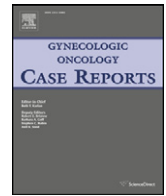




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Case report

Papillary squamous cell carcinoma of the cervix: Two cases and a review of the literature☆

Lauren B. Turker, MD^{a,b}, Gregory M. Gressel, MD^{a,b}, Maria Abadi, MD^c, Marina Frimer, MD^{a,b,*}^a Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Jacobi Medical Center, United States^b Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Montefiore Medical Center, United States^c Department of Pathology, Albert Einstein College of Medicine, Jacobi Medical Center, United States

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ABSTRACT

Objective: Papillary squamous cell carcinoma of the cervix (PSCC) is a rare and distinct form of cervical carcinoma. Detecting stromal invasion on biopsy is difficult due to the papillary growth of the tumor. Here we present two cases that highlight the diagnostic and clinical challenges of PSCC.

Case 1: A 50-year-old woman found to have carcinoma on a routine pap-smear. The patient was diagnosed with PSCC on colposcopic biopsy and underwent a radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection. Her final pathology demonstrated PSCC with no evidence of stromal invasion. At her 3-month follow up visit, she was noted to have a tumor recurrence at the vaginal cuff, again with no stromal invasion. She is currently undergoing definitive radiation therapy with sensitizing cisplatin.

Case 2: An 82-year-old woman presented with post-menopausal bleeding and was found to have an exophytic mass. Biopsies were taken and showed PSCC with no stromal invasion identified. She underwent a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Final pathology indicated no invasion. She is currently being followed for persistent vaginal dysplasia.

Conclusion: PSCC is a rare tumor that has previously been described as less aggressive than classical squamous cell carcinoma. These two cases demonstrate the complex behavior of the disease. Case 1 highlights that PSCC may recur even when stromal invasion cannot be confirmed pathologically.

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1. Introduction

Papillary squamous cell carcinoma of the cervix (PSCC) is a rare subtype of squamous cell carcinoma of the cervix. It has been reported to represent 1.6% of all cervical cancers (Randall et al., 1986). Due to its rarity, very little is known about the clinical behavior of the disease. PSCC grows superficially in an exophytic manner similar to other papillary lesions of the cervix. However, PSCC is histologically unique and clinically more aggressive and therefore should be distinguished from verrucous and condylomatous carcinoma (Randall et al., 1986; Koenig et al., 1997). It has also been reported that PSCC may differ from traditional squamous cell carcinoma in that it has a tendency for late metastasis and recurrence (Randall et al., 1986; Koenig et al., 1997). The papillary growth and histology make it difficult to diagnose invasion on routine biopsies

(Randall et al., 1986; Koenig et al., 1997; Nagura et al., 2014; Mirhashemi et al., 2003). We present two cases of PSCC in situ.

2. Case 1

A 50-year-old Guianese, gravida 2 with no significant past medical history was referred to our clinic for evaluation of squamous cell carcinoma incidentally identified on pap smear. Her pap smear also returned positive for high risk human papilloma virus (HPV). The patient denied any abnormal bleeding, discharge or abdominal pain. Her last pap smear in 2008 was normal. On exam she was found to have a 2.5 cm cervical lesion at 3 o'clock that was "bulging" and noted to be exophytic in nature. Biopsy of the lesion was performed which showed fragments of carcinoma with a papillary pattern showing full thickness atypia and mitotic activity, representing at least carcinoma in situ without obvious stromal invasion. Based on her initial biopsy and due to the morphologic resemblance to a transitional cell neoplasm, PSCC could not be excluded, as seen in Figs. 1 and 2.

Computerized tomography (CT) scan of the chest, abdomen and pelvis was performed and showed no signs of extra-cervical disease. The patient was diagnosed with clinical FIGO stage IB1 cervical squamous cell carcinoma and subsequently underwent an exploratory

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* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Jacobi Medical Center and Montefiore Medical Center, 1400 Pelham Pkwy S, Bronx, NY 10461, United States.

E-mail address: marina.frimer@nbhn.net (M. Frimer).

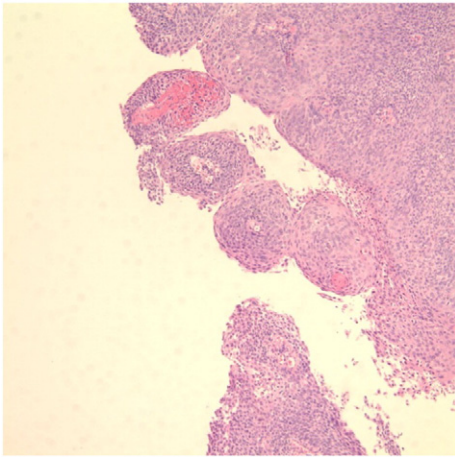


Fig. 1. Papillary squamous cell carcinoma composed of fibrovascular cores with multilayered epithelium (H&E stain, 10 \times).

laparotomy, radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection. Her final pathology results showed squamous cell carcinoma-in-situ, both conventional and papillary type confined to the cervix with no evidence of nodal disease. All margins were negative for invasive disease or high grade lesions. The cervical margin was positive at 3 to 9 o'clock for a low-grade intraepithelial lesion. No stromal invasion was identified despite thorough sampling of the cervix.

The patient was seen for 3-month follow up and was noted to have a 1 cm lesion at the vaginal cuff. A biopsy showed recurrent PSCC without stromal invasion. She is currently undergoing radiation therapy with cisplatin chemo-sensitization.

3. Case 2

An 82-year-old Ghanaian woman, gravida 4, with a history of hypertension, presented to our clinic for evaluation of post-menopausal bleeding. On exam she was found to have a 4–5 cm exophytic mass occupying and completely replacing the cervix.

Biopsies were performed showing dysplastic squamous mucosa with full-thickness cytologic atypia in a papillary configuration with abundant mitoses (Fig. 3). These biopsies showed high risk HPV expression. The base of the lesion was not identified however no definitive stromal invasion was seen on deeper sections. It was felt that this lesion might represent a superficial component of squamous cell carcinoma

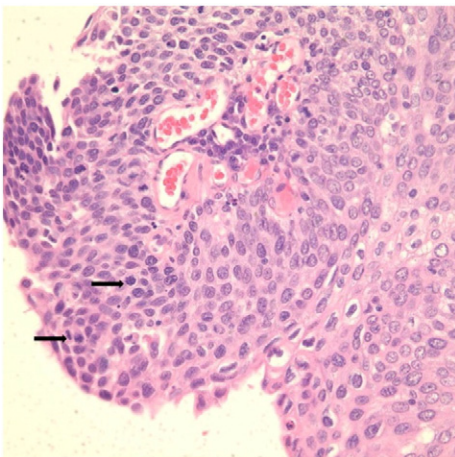


Fig. 2. The appearance of the tumor varies from squamous to squamotransitional. The mitoses are present throughout the epithelium (black arrows) (H&E stain, 40 \times).

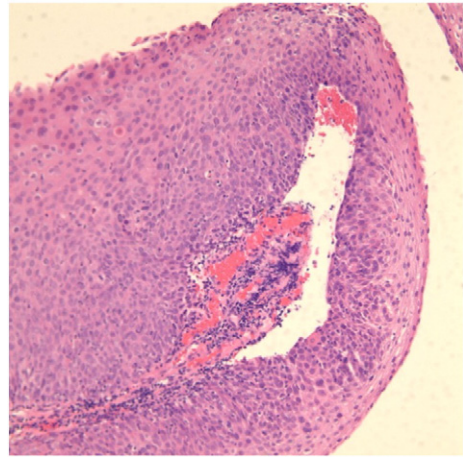


Fig. 3. In this variant of squamous cell carcinoma, the cells can exhibit eosinophilic cytoplasm and full thickness hyperchromasia. No invasion was identified in this specimen (H&E stain, 40 \times).

variant such as PSCC given the arrangement and appearance of the cells lining the fibrovascular cores (Fig. 4).

The patient underwent a CT scan that showed an exophytic mass measuring 4.2 \times 3.6 cm along the left body of the uterus. There was no evidence of extra-cervical disease. She subsequently underwent clinical staging with examination under anesthesia, sigmoidoscopy and cystoscopy and was found to have 4–5 cm mass at the apex of the vagina. The majority of the exophytic mass was excised on endocervical curettage, and the remaining cervix retracted and was flush with the vagina. There was no involvement of the urinary bladder or rectum. The pathology again returned as dysplastic squamous mucosa with full-thickness cytologic atypia in a papillary configuration with no stromal invasion. She subsequently had a positron emission tomography (PET) scan which showed focal activity in the cervix (SUV 3.9). Given that invasion could not be confirmed and that the cervix now appeared normal on examination with no concern for parametrial invasion, the decision was made to proceed with a simple total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Final pathology showed a high grade squamous intraepithelial lesion and histologic papillary features without invasive carcinoma. All surgical margins were clear of cancer and dysplasia. The patient has been followed in clinic and 6 months following hysterectomy has recurrent low-grade dysplasia at the apex of the vaginal cuff.

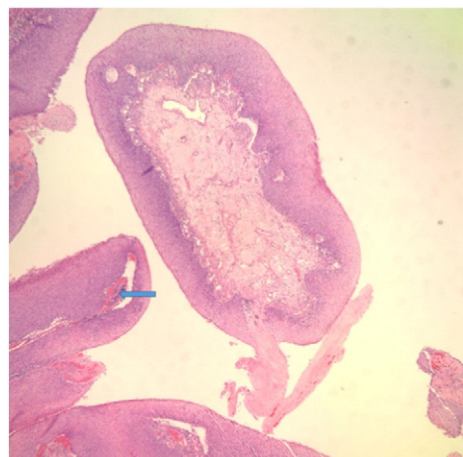


Fig. 4. PSCC showing a hyalinized fibrovascular core. The cores are usually slender, such as the one below (blue arrow) (H&E stain, 20 \times).

4. Discussion

Papillary cervical lesions were first described in 1952 by Marsh: 31 cases were reported, three of which were malignant (Marsh, 1952). In 1986, Randall et al. presented 9 cases of papillary squamous carcinoma of the cervix and defined pathologic criteria for diagnosis: full-thickness dysplastic cells in a papillary architecture with fibrovascular cores and the invasive component that is usually deep to the papillary excrescences (Randall et al., 1986). From this definition, Koenig further differentiated PSCC into three groups: predominantly squamous cell, predominantly transitional cell, and mixed. In this review of 32 patients, the majority of the patients were found to have a mixed histology (Koenig et al., 1997). In 2014, Nagura et al. evaluated 28 cases of PSCC on superficial biopsy and found that only 12 were predominantly PSCC on final diagnosis (Nagura et al., 2014).

Original data suggested that PSCC behaves clinically similar to traditional squamous cell carcinoma (Randall et al., 1986; Koenig et al., 1997). Recently, the disease has been suggested to be less aggressive than typical squamous cell carcinoma (Nagura et al., 2014; Mirhashemi et al., 2003). It is further distinguishable from typical squamous cell carcinoma in that it has a tendency for later recurrence; Koenig reported an isolated recurrence 12 years later (Koenig et al., 1997). In a retrospective study of 12 patients with PSCC, the rate of high risk HPV expression in PSCC was found to be significantly less than that of squamous cell carcinoma (50% vs. 90%) (Mirhashemi et al., 2003). Therefore, there may be a different mechanism of carcinogenesis. In that same study, the patients with HPV expression were more likely to present at an advanced stage. Further, the two patients with recurrence both had high risk HPV expression (Mirhashemi et al., 2003). More recent case reports have detected HPV expression in PSCC (Tang et al., 2013; Sawada et al., 2010; Eleuterio et al., 2009; Brinck et al., 2000). One case report notes no evidence of recurrence after 10 months (Sawada et al., 2010). The other case reports do not remark on recurrence or risk of recurrence. Our cases both have HPV expression consistent with the recent case reports. The pathologic significance of HPV expression and development of PSCC is an area that deserves further exploration. Furthermore, the HPV testing and detection rates have increased significantly in the last 10 years and may contribute to the increasing HPV association in these specific tumors.

The National Comprehensive Cancer Network (NCCN) treatment guidelines for cervical cancer do not specifically address PSCC (Koh et al., 2015). However experts suggest treatment of PSCC should follow the same treatment guidelines as squamous cell carcinoma of the cervix (Randall et al., 1986; Koenig et al., 1997; Nagura et al., 2014). PSCC grows in an exophytic fashion making the diagnosis of stromal invasion on routine biopsies difficult; invasion is only diagnosed in 50–60% of cases with superficial biopsies (Koenig et al., 1997; Nagura et al., 2014). The majority of PSCC cases are found to have invasion on final pathology (Randall et al., 1986; Koenig et al., 1997; Mirhashemi et al., 2003). PSCC is often confused with squamous cell carcinoma in situ. Invasion can appear as nests at the base of the lesion, and in some cases the actual papillae may invade. The diagnosis is even more difficult because biopsies may have superficial papillary features, but are found to be conventional squamous cell carcinoma on final pathology (Nagura et al., 2014). Our cases confirm the difficulty of diagnosing invasive cancer on initial biopsies and final definitive treatment.

Given that invasion is difficult to diagnose on biopsy, Nagura et al., performed magnetic resonance imaging to evaluate for stromal invasion. If magnetic resonance imaging showed less than 3 mm of invasion, a simple hysterectomy or cervical conization was performed. This study showed that invasion could accurately be diagnosed on MRI and reported no recurrence 49 months after hysterectomy or cervical conization (Nagura et al., 2014). This study suggests that PSCC may be amenable to treatment with less invasive procedures and that PSCC may benefit from a different work-up and treatment pathway than typical squamous cell carcinoma (Nagura et al., 2014).

Both cases showed no invasion on biopsy, consistent with previous reports (Randall et al., 1986; Koenig et al., 1997; Nagura et al., 2014). In the first case, stromal invasion was highly suspected after superficial biopsies were taken. Because of this high suspicion of invasive disease, a radical hysterectomy was performed. In the second case, multiple deep biopsies were performed before proceeding to hysterectomy. These biopsies confirmed no stromal invasion. Given low suspicion for invasion and shrinking of the cervix, an extrafascial hysterectomy was performed. Both of our patients had no stromal invasion on final pathology. Pathologic consultation was obtained in both cases with agreement of no stromal invasion. Our first patient now has recurrence of disease three months after a radical hysterectomy. To our knowledge, this is the first reported case of recurrence without any invasion diagnosed on pathology. The second patient has persistent local dysplasia. Given these findings, PSCC lesions without stromal invasion should be treated clinically as cancer according to the corresponding clinical stage. These findings emphasize the clinically challenging nature of the disease. In our second case, cone biopsy was considered; however, once the tumor was extensively biopsied, the cervix was flush with vagina and cone biopsy was considered unsafe. MRI could have been potentially used in this case to estimate invasion before undergoing her procedure.

In conclusion, PSCC is a rare variant of squamous cell carcinoma of the cervix and it is important to recognize it as a distinct clinical entity pre-operatively. Given the indeterminate nature of the disease and difficulty diagnosing stromal invasion, conization or imaging with MRI should be performed to assess for invasion prior to proceeding with definitive surgery. Furthermore, a pathology consultation may be helpful in providing agreement regarding stromal invasion and further management. In our cases, pathology, radiation oncology, as well as gynecologic oncologists were instrumental in diagnosis and treatment of the patients. A multi-disciplinary approach should be considered in the treatment of patients with PSCC.

Consent

Written informed consent was obtained from the patients 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, upon request.

Conflict of interest

The authors have no personal or financial affiliations to disclose.

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