Case Report

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A rare case of a primary signet-ring cell carcinoma of the cervix

Riezyl B. Culminas[1], Aida J. Bautista[1], Sabrina Ang-Sy[1]

Abstract:

A 44-year-old woman presented with an abnormal vaginal discharge. She was initially diagnosed with cervical intraepithelial neoplasia-1 through Papanicolaou smear and was managed with cryotherapy and completed human papillomavirus vaccinations. Nine years later, gynecologic examination showed a cervical mass, and biopsy revealed a signet-ring cell-type mucinous adenocarcinoma. Extensive systemic evaluation performed revealed no other malignancies. Radical hysterectomy was performed, and final pathology report showed a primary signet-ring cell cervical carcinoma stage 1B2. Concurrent chemotherapy with adjuvant external beam radiation therapy was then given. The patient has no evidence of disease for 24 months now since diagnosis. Primary signet-ring cell carcinoma of the cervix is rare. It is diagnosed when no other tumor is found in extragenital sites, histology consists of signet-ring morphology, tumor includes areas of adenocarcinoma *in situ*, and case has a prolonged survival. Overall patient education plays a vital role in management.

Keywords:

Cervical carcinoma, cervical intraepithelial neoplasia-1, signet-ring cell

Introduction

Cervical cancer is the third most common cancer among women worldwide. In the Philippines, it is found to be the second most common cancer among Filipino women aged between 15 and 44 years.[1]

The most common histological types of uterine cervical cancer are squamous cell carcinoma (69%) and adenocarcinoma (25%). The histological types of uterine cervical adenocarcinomas are mucinous, endometrioid, papillary, and clear cell. Mucinous adenocarcinoma of the cervix includes subtypes of endocervical, intestinal, and signet ring cell. Cervical adenocarcinoma occurs in 10%–25% of all cervical carcinomas, and most of them are of the endocervical type.[2]

Signet-ring cell carcinoma (SRCC) rarely presents as a primary cervical tumor. It usually presents as a metastasis from carcinoma of the gastric, colonic, ovarian, or breast. Ninety percent of this type occurs in the stomach, 1% in other parts of the gastrointestinal tract (GIT), and 0.5% in other cancer sites.[3] SRCC is histologically characterized by the appearance of signet-ring cells, which acquire a signet cell morphology due to the accumulation of abundant mucin in the cytoplasm, displacing the nucleus to the periphery. SRCC is labeled if greater than 50% of the tumor cells show prominent intracytoplasmic mucin and an eccentrically placed crescent-shaped nucleus.[4]

As of 2018, there are less than 24 cases of primary signet-ring carcinoma of the cervix recorded in the literature.[5] In the Philippines, no available published reports for primary SRCC of the uterine cervix are seen on *The Philippine Journal of Obstetrics and Gynecology* and HERDIN Plus data search.

[1]*Department of Obstetrics and Gynecology, Manila Doctors Hospital, Manila, Philippines*

Address for correspondence:
Aida J. Bautista, MD, FPOGS, FSGOP, 414 San Antonio St, Paco, Manila.
E-mail: aidabautista85@yahoo.com
Sabrina A. Sy, MD, FPOGS,FPSCPC, 1352 Mahatma Gandhi, Paco Manila.
E-mail: shangsy57@gmail.com

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This paper reports a case of primary SRCC of the uterine cervix in a 44-year-old presenting with an abnormal vaginal discharge and a cervical mass. An analysis in relation to the 20 previously reviewed cases of primary SRCC of the cervix [Table 1][6] was also done to further understand the disease entity and its implications in patient management and prognosis. Emphasis on patient education and follow-up are discussed as well.

Case report

The patient is a 44-year-old female who presented with a yellowish, nonfoul smelling vaginal discharge 10 years before diagnosis. The past medical, family, obstetric, and gynecologic history is all unremarkable. She had coitarche at 21 years old with one sexual partner who denies promiscuity. Consultation with a gynecologist who performed a Papanicolaou (Pap) smear showed cervical intraepithelial neoplasia-1 (CIN-1). She was treated with cryotherapy and was subsequently given three doses of quadrivalent human papillomavirus (HPV) vaccinations. The patient was then lost to follow-up for 9 years, until 10 months before diagnosis when she experienced recurrence of the abnormal vaginal discharge, now associated with postcoital spotting. Gynecologic examination revealed a cervical mass. Transvaginal ultrasonography with Doppler studies showed cervix with two discrete hypoechoic structures [Figure 1]. One located at the right posterior distal cervix measuring 1.39 cm × 1.62 cm × 1.14 cm and another mass at the left posterior distal cervix measuring 2.29 cm × 1.97 cm × 1.52 cm. Ultrasonographic impression showed a moderately vascular right cervical mass, probably a cervical tumor, while only minimal vascularity was noted on the left cervical mass, probably a polyp.

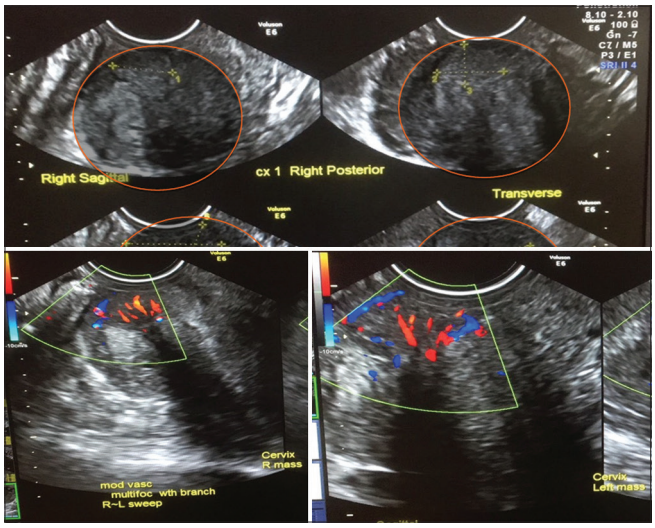

Figure 1: Images of patient's transvaginal ultrasonography with Doppler studies. Impression: Normal-sized uterus with small myomata. Normal secretory endometrium. Normal right ovary with corpus luteum. Normal left ovary with cystic follicle. Cervical masses. Doppler studies: Moderately vascular right cervical mass, probably a cervical tumor. Minimally vascular left cervical mass, probably a polyp

Cervical punch biopsy of the 3.5 cm mass at the posterior cervix was consistent with a SRCC. Both parametria were smooth and pliable.

Subsequently, further workup was done to look for the primary tumor site. Chest and whole abdominal computed tomography (CT) scan, mammography and breast ultrasonography, gastroscopy, and colonoscopy studies revealed unremarkable findings. The patient was cleared by the gastrointestinal and surgery services.

Primary cervical carcinoma stage 1B2 was considered. Radical hysterectomy with bilateral salpingo-oophorectomy and pelvic and para-aortic lymph node dissection was then performed. Gross findings [Figures 2 and 3] showed a 3.5 cm × 2 cm × 1.5 cm solid, firm mass at the posterior lip of the cervix, extending to the isthmic area, with more than 50% stromal invasion. Microscopic findings [Figures 4 and 5] confirmed the initial biopsy revealing mucinous carcinoma, signet-ring cell type. There was no lymphovascular invasion noted. The vaginal cuff, ovaries, fallopian tubes, parametria, and pelvic and para-aortic lymph nodes were negative for tumor. Other uterine findings showed focal adenomyosis, leiomyoma uteri, intramural, secretory phase, and endometrium and cystic follicles on bilateral ovaries. Based on the 2018 FIGO Cervical Cancer Staging,[1] the patient was diagnosed and managed as cervical carcinoma stage IB2, with a final diagnosis of G2P2 (2002) cervical carcinoma stage 1B2, signet-ring cell-type mucinous carcinoma, status postcervical punch biopsy. The patient was subsequently treated with adjuvant external beam radiation therapy with concurrent weekly low-dose cisplatin chemotherapy. At present, the patient is disease-free for 24 months.

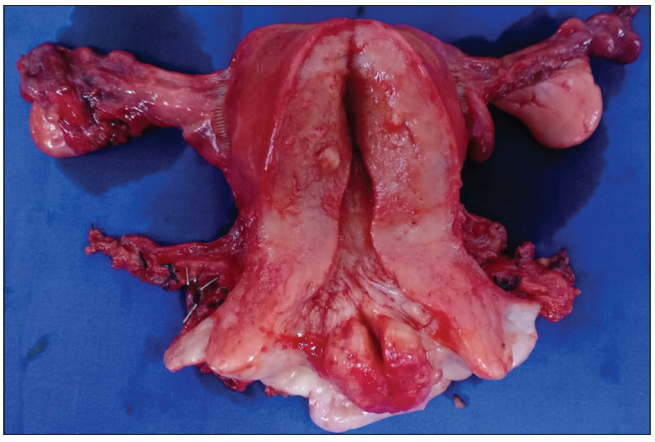

Figure 2: Gross specimen of the index patient

Table 1: A review of literature of 20 cases of primary signet-ring cell carcinoma of the cervix

Authors, years	Age	Presenting symptoms	FIGO stage	Immunohistochemical studies other than ER/PR	ER, PR	HPV	Treatment	Outcome
Moll *et al.* 1990	50	Postcoital bleeding, menometrorrhagia	III	NA	NA	NA	Sx, RT	DOD 10 months
Mayorga *et al.* 1997		Postcoital bleeding	Ib	NA	NA	NA	Preoperative chemotherapy, Sx	NED 35 months
Case 1	68							
Case 2	74	Postmenopausal bleeding	Ib	NA	NA	NA	Sx	NED 25 months
Haswani *et al.* 1998		Postcoital vaginal bleeding in both cases	III	NA	ER–	HPV type 18+	Palliative RT and chemotherapy	DOD 10 months
Case 1	33							
Case 2	38		Ib	NA	ER– PR–	NA	Sx and RT	NED 18 months
Cardosi *et al.* 1990	53	Perimenopausal bleeding	Ib	NA	ER + PR +	NA	Sx, RT, chemotherapy	NED 6 months
Moritani *et al.* 2004	29	Persistent abnormal genital bleeding	III	Positive for CK, MUC5AC Negative for vimentin, MUC2, MUC6	ER– PR–	-	Chemotherapy	NED 6 months
Insabato *et al.* 2009	46	Vaginal bleeding in cervical polypoid lesion	Ib	NA	NA	NA	Sx, RT, Chemotherapy	NED 8 years
Suarez *et al.* 2007	80	Vaginal Discharge	IIIb	Positive for CK AE1-AE3, CK20, CEA, chromogranin A, and synaptophysin Negative for vimentin, S-100 protein, HMB-45, ACTH, prolactin, TSH, FSH, LH, GH, GCDFP-15	NA	NA	RT, chemotherapy	DOD 18 months
Mc Cluggage *et al.* 2008	NA	Two cases NA	NA	Positive for CK7 and CK16	NA	NA	NA	NA
2 cases				Negative for CK20 and CDX2				
Versas *et al.* 2016		Thromboembolic events (Trousseau syndrome)	IV	Positive for p16 and CK7	ER– PR–	+	Chemotherapy	NA
2009	36			Negative for CK20, CDX2, and Dpc4				
Case 2	43	Metastases of lung and lymph nodes	IV	Positive for p16 and CK Negative for CK20, CDX2, and mammoglobin			Chemotherapy	DOD 2 months
Lowery *et al.* 2011	60	Postmenopausal bleeding	Ib1	NA	NA	NA	RT, brachytherapy, Sx	DOD >10 years
Balci *et al.* 2010	53	Post-menopausal bleeding	IIb	Positive for CK, p16, CEA, MUC1, and MUC5 Negative for CK20, GCDFP15, MUC2, chromogranine, synaptophysin, PGP 9.5, CD56, vimentin, CDX-2, TTF-1, and mammoglobin	ER– PR–	HPV type 18 +	Sx	NR
Yoon *et al.* 2011	47	Post-coital bleeding	Ib	Positive for p53 and Rb	NA	NA	Sx	NED 6 months
Giordano *et al.* 2012	45	Vaginal discharge	IIb	Positive for CK 7, CA-125, CEA, and p16 Negative for vimentin	NA	HPV type 18+	Sx	NA
O. Kaider-Person 2013	37	Postcoital bleeding	IIb2	Negative for chromogranin, synaptosin, CEA	NA	NA	Concomitant chemotherapy, radiotherapy, brachytherapy, Sx	NED 4 months
Washimi *et al.* 2015	31	Abnormal vaginal bleeding	IIa	Positive for MUC2, CDX2, CEA, CK7 Negative for MUC1, MUC5AC, MUC6, p53, CK20, TTF-1, GCDFP-1, mammoglobin, chromogranin-1, p16, and HIK1083	ER– PR–	HPV type 18+	Sx and chemotherapy	Disease free at 41 months
Cracchiolo *et al.* 2015	64	Abdominal fullness	IVB	Cytokeratin 7, CEA, P16 positive GCDFP, S-100 protein, synaptosin, SMA, CDX-2 colon carcinoma, and cytokeratin 20 negative	ER + PR +	-	Palliative	+ 3 months

Contd...

Table 1: Contd...

Authors, years	Age	Presenting symptoms	FIGO stage	Immunohistochemical studies other than ER/PR	ER, PR	HPV	Treatment	Outcome
Sal *et al.* 2016	48	Postcoital vaginal bleeding	Ib	Positivity for p16, CDX-2, MUC1, MUC2, and MUC5AC Negativity for synaptophysin, chromogranin A, and CK-20	ER– PR–	HPV type 18 +	Sx	Disease-free at 18 months

CK: Cytokeratin, MUC: Mucin, GCDFP: Gross cystic disease fluid protein, ER: Estrogen receptor, PR: Progesterone receptor, NA: Not available, Sx: Surgery, RT: Radiation therapy, DOD: Died of disease, NED: No evidence of disease, CEA: Carcinoembryonic antigen, CDX-2: Caudal-type homeobox 2, SMA: Smooth muscle actin, PGP: Protein gene product, TTF: Thyroid transcription factor, TSH: Thyroid-stimulating hormone, GH: Growth hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing Hormone, HPV: Human papillomavirus, FIGO: International federation of obstetrics and gynecologists

Case Discussion

The patient was diagnosed with a primary signet-ring cell carcinoma (SRCC) of the cervix stage 1B2. There are limited reports on primary SRCC of the uterine cervix. However, what brings interest to this case is not just the rarity of this cervical carcinoma, but more so, it leads us to ask, how did the patient's CIN-1 lesion progress to cervical carcinoma? Moreover, how did it lead to a signet-ring cell type of cervical carcinoma? This case has salient features that warrant further discussion. First, the history of CIN-1 lesion detected from her Pap smear 10 years before the diagnosis. Second, the choice of cryotherapy for such diagnosis. Third, the fact that she had recurrence of her symptoms despite receiving HPV vaccinations. At last, the interval history in which no follow-up consultations were done.

Vaginal discharge is a common presenting complaint in women of reproductive age. It may be from an infectious and noninfectious cause. Ten years before diagnosis, the patient consulted due to a yellowish, nonfoul smelling vaginal discharge. With the history of the patient, gynecologic examination through inspection, bimanual examination, and obtaining appropriate vaginal swabs was done. In this case, a Pap smear revealed CIN-1 lesion.

A factor that causes CIN lesion is infection from an HPV genotype. CIN-1 lesions usually regress to normal after 1 year even without treatment. As per the 2019 guidelines set by the American Society for Colposcopy and Cervical Pathology, since the patient was more than 25 years old at the time of her CIN-1 diagnosis, follow-up without treatment and co-testing at 12 months should have been done. If HPV co-test is positive, colposcopy should be done. If CIN-1 persists for at least 2 years, observation may still be an option, but treatment through an excision or ablation is acceptable.[7]

Cervical cryotherapy was the choice of treatment for this patient. Cryotherapy is initially successful in eliminating cervical dysplasia 85% of the time when a double-freeze technique is used, even when the lesion extends up to 5 mm into the endocervical canal. Results of the comparative study done by Stienstra *et al.*, between use of a shallow and a conical tip for cryotherapy, failed to show a statistically significant difference between the effectiveness of treatment between the two tips for eliminating CIN. This study did not support the assumption that the shallow conical tip provides a better freeze zone into the canal.[8] It is then safe to assume that both types of tips are effective in eliminating CIN.

Our patient completed three doses of a quadrivalent HPV vaccine. All HPV vaccines protect against HPV types 16 and 18 that cause most HPV cancers. Several studies have implicated the prevention of cervical cancer after HPV vaccinations. It is emphasized however that HPV vaccination is not recommended for women over age 26 as it has limited or no protection against HPV-related diseases. The best way to prevent cervical cancer is to get routine cervical cancer screening.[8] Our patient received an HPV vaccine only upon the diagnosis of a CIN-1 lesion. It is likely that the vaccinations, although completed, did not function as a preventive measure in this case. It may also be considered that she may be infected with other HPV strains and that other possible cofactors such as a weakened immune system may have contributed to the persistence and eventual progression to carcinoma.

The patient was however lost to follow-up for 9 years. The recommended follow-up with a colposcopy and HPV cotesting was not done. The progress of a CIN-1 lesion to CIN-2 or 3 or to invasive carcinoma takes years. Moreover, with effective patient education and follow-up, disease progression is well prevented.

This case eventually progressed to cervical carcinoma. The patient sought consult due to a cervical mass associated with the recurrence of the abnormal discharge and postcoital spotting. At this time, it is important to consider that when presented with a cervical mass, one needs to identify whether the mass is benign or malignant. Cervical mass biopsy revealed a signet-ring cell-type mucinous carcinoma.

In general, SRCC is a rare histologic subtype of adenocarcinomas. It is said that 90% of this type occurs in the stomach, 1% in other parts of the GIT, and typically

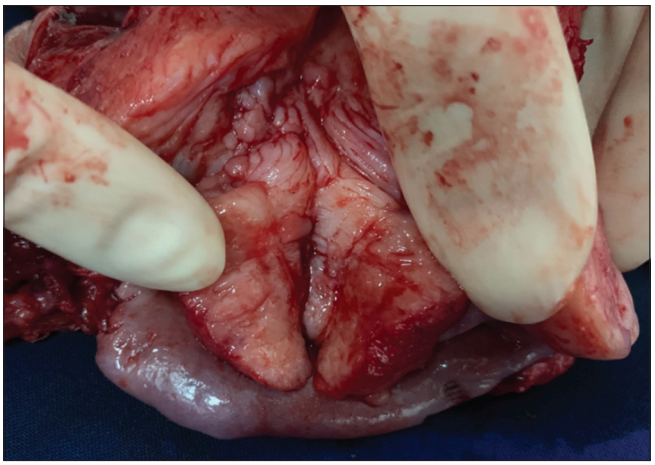

Figure 3: Gross specimen of index patient showing the cervical mass

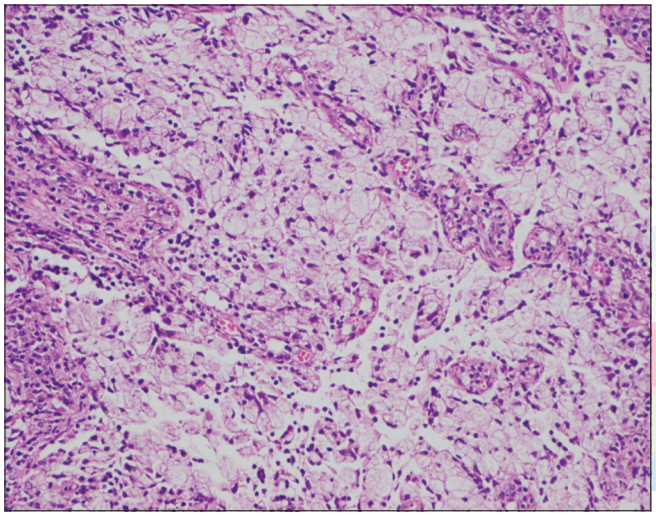

Figure 4: Microscopic Findings of Signet-ring Cell Carcinoma of the Cervix of the Index Patient. Low power view showing abundant mucin that distends the 35 cytoplasmic vacuoles displacing the nuclei to the periphery

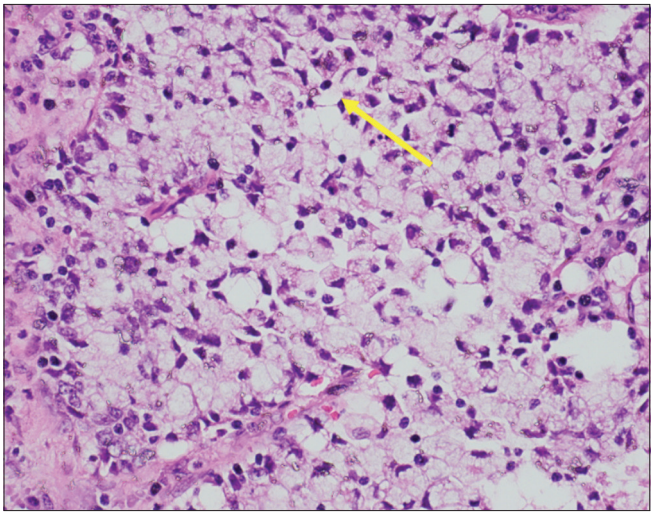

Figure 5: Microscopic Findings of Signet-ring Cell Carcinoma of the 52 distends the cytoplasmic vacuoles displacing the nuclei to the periphery

less than 0.5% of the diagnosis for other cancer sites.[3] On the account that SRCC of the cervix is rare, it is hence important to differentiate primary versus metastatic cervical carcinoma.

The case report by Giordano *et al*. in 2012 presented a case of a 45-year-old diagnosed with a primary cervical SRCC characterized by prominent endometrial and myometrial involvement, simulating primary endometrial adenocarcinoma with cervical extension. Immunohistochemical and molecular studies were needed to provide sufficient information for accurate diagnosis. It was found that a positive HPV-DNA using molecular analysis provides diagnostic evidence of primary SRCC of the cervix. The presence of HPV-18 has been determined in five cases of primary SRCC of the cervix. Only one case was reported with negative p16 immunohistochemical staining results. This same study however claimed that immunohistochemical studies are not sufficient enough to support a primary origin of the tumor.[9]

Given this, it is important to consider that this type of adenocarcinoma is linked to the HPV-associated adenocarcinoma of the uterine cervix. They have a glandular stromal invasion and/or expansile-type invasion, associated with the high-risk type HPV infection. The most common are HPV types 18, 16, and 45 that account for 95% of cases.[4]

In a study done by Mayorga *et al*. in 1997, a criterion for primary SRCC in the cervix without immunohistochemical studies was presented. These include (1) no other tumor was found in the evaluation for an extragenital neoplasm, (2) the histology consists of a prominent signet-ring cell morphology and a diffuse pattern of infiltration, (3) the tumors include areas of adenocarcinoma *in situ*, and (4) the cases have a prolonged survival. In contrast, in metastatic disease, the presence of tumor cells can be found in dilated lymphatics or blood vessels. In addition, there is a lack of an associated *in situ* carcinoma.[10]

In our case, immunohistochemical and molecular studies were not done. However, it is important to note that the patient had a history of CIN-1 lesion 10 years before the diagnosis. This claim is further strengthened as the WHO classification for tumors stated that "There is a tight correlation between HPV-associated pathogenesis and morphology, meaning that HPV testing and related analyses are usually not required for diagnosis."[4]

A study by Doghri *et al*. in 2017 reviewed 20 cases of primary cervical carcinoma with a signet-ring cell morphology [Table 1].[6] The reports have been considered primary cervical cancer only after a thorough

systemic evaluation is performed to ascertain that this is not a metastasis. From this review, it showed that the mean age at diagnosis was at 49 years old. Seventy percent presented with abnormal vaginal bleeding, while 30% with postcoital bleeding and 40% with postmenopausal bleeding. While only 10% presented with an abnormal vaginal discharge. The mean stage at diagnosis was stage IIb. Not all of these cases underwent immunohistochemical studies. Eight cases have been found be diagnosed at stage IB, as with the case of our patient. For those who were diagnosed at an early stage, all were found to have no evidence of the disease ranging from 6 months to 8 years.

In the diagnosis of our case, the history, clinical presentation, physical examination, and other workup such as the CT scan, breast imaging, endoscopy, and colonoscopy were all considered. Moreover, in relation to how cervical carcinoma presents, our case is no different in terms of the characteristic presentation and risk factors for cervical carcinoma. As per the criteria mentioned from the study by Mayorga *et al.*, the cervical origin of the tumor in our case was further supported by the absence of other neoplasms on systemic evaluation; the patient's histologic findings are consistent with the characteristic morphology described for a SRCC of the uterine cervix [Figure 3]. At last, the case were showed to have a prolonged survival.

Doghri *et al.*'s case report has provided further evidence to this case. The history, clinical presentation, and physical examination of SRCC of the uterine cervix have basically the same characteristics from other cervical adenocarcinomas. Our case belonged to the 10% who presented with an abnormal vaginal discharge. At last, our patient was diagnosed at stage IB2 and has no evidence of disease for 24 months since diagnosis.

Summary

In conclusion, primary SRCC has a predilection for the GIT but may also present as a primary cervical tumor. Awareness of this entity is important as management of the case is still dependent on clinical stage at diagnosis once a primary tumor is identified.

Our diagnosis of a primary SRCC was based on patient's history, clinical presentation, and physical examination. These were further strengthened by the negative findings on CT imaging, endoscopic and colonic findings, breast imaging, and histopathological reports. Furthermore, with the management given for the stage at diagnosis, the patient's response was good. Our patient has currently no evidence of disease for the past 24 months.

SRCC has not been sufficiently studied in terms of its prognosis. However, it is interesting to know that such a histopathological kind of cervical cancer exists as it can give us an awareness that despite its rarity, it can have a good prognosis if diagnosed early and managed appropriately.

However, in the greater scheme, it is important to consider that overall, the prevention of progression of a simple CIN-1 lesion to a carcinoma would depend on effective patient education.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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