Cytology of Uterine Cervical Verrucous Carcinoma

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Verrucous carcinoma is a rare variant of well-differentiated squamous cell carcinoma, and frequently arises in the vulva as well as in the nasopharynx and larynx, but rarely in the uterine cervix [1]. It is known to be radioresistant and recur locally, but distant metastasis is rare [2]. Diagnosis is notoriously difficult, because biopsied material either is inadequate or may exhibit epithelial maturation and a deceptive lack of cytologic atypia.

Human papillomavirus (HPV) strains, typically type 6 and its variants, have been reported to be associated with verrucous carcinoma; however, HPV has not been detected in many cases [2]. We present a case of uterine cervical verrucous carcinoma involving the cervix in which the Pap smear and HPV infection facilitated the diagnosis, and discuss the difficulties in reaching a diagnosis on biopsy along with occasional histopathologic misinterpretation that often lead to further delays in diagnosis and treatment.

A 70-year-old woman, gravida 2, para 2, complained of an abnormal vaginal discharge. Although the previous Pap cervical smear at a regional clinic had been abnormal a few years previously, she had not sought further examination. On pelvic examination, the cervix had slight erosion and the uterus was atrophic. The adnexa were normal and no lymphadenopathy was noted. At our hospital, a Pap smear was performed and diagnosed as Class IIIb (high-grade squamous intraepithelial lesion according to the Bethesda III system). Colposcopy showed persistent acetic white changes and prominent vascularity.

Umbilicated mosaic patterns with punctuation in the middle of the tiles suggested cervical intraepithelial neoplasia grade III (CIN III). Cervical punch biopsy was performed and diagnosed as moderate dysplasia. Because of the colposcopy findings and continuing abnormal cytology of the cervix, conization was recommended and performed with informed consent.

Conization pathology demonstrated a hyperplastic cervical mucosa composed of well-differentiated squamous epithelium forming papillary structures lacking central fibrovascular cores. Focal cytoplasmic vacuolization was widely presented superficially. Koilocytosis and gland involvement were found, and a well-demarcated deep margin was notable for a broad, pushing edge. Occasional mitotic figures were found in the basal layers. There was no stromal invasion. Histologic examination diagnosed verrucous carcinoma *in situ* (Figure). Conization pathology suggested a residual tumor on the stump. Hence, extended hysterectomy with pelvic node sampling was performed following conization. Microscopic examination did not show any residual tumor and there was no nodal metastasis.

A cervical swab was tested for HPV DNA using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method prior to hysterectomy. There was, however, no HPV detected. Following the histologic diagnosis of the verrucous carcinoma lesion, unstained paraffin sections were stained by immunohistochemistry and there was no HPV antigen detected in the present case.

Postoperatively, the patient had been doing well, without evidence of tumor recurrence at the 10-month postsurgical follow-up visit.

Verrucous carcinoma of the uterine cervix is a very rare, specific, histologic type, and its slow growth could cause a delay in diagnosis. Therefore, close communication among the gynecologist, cytologist and pathologist is required. Colposcopy typically does not provide sufficient diagnostic information during the incipient stage of the disease, because superficial tissue biopsy cannot include sufficient amounts of verrucous carcinoma and the cytologic criteria of malignancy may typically be absent.

These histopathologic misinterpretations often lead to further delays in diagnosis and treatment. Pantanowitz et al reviewed 26 cases of uterine cervical verrucous carcinoma and reported that 23% (six of 26 cases) of

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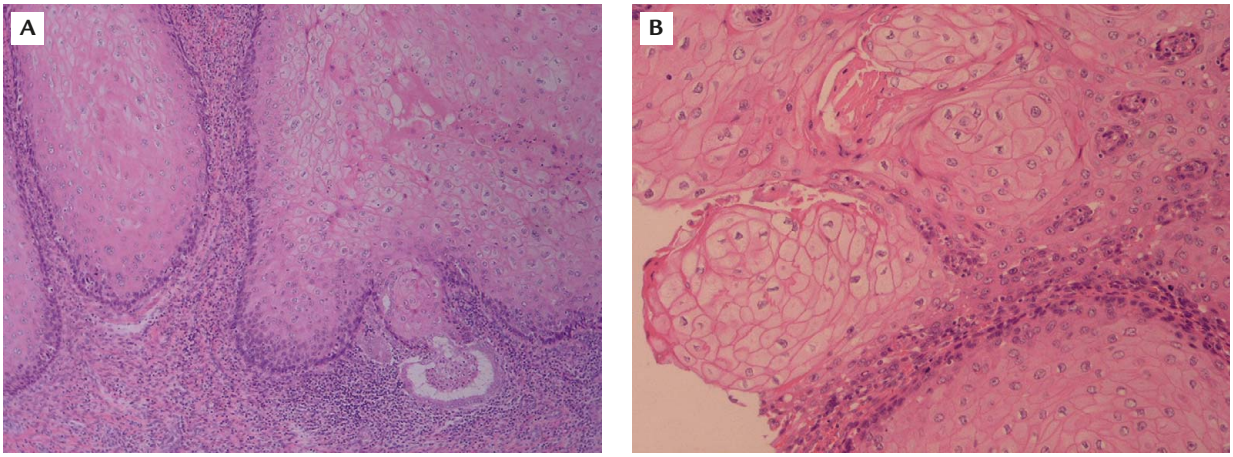

Figure. Histologic section of the cervix. (A) The tumor is characterized by large bulbous masses of squamous epithelium invading in a "pushing" fashion (original magnification ×100). (B) Focal cytoplasmic vacuolization was widely presented superficially. Koilocytosis was found and the neoplastic squamous cells have almost no nuclear atypia (original magnification ×200).

Table. Human papillomavirus (HPV) status of reported cervical verrucous carcinoma cases. HPV has not been detected in many verrucous carcinomas, including the present case

Author	Method	Result
Maeyama et al [6]	Immunohistology	(−)
de Jesus et al [7]	Immunohistology	(−)
de Jesus et al [7]	*In situ* hybridization	(−)
Chen et al [8]	PCR	(−)
Matsumoto et al [1]	PCR	(−)
Zbroch et al [9]	PCR	HPV type 16
Pantanowitz et al [2]	PCR	(−)
Peng et al [10]	Not mentioned in detail	HPV types 11 and 53
Present case	Immunohistology	(−)
Present case	PCR-RFLP	(−)

(−) = negative; PCR = polymerase chain reaction; PCR-RFLP = polymerase chain reaction–restriction fragment length polymorphism.

these showed a negative cervical smear [2]. Hando et al also reported that the cytology of a verrucous cervical carcinoma had been negative for 4 years and there was a delay in diagnosis [3]. This high false-negative rate on cytology might be brought about by the high degree of orderly maturation and minimal or absent nuclear atypia. However, the cytologic specimen obtained from verrucous carcinoma could be diagnostically helpful in many other cases as well as the present case.

A strong relation between uterine cervical dysplasia or cancer and HPV infection has been firmly established. It is indicated that HPV types 16 and 18 are associated with uterine cervical squamous cell carcinoma (SCC), whereas types 6, 11 and 16 are associated with warty (condylomatous) carcinoma and condyloma acuminatum [1,4]. The particular HPV strains, typically type 6 and its variants, have been identified within verrucous carcinoma of the vagina [5]. However, HPV has not been detected in many verrucous carcinomas, including the present case. Including our case, HPV was not detected using immunohistochemistry, PCR or PCR-RFLP in 75% of reported cases (Table).

Robertson et al suggested that the detection of HPV in verrucous genital lesions excludes the diagnosis of verrucous carcinoma [11]. They questioned the need to regard verrucous carcinoma as a variant of SCC, because this lesion histologically and clinically resembles a giant condyloma. Maeyama et al could not detect HPV antigen by immunohistochemistry but found intranuclear virus-like particles in koilocytotic cells in a case of cervical verrucous carcinoma [6].

Although the present case failed to demonstrate HPV infection, the possibility that HPV is the etiology of verrucous carcinoma could not be excluded. Further investigation of the possible role of HPV in uterine cervical verrucous carcinoma is needed by accumulating further cases and identifying distinct cytologic findings to prevent delays in diagnosis and treatment.

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