A Case of Difficult-to-Diagnose Non-invasive Papillary Squamous Cell Carcinoma of the Uterine Cervix infected with human papilloma virus 6: A Diagnostic Pitfall

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Abstract

We encountered a case in which a recurrent condyloma-like papillary tumor was repeatedly treated as condyloma. Therefore, the patient was re-diagnosed and treated for non-invasive cervical papillary squamous cancer (PSCC) with HPV6 infection. To the best of our knowledge, this is the first report of HPV6 infection in PSCC.

Introduction

Papillary squamous cell carcinoma (PSCC) of the uterine cervix is an extremely rare histological type of cervical cancer, which accounts for approximately 1.6% of all cervical cancers.[1] PSCC cannot be easily diagnosed by colposcopy, and it is difficult to determine the degree of invasion.[1] We diagnosed a patient with condyloma and treated her with condyloma several times, but the patient relapsed repeatedly. She was re-diagnosed as having PSCC and underwent surgery. We present this case report and discuss the diagnosis of PSCC and its pitfalls. In addition, we encountered PSCC infected with HPV6, which has not been previously reported.

Case Presentation

A 47-year-old woman with 1 pregnancy 1 parity and no relevant medical history, family history, or menstruation history presented to our hospital. The patient was followed up from CIN 1 to 2 at a previous hospital for 8 years. The high-risk HPV test was negative twice. Subsequently, a papillary mass was found in the cervix, and histological examination of the cervix suggested CIN 3 or condyloma. Conization was performed for diagnosis at another hospital. The diagnosis was cervical condyloma with a positive margin.

Subsequently, the patient returned to the previous hospital and was followed up. However, 3 months later, there was recurrence of papillary tumor in the cervix; a biopsy was performed, which led to the diagnosis of

condyloma. Cervical laser ablation was performed to treat the tumor. Two months later, the cervical tumor relapsed. Although laser vaporization was performed, the tumor relapsed again after 1 month. Cryotherapy was performed to treat the relapsed tumor, but the cervical tumor relapsed. Since the tumor recurred repeatedly in a short time, pathohistological examination was performed by a pathologist at another hospital, and the possibility of PSCC was indicated; the patient was then referred to our hospital for examination.

Colposcopy revealed a condyloma-like papillary tumor approximately 1.5 cm in diameter (Figure 1a). No abnormalities were observed in other internal examination findings. Transvaginal ultrasonography revealed no abnormal findings in the uterus or ovaries. The results of a cervical biopsy under colposcopy were atypical epithelium, which was difficult to diagnose by biopsy alone. There were no apparent abnormalities in the MRI findings (Figure 1b), CT findings, or tumor markers. Cervical conization was performed to confirm the diagnosis (Figure 1c), and the patient was diagnosed with non-invasive PSCC (Figure 2a, b). Immunohistochemistry analysis showed that p 16 was strongly positive in surgical samples (Figure 2c). A cervical test for high-risk HPV was negative in our hospital. Laparoscopic total hysterectomy and bilateral salpingo-oophorectomy were performed. The patient was discharged with a good postoperative course and was followed up as an outpatient. After surgery for PSCC, a cervical specimen was removed and tested for HPV-DNA, which revealed HPV type 6.

Discussion

We encountered a case in which a condyloma-like papillary tumor was repeatedly treated as condyloma; however, there was repeated recurrence. Therefore, the patient was re-diagnosed and treated for non-invasive cervical cancer with HPV6 infection. In 1986, Randall reported nine cases of PSCC for the first time worldwide. The characteristic pathological finding of PSCC is full-thickness dysplasia cells in a papillary architecture with fibrovascular cores and an invasive component that is usually deep to the papillary excrescences.[2] Colposcopy findings of PSCC are characterized by the development of a condyloma-like mass with exophytic growth.[1] However, they clearly distinguished PSCC from squamous papilloma, condyloma, and verrucous carcinoma.[2] Compared to conventional SCC, PSCC is characterized by slow progression of lesions. In addition, the possibility that PSCC is different from traditional SCC, in terms of the high frequency of late metastasis and recurrence, is also indicated.[3] For instance, Randall reported that two cases of PSCC recurred over more than 7 years (87 months and 106 months) after resection, and Koenig also reported vaginal recurrence of PSCC 12 years after the initial diagnosis.[2,3] Because PSCC is a rare histological type, the treatment strategy is the same as that for conventional SCC.[1,3]

In this case, treatment for condyloma was performed several times for non-invasive PSCC. However, despite inadequate treatment for non-invasive PSCC, the tumor did not invade or spread, indicating slow progression of PSCC, as previously reported.[1]It is also known that PSCC is difficult to be diagnosed preoperatively. Nagura et al. reported 28 cases of PSCC diagnosed by colposcopic biopsy, of which 12 (43%) were true PSCC and the other cases were non-keratinized or microinvasive SCC.[1] They also reported that PSCC is difficult to be diagnosed via biopsy specimens because of the degree of stromal invasion. If MRI shows stromal invasion of [?] 3 mm, radical hysterectomy or radical trachelectomy is considered. It has been reported that conization or simple hysterectomy is considered if stromal invasion of [?] 3 mm is suspected on MRI.[1]

It is also necessary to pay attention to the difficulty in diagnosis and pitfalls, and it is necessary to consider PSCC when an intractable condyloma-like mass is observed. Additionally, it is necessary to consider a re-diagnosis of the pathology if PSCC is suspected. It has been reported that the positive rate of high-risk HPV in PSCC is lower than that in cases of conventional SCC (50% vs. $> 95\%$). High-risk HPV positivity in PSCC is often associated with type 16.[4,5] Immunochemistry data from previous reports showed that the expression of Ki 67, p 63, and p 16 is higher in PSCC than in condyloma.[6,7] A strong positive result for p 16 was also observed in our case. We performed high-risk HPV screening tests several times before surgery, but they were negative; HPV6 was identified by HPV DNA genotyping of tumor samples after surgery. Sixteen HPV infections were specifically detected in cryosurgery specimens using the PapiPlexTM method. To the best of our knowledge, this is the first report of HPV6 infection in PSCC. The possibility of HPV6 infection

in a high-risk HPV-negative case in a previous report has been indicated. Although HPV6 is not a high-risk HPV, a report showed that HPV6 infection was observed in CIN 2/3, [8] and a report of laryngeal cancer reported integration of HPV6 causing malignant transformation.[9] It is considered that HPV6 infection can be a cause of non-invasive PSCC based on the above report and the slow progress in this case.

From the above, it is possible that the mechanisms of generation and progress of PSCC and conventional SCC are different. However, further investigation is necessary in the future.

Author Contributions:

KS, MH, MI prepared the manuscript and figures

, and the data were analyzed and interpreted by KS, FI, AT, YM, and TO; MT, TI, MMU, and TT reviewed the manuscript; and KS, MM, and YO revised the manuscript for important intellectual content. All authors have read and approved the final version of this manuscript.

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Ethical Approval

The study design was approved by the ethics committee of the University of Tokyo.

Disclosure

We have no conflicts of interest to declare regarding this case.

Patient consent

The patient provided written informed consent for the publication of any associated data and accompanying images.

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Figure Legends

Figure 1

(a) Colposcopic findings. A papillary mass approximately 1.5 cm in diameter

(b) MRI T2-weighted sagittal images. There is no obvious cervical mass

(c) Cervical conization specimen also showed a papillary mass in the cervix

Figure 2

(a) (b) Pathologic images of cervical conization specimens (HE staining). Full-thickness dysplasia cells were observed in a papillary architecture with fibrovascular cores. No invasion was observed in this specimen. (a) weak magnification (b) strong magnification

(c) Immunohistochemistry of cervical conization specimens: p 16 was strongly positive

Figure 1

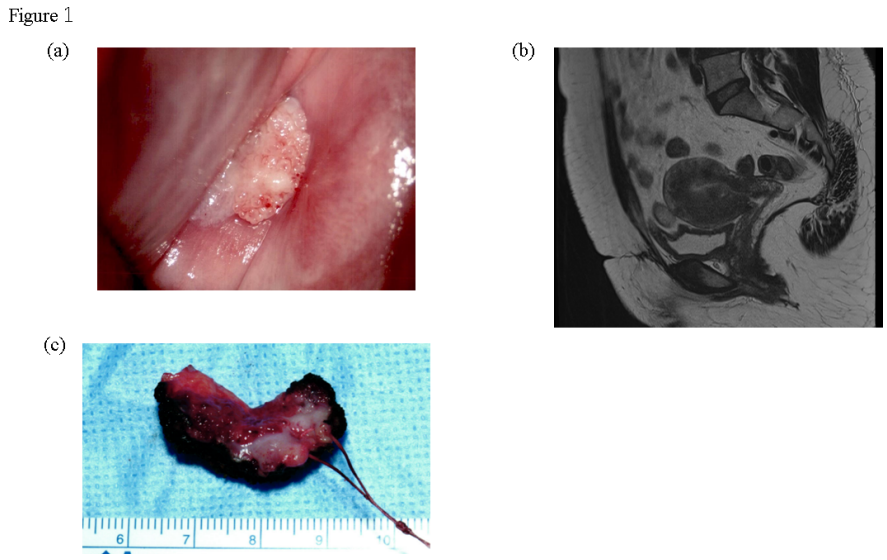

Figure2