

HPV associated adenocarcinoma, signet ring morphology of uterine cervix: A rare presentation

Kricha Pande¹, Gopi Aryal¹, Reena Rana¹, Anuj Poudel¹, Niki Thakur¹, Pralisha Maharjan²

¹MD, Department of Laboratory Medicine and Pathology, Nepal Medcity Hospital, Lalitpur, Nepal

²Resident doctor, Department of Laboratory Medicine and Pathology, Nepal Medcity Hospital, Lalitpur, Nepal



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ABSTRACT

Cervical cancer continues to be the leading cancer among women in Nepal with most cases being squamous cell carcinoma. Signet ring cell carcinoma is defined as mucinous adenocarcinoma with over 50% of cells showing signet ring cell morphology. Adenocarcinomas of the uterine cervix have increased in both relative and absolute frequency, they represent only 10 to 25 % of cervical carcinomas; with HPV associated endocervical as the most frequent histological type, followed by mucinous adenocarcinoma. A middle aged lady presented with history of intermenstrual bleeding along with abdominal pain. She was known case of HPV DNA 16 positive (detected 2 years back). Cervical biopsy revealed presence of signet ring cells arranged in diffuse sheets. Individual tumor cells (>50%) were signet ring type of cells with hyperchromatic peripherally pushed nuclei and abundant vacuolated cytoplasm. Glands, tubule formation as well as sheets of tumor cells, some revealing marked atypia and bizarre nuclei were also seen. Villo-glandular projection of endocervical epithelium revealing dysplastic changes were also noted. The diagnosis of HPV associated adenocarcinoma, signet ring type was given since HPV DNA 16 was also positive. IHC report showed P16, PAX8 and CK7 all with diffuse positive in atypical cells. ER was positive in atypical cells meanwhile CDX2, WT-1, CK20 and cyclinD1 were negative, compatible with the diagnosis of adenocarcinoma of cervix, HPV associated. Metastatic work up done for signet ring adenocarcinoma was negative. Here, we present a rare case of HPV 16 associated primary signet ring adenocarcinoma of uterine cervix.

KEY WORDS

Adenocarcinoma, Cervix, HPV 16, Signet ring carcinoma

*Corresponding Author |
Dr. Kricha Pande
Associate Consultant Pathologist
Department of Laboratory Medicine and Pathology
Nepal Medcity, Sainbu, Bhaisepati, Lalitpur
E-mail: krichapande@gmail.com
Orchid No: 0000-0002-9303-831X

INTRODUCTION

Cervical cancer continues to be the leading cancer among women in Nepal, with an annual incidence of 2,244 new cases and 1,493 deaths.¹ Nepal has a cervical cancer incidence of 16.4 per 1,00,000 women in contrast to the WHO's desired target of 4 per 1,00,000 women, nearly four times the target to eliminate the public health issue of cervical cancer.²

Carcinoma of the uterine cervix is the most common malignancy in female genital tract and squamous cell carcinoma is the commonest of them.³ Even though adenocarcinomas of the uterine cervix have increased in both relative and absolute frequency, they represent only 10 to 25 % of cervical carcinomas; with HPV associated endocervical as the most frequent histological type, followed by mucinous adenocarcinoma.^{4, 5}

As with squamous cell carcinomas, adenocarcinoma type also generally tend to arise from the squamocolumnar junction. They may arise from a precursor lesion, cervical adenocarcinoma in situ, and are almost always associated with HPV.^{18,6}

Mucinous type adenocarcinoma of the uterine cervix includes endocervical, intestinal, signet ring cell, minimal deviation and villoglandular types.⁷ The uterine cervix represents an exceptional localization of signet-ring cell adenocarcinoma (SRCA).⁸ This type of cancer is considered aggressive and it is typically diagnosed at advanced stages resulting in shorter survival.⁹ HPV 18 and less frequently HPV 16 are often detectable in cervical adenocarcinomas by using in situ hybridization and/ or PCR techniques.¹⁰

Here, we present a case of primary HPV associated adenocarcinoma of uterine cervix with signet ring cell morphology.

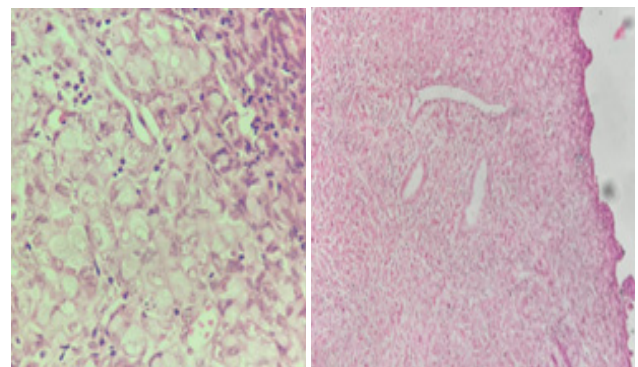
CASE REPORT

This is a case of 44 years old lady who was on regular follow up and screening programme in gynecologic department of this hospital. Pap smear was within normal limit, however PCR for HPV 16 was positive 2 years back. At present, she presented with pain on right side of abdomen, which increased on coughing and on movement. She had history of intermenstrual PV bleeding and was also a known case of Autoimmune hypothyroidism under medication. Her menstrual cycles were regular and uneventful. On examination, cervix was unhealthy and suspicious for malignancy. Pap smear was done however failed to detect any abnormality. Cervical biopsy with repeat HPV PCR was done.

Cervical Biopsy: Multiple pieces of grey white tissues were received in the Department of Pathology at Nepal Medcity Hospital. Sections examined showed multiple

fragmented pieces of ectocervical as well as endocervical tissues infiltrated by tumor cells arranged in diffuse sheets. Individual tumor cells (>50%) were signet ring type of cells with hyperchromatic peripherally pushed nuclei and abundant vacuolated cytoplasm. Glands, tubule formation as well as sheets of tumor cells, some revealing marked atypia and bizarre nuclei were also seen. Villo-glandular projection of endocervical epithelium revealing dysplastic changes were also noted. Ectocervical part was unremarkable. The diagnosis of HPV associated adenocarcinoma, signet ring type of uterine cervix. Repeat PCR for HPV DNA detected High risk HPV16. Immunohistochemical examination (IHC) report showed P16, PAX8 and CK7 all with diffuse positive in atypical cells. ER was positive in atypical cells meanwhile CDX2, WT-1, CK 20 and cyclinD1 were negative, compatible with the diagnosis of adenocarcinoma of cervix, HPV associated (Figure 2). CT scan done post cervical biopsy showed heterogeneously enhancing bulky cervix with need for MRI Pelvis for proper evaluation of cervical lesion. As a part of diagnostic workup, she was referred to Gastro-Enterology unit. Upper GI and lower GI endoscopy was done. Raised mucosal lesion with overlying erythema was noted in the sigmoid colon. Biopsy of sigmoid colon showed focal active colitis and was negative for malignancy.

Hysterectomy: She underwent radical hysterectomy with bilateral pelvic lymph node dissection. Tumor was present in left superior (anterior) 12 O'clock to right superior (anterior) quadrant 12 O'clock of the cervix. The tumor with morphology similar to cervical biopsy showed involvement limited to the upper two of vaginal without parametrial invasion. Size of invasive carcinoma of 4.5 cm in maximum diameter. The histopathology report reconfirmed the diagnosis adenocarcinoma of uterine cervix, HPV associated, signet ring type. FIGO stage III C1 and pTNM stage pT2a2 N1a was given. All the surgical margins were negative for invasive carcinoma. One (1) out of fifteen (15) lymph nodes show tumor infiltration. Patient had uneventful post operative period and is on regular follow up since then.



A

B

Fig. 1 A. Histopathological analysis of cervical biopsy (H & E 40X) and B. hysterectomy specimen (H & E 40X) revealing presence of signet ring cells diffusely infiltrating into the cervical stroma.

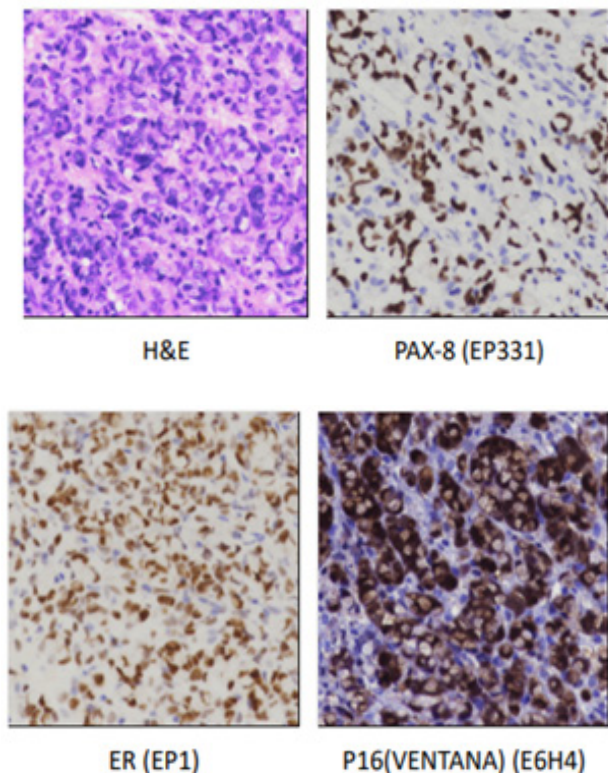


Fig. 2 Immunohistochemical examination showed signet ring cells (H & E: 40X) positive for PAX-8 (20X), ER (20X) and P16 (40X)

DISCUSSION

Primary adenocarcinoma of the cervix is usually endocervical or endometrioid in histology, with intestinal, villoglandular, and minimal deviation subtypes less common.¹¹ Primary pure or almost pure signet ring adenocarcinoma (SRCA) of the uterine cervix are extremely rare while more often they may be seen admixed with other more conventional subtypes of adenocarcinoma and adenosquamous carcinoma.⁸ Signet ring cells exhibit round shapes with eccentric nuclei and have abundant mucus granules in the cytoplasm. Signet ring cell carcinoma are mucinous adenocarcinoma with over 50% of cells showing signet ring cell morphology. This type of cancer is considered aggressive and it is typically diagnosed at advanced stages resulting in shorter survival.¹²⁻¹⁴

Our case presented with intermenstrual bleeding and lower abdominal bleeding. Presenting symptoms on reported cases are similar to more usual cervical cancers, including abnormal bleeding, including post-coital bleeding. Detection rate of signet ring carcinoma in Pap smear is very low as seen in our case. Literature also suggest that rarely abnormal

glandular cells may be seen on pap smears¹⁵. Even when signet ring cells on a pap smear may also reflect metastatic carcinoma to cervix, or even gastrointestinal carcinoma with ascites without cervical involvement^{16, 17}. Our case was HPV positive two years earlier than the cervical lesion was detected clinically, this very fact depicts the importance of following up with HPV DNA HR positive patients. There is the need to rule out metastatic disease to the cervix, and note that identification of human papilloma virus in the tumor supports a cervical primary.¹¹

To date, only the HPV18 genome has been identified in cases of primary signet-ring cell cervical carcinoma in four publications. Kawai reported the first case of primary signet-ring cell carcinoma of the cervix containing the full HPV 16 genome.¹⁸ This cervical carcinoma also shows HPV16 positivity which is rare phenomena for signet ring uterine adenocarcinoma, emphasizing the importance of routine and regular screening as well as follow up of the HPV positive cases.

Positivity to p16 protein and molecular analysis using PCR revealed that this rare entity is related to HPV infection in the same way as other subtypes of primary adenocarcinoma.¹⁹

The expression with immunohistochemical and molecular techniques for the human papilloma virus can help confirm the gynecological primary, but its diagnosis is one of exclusion, since its morphological pattern is related to other primaries, mainly digestive.²⁰

Our case also had thorough metastatic work-up to rule out the metastatic deposit of signet ring carcinoma of cervix. Endoscopic and colonoscopic evaluation with histopathological examination revealed no abnormalities. There is always the need to rule out metastatic disease to the cervix, and to note that identification of human papilloma virus in the tumor supports a cervical primary.¹¹ All the literature also emphasized on the importance of distinguishing primary signet ring cell carcinoma of cervix from metastatic lesion.²¹

CONCLUSION

This case depicts the importance of regular follow up of a patient who is HPV high risk positive. Our case had a history of HPV HR detection but was asymptomatic for 2 years. Screening measure like Pap smear was not able to detect signet ring carcinoma. IHC proven biopsy was able to make the correct diagnosis. Hence, we emphasize on regular follow up of all the patients with positive HPV so as to detect any clinical lesion as early as possible.

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