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Olivia Nicolais
Thomas Jefferson University

Mackenzie Cummings
Thomas Jefferson University

Tommy R. Buchanan
Thomas Jefferson University

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Case Report: Low-Risk HPV associated Verruco-Papillary squamous cell carcinoma of the cervix

Olivia Nicolais [a,*], Mackenzie Cummings [a], Tommy R Buchanan [b]

[a] Department of Obstetrics and Gynecology, Abington Hospital-Jefferson Health, 1200 Old York Road, Price 109, Abington, PA 19001, United States
[b] Hanjani Institute for Gynecologic Oncology, Asplundh Cancer Pavilion, Abington Hospital-Jefferson Health, 3941 Commerce Avenue, Willow Grove, PA 19090, United States

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1. Background

As of 2018, cervical cancer is the fourth most prevalent and fourth highest cause of cancer mortality for females (Bray et al., 2018). In the United States and other developed countries, the incidence and mortality of cervical cancer has declined significantly by screening with pap smears and human papilloma virus (HPV) vaccination (McGraw and Ferrante, 2014). As HPV is one of the most common causes of sexually transmitted infections worldwide, the study of its pathophysiology and understanding of disease progression remains paramount in attempting a continual increase in detection of cancer progression and decrease in cervical cancer morbidity and mortality (Backes et al., 2009).

While high-risk HPV is typically associated with progression to cancer, there are several factors that influence if HPV will progress to cancer and exceptions have been reported in the literature where low-risk HPV subtypes have been associated with malignant transformation to squamous cell carcinoma in anogenital cancers (Backes et al., 2009). While most cases of low-risk HPV associated squamous cell carcinomas are reported in the external anogenital region, rare cases have been reported in the cervix (Masuda et al., 2018; Liu et al., 2018; Guimera et al., 2013). Here, we report another case of cervical cancer associated with low-risk HPV 6/11 and the challenges associated with diagnosis and treatment.

2. Case report

The patient is a 31 year old female with a history of smoking and ASCUS pap three years prior presenting to clinic with a suspicious appearing lesion of the cervix. She had no history of HPV vaccination. She reported irregular vaginal bleeding. On specialist exam, the patient was noted to have a friable cervix with a 2 cm lesion protruding from the cervical os with no appreciable parametrial disease or sidewall involvement. Pap smear collected at the time of presentation was HSIL. The patient had a biopsy in the office followed by a LEEP procedure in the OR. Pathology for both samples resulted as verruco-papillary neoplasm favoring well differentiated squamous carcinoma. In the pathology report, it was noted that this lesion was a rare example of HPV6/11-associated verruciform lesion which is analogous to a high grade squamous intraepithelial lesion (CIN II-III) of the cervix with small foci suggesting early stromal invasion within the papillae. While the in-situ hybridization results were negative for high-risk HPV, the tumor was still morphologically high-grade, mitotically active and noted to likely have association with p53 mutation(s). Overall, the classification favored a form of squamous carcinoma. The pathology was positive for Ki-67 (80% elevated) and negative for p-16, p53-biphasic, overexpressed and null phenotypes. (See Fig. 1 for slide photographs) MRI imaging was completed showing disease confined to the cervix with a greatest dimension of 3.6 cm and PET scan showed no evidence of metastatic disease. The patient underwent a radical hysterectomy, bilateral salpingectomy with sentinel lymph node biopsies as she did not

* Corresponding author at: 1200 Old York Road, Abington PA, 19101.
E-mail address: Olivia.nicolais@jefferson.edu (O. Nicolais).

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desire future childbearing. During the surgery, no pelvic disease was noted and sentinel lymph nodes were removed bilaterally with an additional enlarged non-sentinel lymph node. Pathology from surgery noted no other disease location. The cervix contained the verrucopapillary squamous cell carcinoma 3.8 cm in size with focal stromal invasion into the endocervical glands measuring 2.5 mm in depth and 3.4 mm in horizontal extent. No LVSI was identified. Other findings included adenomyosis and uterine serosa with focal endometriosis. The tumor was staged as 1B2 carcinoma of the cervix. The patient did not have adjuvant treatment after the surgical procedure. She had no current or past medical history concerning for immunosuppression, and therefore did not have an extensive workup. The patient was seen 5 months after her TAH, BS and SLN biopsy and had no clinical evidence of disease. Pap smear collected at that time was NILM, HPV negative. The plan at that time was for the patient to return for exams every 3 months for two years followed by every 6 months for 5 years after diagnosis with imaging as necessary based on her clinical picture. Currently the plan is to do pap smears every 6 months given the lack of guidelines for this patient's particular scenario. The patient is now 3 years post-surgery and is currently without evidence of disease.

3. Discussion

This case represents one that provides further evidence of the difficulties of diagnosis and treatment decision in regards to a very rare case of cervical carcinoma associated with only low-risk HPV subtypes. The typical pathophysiology in low-risk HPV progression to carcinoma is not well understood. Typically, high-risk HPV employs host factors to regulate viral transcription and regulation. This process begins with transcription of viral E6 and E7 genes whose products bind and inactivate tumor suppressor proteins, cell cyclins and cyclin-dependent kinases (Burd, 2003). The function of E6 is to bind p53, which is usually wild type in cervical cancers, and cause degradation of the protein leading to unregulated cell cycles. It is thought that low-risk HPV E6 proteins do not bind p53 at detectable levels and in vitro, do not affect p53 stability. The HPV E7 gene products bind to hyperphosphorylated retinoblastoma proteins (Rb/pRB). E7 disrupts the complex of pRB and E2F1 which serves as a transcription factor. Without pRB, E2F1 allows for production of products required for S phase cell cycle initiation (Burd, 2003). In normal cells p16 suppresses the phosphorylation of Rb which will in turn ceases cellular proliferation. However, when high-

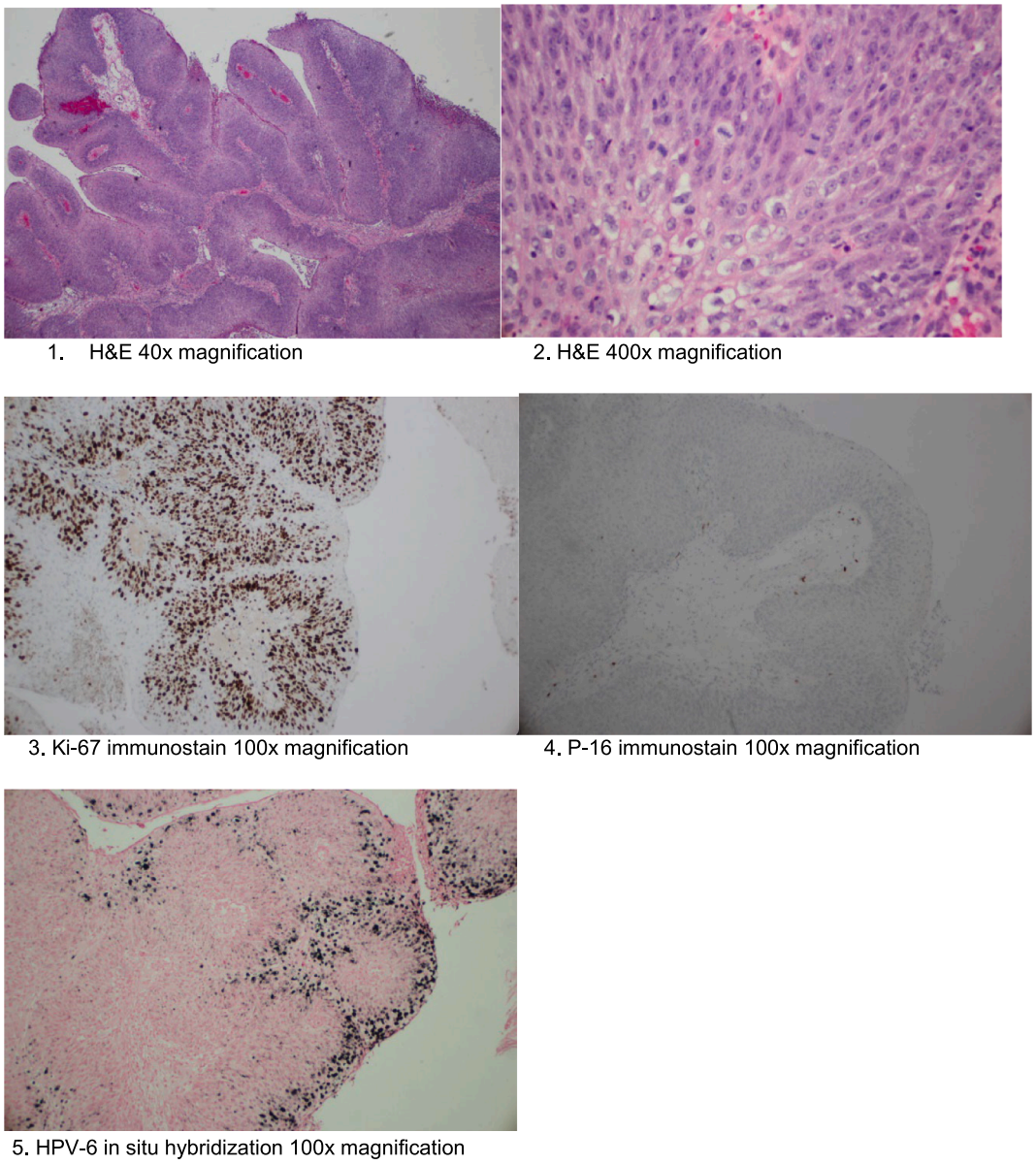

Fig. 1.

risk HPV inactivation of Rb by E7 occurs, this causes continued proliferation of p16. Therefore, high levels of p16 usually indicate high expression of E7 and can be used as a good indicator for HSIL or invasive cancer (Burd, 2003). It has been shown that high-risk HPV-16 is associated with a conserved Asp21 residue that has been identified as causing increased pRB affinity whereas the low-risk HPV6 E7 has a Glycine (Gly) residue at that same position which decreases pRB binding affinity and transformation capacity leading to decreased p-16 expression (Guimera et al., 2013). As seen in our case the tumor was negative for p-16 and p53-biphasic, overexpressed and null phenotypes indicating an alternate carcinomatous pathway than that typically associated with high-risk HPV. This finding is consistent with other case reports of low-risk HPV associated cervical cancers where had minimal to patchy uptake of p16 and p53 expression varies from weak to strong expression suggesting a possible p53 mutation component which differs from typical high-risk HPV associated cervical carcinomas (Evans et al., 2021; Masuda et al., 2018; Liu et al., 2018; Guimera et al., 2013). Ki-67 is also noted in pathology in regards to differentiating papillary immature metaplasia (PIM), which may have a similar presentation and association with low-risk HPV subtypes, from carcinoma. A study by Trivijitsilp et al suggests that PIM shows marked reduction in Ki-67 staining in superficial cell layers while the papillary carcinomas showed moderate to diffuse staining. Our case is consistent with this finding in that the tumor showed high 80% staining for Ki-67 (Trivijitsilp et al., 1998 Jun). Further studies are needed to better elucidate the pathways associated with low-risk HPV associated squamous carcinomas of the cervix but this proves difficult given the rarity of disease.

Due to the lack of typical markers for high-risk HPV associated lesions, which are more likely to progress to cancer, the diagnosis of carcinoma becomes more difficult in these cases. In our case, the cellular description was noted to be morphologically high-grade and mitotically active. As noted in the Liu et al case report including three HPV-6 cervical HSIL/SCC cases, the HPV-6 associated HSIL/carcinomas showed nuclear overlap, variable nuclear density and anisokaryosis compared to the LSIL-associated uniform nuclear morphology, nuclear membranes and uniform nuclear spacing (Liu et al., 2018). Cervical verrucopapillary squamous or transitional cell carcinomas are rare but noted to be associated with local spread and late recurrence which is why distinguishing these lesions from non-invasive, papillary immature metaplasia, squamous papillomas and condyloma acuminatum is imperative (Guimera et al., 2013). These cases show the importance of thorough pathologic evaluation as these findings separate an assumed low-risk HPV associated LSIL from a potential SCC. Additionally, thorough pathologic evaluation in our case of the LEEP specimen found early stromal invasion within the papillae, which further supports a diagnosis beyond a low-risk HPV associated condyloma. Findings such as these should absolutely warrant further investigation and more definitive surgical treatment and resection.

In addition to difficulty with diagnosis, determining mode of treatment also proves difficult in these cases given limited data. At this time, treatment recommendations fall under the larger umbrella of cervical cancer without sub-categorization of pathologic HPV subtype. Our patient was diagnosed with stage IB2 cervical carcinoma given 2.5 mm invasion and carcinoma confined to the cervix measuring 3.6 cm in maximum diameter. Due to this patient's age of 31, discussion of fertility preservation was paramount in this case and would determine the mode of treatment. Upon discussion with this patient, she did not desire any future fertility and therefore underwent a radical hysterectomy. Given that her pathology resulted with negative sentinel lymph nodes, negative margins, no disease in the parametrium and she did not meet Sedlis criteria, she was chosen for observation surveillance. Had the patient presented with more extensive invasion such as LVSI, chemotherapy or radiation would have been indicated. Had the patient desired fertility sparing treatment, a radical trachelectomy with pelvic lymphadenectomy with or without *para*-aortic lymphadenectomy with consideration for SLN mapping would have been the recommended surgical approach. At this time, our case report and others that discuss treatment for low-risk associated HPV cervical squamous carcinomas (Masuda et al., 2018; Evans et al., 2021) are not noted as a separate subgroup for treatment algorithms in regards to cervical cancer. These cases do however raise the question of whether low-risk HPV associated cervical carcinomas may warrant further study for possible distinct treatment algorithms given the apparent distinct pathophysiologic process of disease compared to the more common high-risk HPV associated cervical carcinomas.

Informed consent statement:

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors' contributions:

Olivia Nicolais, MD: Resident physician involved in case, reviewed and obtained data from the EMR, provided literature review, wrote manuscript.

Mackenzie Cummings, MD: Resident physician involved in case, reviewed data from the EMR, assisted in literature review, edited manuscript.

Tommy R Buchanan, MD: Attending physician involved in case, assisted in literature review, overseeing physician in editing the manuscript.

CRediT authorship contribution statement

Olivia Nicolais: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Mackenzie Cummings:** Writing – review & editing, Conceptualization. **Tommy R Buchanan:** Supervision, Investigation, Conceptualization.

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