenopausal	Abnormal Vaginal Bleeding	IB3	–	NA	NA	Positive for P16	NA	Sx, CT, RT	NED 12 M
Purwoto (2022)	1	39	Premenopaus	Postcoital Beeding	IB2	–	NA	NA	Positive for P16	NA	Sx, RT	NED 12 M
Lazhar (2023)	1	68	Postmenopaus	Pelvic pain	IVA	Bladder, Urethra,rectum, left iliac lymph nodes	NA	ER- PR-	Positive for p16, CK7. Negative for CK20	NA	Palliative CRT	DOD 1 M
Present Case	1	37	Premenopaus	Postcoital Beeding	IIIC	Paraaortic lymph nodes, bilateral pelvic lymph nodes	NA	ER- PR-	Positive for pancytokeratin, monoklonal CEA, PAX8. Negative for p16, p63, CD10	Cx	Sx, CT, RT	NED 24 M

Abbreviations: CK, cytokeratin; CEA, carcinoembriyonic antigen; MUC, mucin; TTF, thyroid transcription factor; ER, estrogen receptor; PR, progesterone receptor; NA, not available; SMA, smooth muscle actin; GCDFP, gross cystic disease fluid protein; M, months; Y, years; W, weeks; CDX2, caudal-type homeobox 2; PGP, protein gene product; Sx, surgery; CT, chemotherapy; RT, radiotherapy; DOD, died of disease; NED, no evidence of disease; NACT, neoadjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; NED, no evidence of disease.

and negativity for p16, p63, CD10, estrogen receptor (ER) and progesterone receptor (PR) (Fig. 1A and B). The case was classified as a diffusable type carcinoma, compatible with slightly different adenocarcinomas containing a signet-ring cell component. Laboratory tests showed normal levels of carbohydrate antigen 125 (CA-125) (20 U/ml) and carcinoembryonic antigen (CEA) (1.5 ng/ml). Magnetic resonance imaging (MRI) revealed a 3.0 × 3.5 cm cervical mass extending along the cervical canal, located in the inner fibromuscular stromal layer with heterogeneous intensity on T2-weighted images (Fig. 2A and B). Positron emission tomography (PET) images indicated increased fluorodeoxyglucose (FDG) uptake on the cervical mass extending into the endometrial cavity (SUVmax: 34) (Fig. 2C), with suspicious focal involvement on the left ovarian site. Lymphatic inclusion was not mentioned. Gastroduodenoscopy, colonoscopy, and breast sonography did not detect a primary tumor site, ruling out an extragenital primary tumor.

The patient underwent a type-2 radical hysterectomy, pelvic and paraaortic lymphadenectomy (Fig. 2D). Intraoperative evaluation of upper abdominal and retroperitoneal organs found no evidence of an extragenital primary tumor. Macroscopically, the tumor was measured 4.7 × 3.6 x 1.8 cm, located in the ecto and endocervical parts. Histologic evaluation revealed PAS-Alcian blue positive atypical cells in signet ring morphology containing intracytoplasmic mucin, with an infiltrative pattern extending under the squamous epithelium in the cervix and between the endocervical glands (Figs. 3 and 4). There was no tumor extension to the uterine cavity. Extensive lymphovascular space involvement was noted, but tumor cells were not identified in the uterine serosa or parametria. Tumor metastases were found in bilateral pelvic and paraaortic nodes. The ovaries were negative for tumor.

The case was diagnosed and managed as PCSRCC by International Federation of Gynecology and Obstetrics (FIGO) 2018 classification stage IIIC. The patient had a normal postoperative course and began chemoradiotherapy 4 weeks after surgery. She received adjuvant external beam radiation therapy for 45–50.4 Gy in 25–28 fractions and three-dimensional high-dose-rate adaptive brachytherapy for 15–18 Gy in 3 fractions with adjuvant carboplatin plus paclitaxel based chemotherapy. The patient tolerated the treatment without significant morbidity and is currently disease-free 24 months following surgery.

3. Discussion

Carcinomas with signet ring cell morphology arise more commonly in the gastrointestinal tract or breast. Primary cervical origin of signet ring cell carcinoma is an extremely rare histopathological feature, first reported in 1990 (Moll et al., 1990). Therefore, it is crucial to distinguish a primary tumor from metastasis when signet ring cells are present in a carcinoma within the cervix (Culminas, 2021). To date, a total of 32 cases have been reported in the literature. However, the prevalence is increasing even in developed countries with efficacious screening programs. The reason may be that most of the AC lesions are located at the inner mouth of the cervical canal, which decreases the detection rate through cytological screening (Veras et al., 2009). Therefore, one can conclude that the negative results of the Pap smear, p16 staining or HPV type 16 and 18 do not have evidentiary value to rule out primary cervical cancer.

Presenting symptoms of PCSRCC cases have similar characteristics to other cervical carcinomas. A total of 30 reported cases had the patient's presenting symptoms information. Abnormal uterine bleeding (12/30), postcoital bleeding (8/30) and postmenopausal bleeding (6/30) are the most frequently reported ones. The age at diagnosis ranged from 29 to 80 years and the mean age was 49,04 years with the median age of 48. Moreover, menopausal status was predicted in 23 cases and the number of premenopausal patients (13/23) was slightly more than the postmenopausal (8/23) and perimenopausal (2/23) ones unlike the other types of cervical cancers (Table 1).

Imaging modalities are essential to distinguish possible primary sites other than the cervix. Increased FDG uptake was reported in all 10 reported cases of PCSRCC that might show a high affinity for the primary lesion. PET/CT imaging may also be beneficial in detecting metastasis and recurrence.

IHC studies may also be helpful in differentiating primary from metastatic signet ring cell carcinoma of the cervix, especially when the number of cases rises. In previous cases of PCSRCC, out of all cases, 11 were tested for HPV-DNA, with HPV-18 present in nine cases and HPV-16 in two cases. Only one case was reported to be HPV-DNA negative (Moritani et al., 2004). In addition, p16 positivity, which may show an HPV effect, was reported in 13 cases, while two cases, including ours, were reported as negative for p16 IHC staining. Regarding IHC expression of estrogen and progesterone receptors, out of 31 cases, 13 were tested, with only one being positive (Cardosi et al., 1999). Although they seem to be prominent IHC markers, negative results for ER and PR do not provide diagnostic evidence in the current knowledge. Three cases were negative for mammoglobin, and no positive case was reported. To date, positivity for cytokeratin 7 (CK7) was shown in 12 cases, with only one negative result making it seem to be one of the most prominent IHC markers (Wang et al., 2018; Sal et al., 2016). Based on conflicting results, it can be concluded that IHC studies are not yet close to refusing or confirming the diagnosis of PCSRCC.

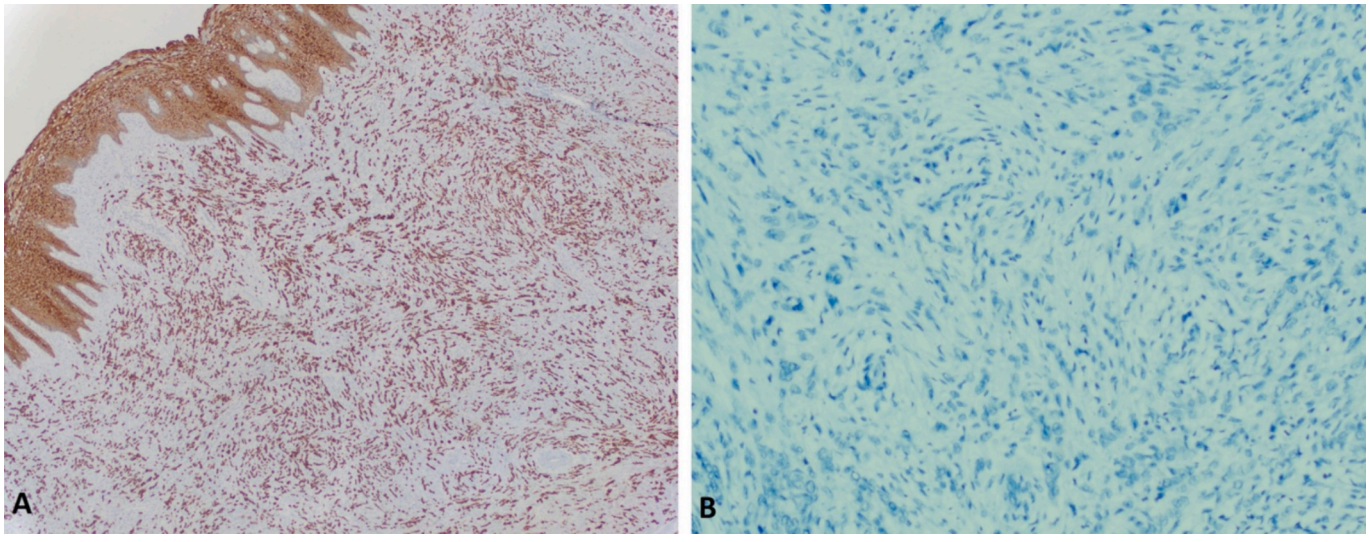

Fig. 1. A. Discohesive tumor cells staining with pankeratin under the squamous epithelium (x40). B. Tumor cells showing p16 negativite staining (x200).

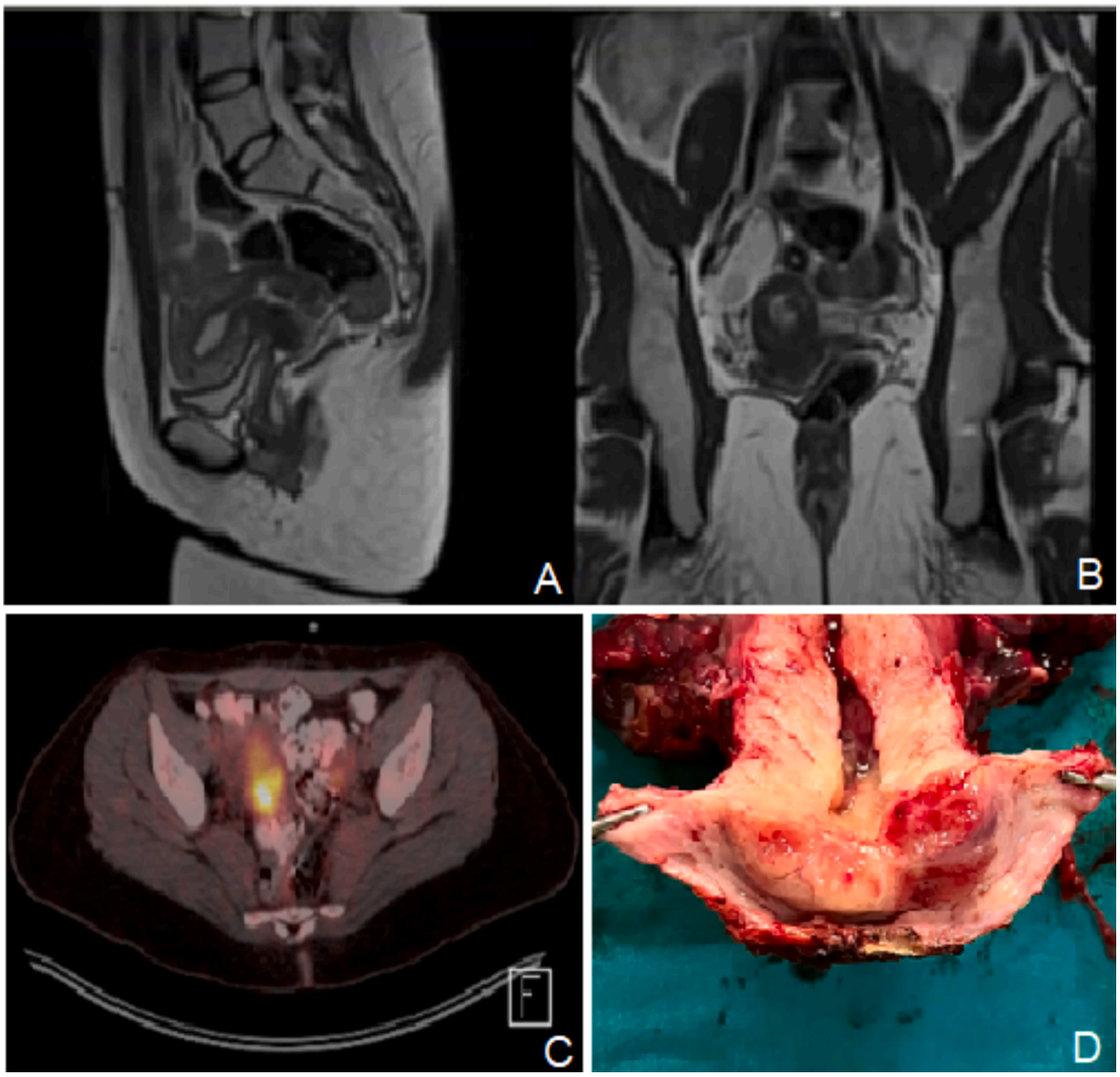

Fig. 2. Sagittal (A) and axial (B) sections of the distal part of cervical canal with the extension of the tumor, MRI. C. Axial section of PET/CT image at the level of the cervix. D. Ulcerative lesion on the cervix, hysterectomy specimen.

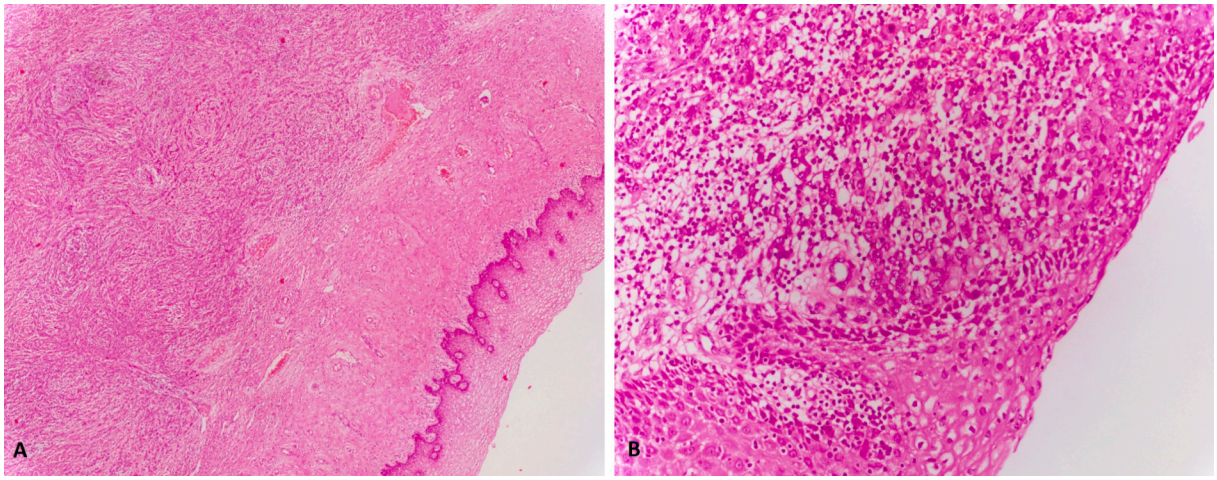

Fig. 3. A. Signet ring cells with intracytoplasmic mucin showing diffuse tissue infiltration with no gland formation under the squamous epithelium (H&E, x40). B. Tumor cells causing ulceration in the endocervical epithelium (upper right) and infiltrating under the squamous epithelium (H&E, x400).

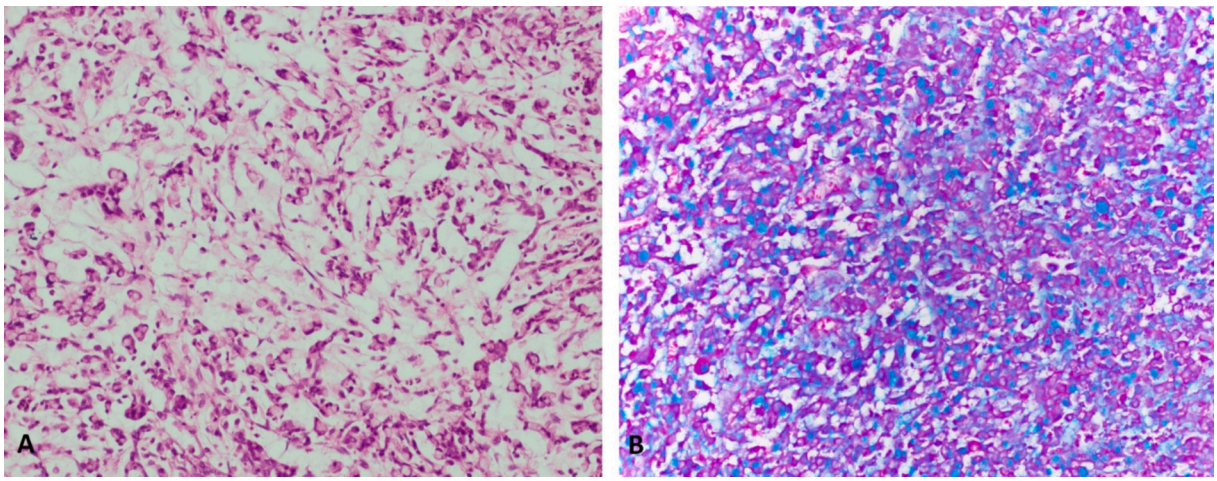

Fig. 4. A. Signet ring cells containing intracytoplasmic mucin (x200, H&E). B. PAS-Alcian blue staining in tumor cells (x200). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the diagnosis of our case, the patient's history, clinical presentation, physical examination, and imaging studies were all taken into consideration. Our case was no different in terms of the characteristic presentation of cervical carcinoma. The cervical origin of the tumor was further supported by the absence of other neoplasms on systemic evaluation. Histological findings were consistent with the characteristic morphology described for signet ring cell carcinoma of the uterine cervix. The case was finally diagnosed as PCSRCC with FIGO stage IIIC. The patient received adjuvant external beam radiation therapy and brachytherapy with adjuvant carboplatin plus paclitaxel based chemotherapy. Data on PCSRCC is insufficient to make a recommendation on treatment strategy due to the limited number of previous reports. Reported cases of early-stage disease demonstrate the effectiveness of surgery followed by radiotherapy or combined chemotherapy (Wang et al., 2018; Agha, 2020). In advanced cancers, palliative chemotherapy is prescribed as an option.

PCSRCC has also not been studied sufficiently in terms of prognosis and survival due to the small number of cases. Based on previous reports, the outcome of PCSRCC is mostly related to the cancer stage (Table 1). In stage IB1 disease; no evidence of disease has been reported to range from six months to more than ten years (Lowery et al., 2009). Patients with advanced stage had poor prognosis and in stage IV, died of the disease has been reported to vary between 4 weeks and eight months (Wang et al., 2018). Since the survival is mostly related to the cancer stage at the time of diagnosis, awareness of such a histopathological kind of cervical cancer is crucial.

CRediT authorship contribution statement

Ezgi Oktay: Writing – review & editing, Writing – original draft, Data curation. **Mürşide Çevikoğlu Kıllı:** Methodology, Data curation. **Gözde Arslan:** Funding acquisition, Formal analysis. **Görkem Ülger:** Resources, Investigation. **Tolgay Tuyan İlhan:** Visualization, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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