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Case Report

Coexistence of adenoid cystic carcinoma and squamous cell carcinoma of the uterine cervix with HPV 16 infection: clinical course of delayed adjuvant treatment

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Abstract: Adenoid cystic carcinoma (ACC) is a rare variant of cervical carcinoma and has an aggressive clinical behavior, and there have been few reports of co-existing ACC and squamous cell carcinoma (SCC) of the uterine cervix. A 76-year-old postmenopausal woman presented with vaginal bleeding. The cervical cytology and polypectomy results were SCC, and magnetic resonance imaging (MRI) of pelvis revealed a 2.3 × 1.8 cm sized lobulated mass at the cervix. Microscopically, the tumor showed infiltrative nests of squamoid cells and a cribriform pattern of basaloid cells. Immunohistochemical studies showed that squamous cells were positive for p63 and that basaloid cells were mainly positive for CD117 and S-100 protein. Both components were strongly positive for p16 immunostaining. The tumor was diagnosed as invasive SCC with concurrent ACC. The disease relapsed after a follow-up of 14 months with no adjuvant therapy. Subsequently, she received concurrent chemoradiotherapy (CCRT) and then combined chemotherapy with paclitaxel, cisplatin, and bevacizumab; finally, imaging revealed no evidence of residual cancer.

Keywords: Adenoid cystic carcinoma, squamous cell carcinoma, human papillomavirus

Introduction

Adenoid cystic carcinoma (ACC) of the uterine cervix is a rare and aggressive malignancy. It mostly occurs in postmenopausal women and has an aggressive clinical course. Also, ACC generally has a high propensity for local recurrence and distant metastasis [1]. Thus, this disease needs to be differentiated from the other less aggressive cervical carcinomas with similar histologic appearances. Immunohistochemistry is a useful tool for differential diagnosis of these similar conditions. Moreover, synchronous occurrence of ACC and SCC of the uterine cervix was reported in fewer than 30 cases in the English literature to date (**Table 1**). The association between HPV infection and SCC, along with adenocarcinoma in the cervix has been well documented, but the relationship between HPV and ACC of the cervix has been not well defined. We herein present a rapidly progressive case of synchronous ACC and SCC of the uterine cervix with HPV 16 infection and discuss pathologic, immunohistochemical, and therapeutic features of the disease, as well as the clinical course of delayed treatment.

Case presentation

A 76-year-old postmenopausal woman (gravida 7, para 3) presented with vaginal bleeding for 2 months. She had no history of any other gynecologic problems. Speculum examination showed a raised polypoid mass located on the posterior lip of the cervix. Cervical cytology and polypectomy results were SCC. Sections showed papillary growths covered by neoplastic squamous cells. They were composed of undifferentiated cells with small, monotonous hyperchromatic nuclei and small amount of cytoplasm, and differentiated cells with large pleomorphic nuclei and keratinized cytoplasm.

Table 1. Summary of cases of synchronous adenoid cystic carcinoma and squamous cell carcinoma of the uterine cervix

Case	Age	Presenting symptom	HPV status	Clinical stage	Primary treatment	Adjuvant therapy	Immuno-profile (ACC component)	Recurrence/ metastasis	Survival	Reference
1	68	NA	16(+)	NA	NA	NA	NA	NA	NA	4*
2	55	NA	16(+)	NA	NA	NA	NA	NA	NA	4*
3	36	NA	Negative	NA	NA	NA	NA	NA	NA	4*
4	36	NA	Negative	NA	Surgery	NA	NA	NA	NA	4*
5	NA	NA	16(+)	NA	NA	NA	NA	NA	NA	4*
6	24	AUB	NA	IB	Surgery	NA	NA	NA	NA	4*
7	NA	NA	NA	NA	NA	NA	NA	NA	NA	4*
8	73	PMB	NA	IB2	Surgery	NA	NA	Yes, 12 mo	Live with disease, 36 mo	4*
9	80	PMB	NA	NA	Surgery	RT	NA	NA	NA	4*
10	NA	NA	NA	NA	NA	NA	NA	NA	NA	4*
11	NA	NA	NA	NA	NA	NA	NA	NA	NA	4*
12	NA	NA	NA	NA	NA	NA	NA	NA	NA	4*
13	72	PMB	NA	IIIB	Surgery	RT	NA	NA	NED, 6 mo	4*
14	76	Spotting	NA	IB	Surgery	RT	NA	NA	NA	4*
15	NA	NA	NA	NA	NA	NA	NA	NA	NA	4*
16	54	NA	NA	IB	Surgery	RT	NA	NA	NED, 12 mo	4*
17	60	PMB	NA	IB	Surgery	RT	NA	NA	NED, 9 mo	4*
18	72	PMB	NA	IB	RT	-	NA	NA	NED, 27 mo	4*
19	63	PMB	NA	NA	Surgery	NA	NA	NA	Live with disease	4*
20	NA	NA	NA	NA	NA	NA	NA	NA	NA	4*
21	78	PMB	NA	III	RT	-	NA	NA	DOD, 3 mo	4*
22	65	Spotting	NA	IIB	Surgery	RT	NA	NA	NED	4*
23	64	NA	NA	NA	Surgery	RT	NA	NA	DOD, 5 mo	4*
24	68	PMB	NA	NA	Surgery	RT	NA	NA	DOD, 27 mo	4*
25	64	Bloody vaginal discharge	Hr-HPV	IB	Conization	RT+CT	CD117, CK7, SMA, Calponin, P63 (patchy)	No	NED, 20 mo	4
26	63	Bloody vaginal discharge	Hr-HPV	IB	Surgery	RT+CT	CD117, CK7, SMA, P63 (patchy)	No	NED, 25 mo	4
27	77	Bloody vaginal discharge	Hr-HPV	IB	Surgery	RT	CD117, CK7, SMA, P63 (patchy)	No	NED, 20 mo	4
28	74	PMB	NA	NA	NA	NA	CD117	NA	NA	5*
29	60	PMB, purulent discharge	NA	IIB	CCRT	Surgery	CD117, P63 (focally)	NO	NED, 24 mo	5*
30	76	Spotting	16(+)	IB	Surgery	RT+CT	CD117, S100	Yes, 14 mo	NED, 37 mo	Present

ACC, adenoid cystic carcinoma; SCC, squamous cell carcinoma; PMB, postmenopausal bleeding; AUB, abnormal uterine bleeding; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; N/A, not available or not applicable; NED, no evidence of disease; DOD, died of disease; Hr-HPV, high risk HPV. *4: cited in reference 4, *5: cited in reference 5.

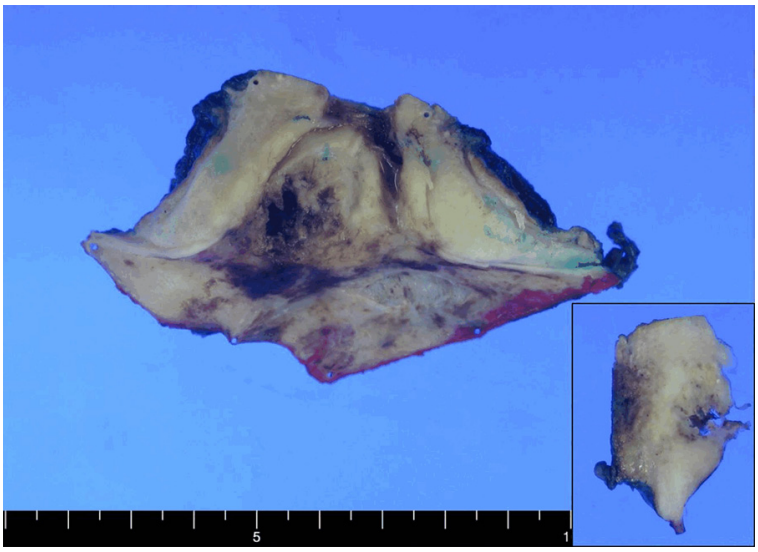

Figure 1. Gross findings of the tumor. Uterine cervix reveals an exophytic and ulcerated tumor lesion. The cut surface (right lower) shows an infiltrative lesion through nearly the whole wall.

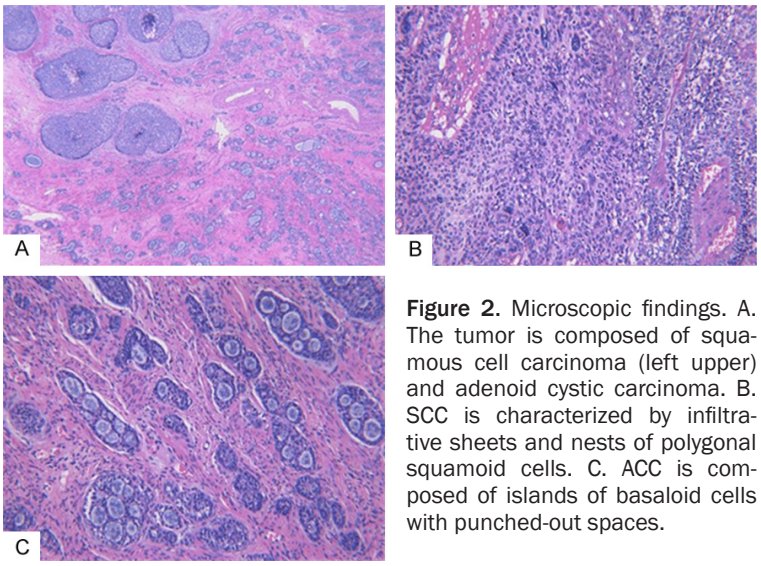

Figure 2. Microscopic findings. A. The tumor is composed of squamous cell carcinoma (left upper) and adenoid cystic carcinoma. B. SCC is characterized by infiltrative sheets and nests of polygonal squamoid cells. C. ACC is composed of islands of basaloid cells with punched-out spaces.

Pelvic magnetic resonance imaging (MRI) revealed an about 2.3 × 1.8 cm sized lobulated mass at cervix and no significant lymph node enlargement. Preoperative serum SCC level was within normal limits.

The patient underwent radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Grossly, the mass was confined to the cervix. The cut surface of the cervix showed an ill-defined brown exophytic mass throughout the whole wall and multiple foci of hemorrhage (**Figure 1**). Microscopically, the tumor was composed of two components. One was characterized by infiltrative sheets of polygonal squamoid cells without keratinization. It was the usual type of squamous cell carcinoma. The other components consisted of basaloid cells forming cribriform and a tubular growth pattern, compatible with adenoid cystic carcinoma (**Figure 2**). Immunohistochemical studies were performed to distinguish these tumors. SCC component was diffusely positive for p63, but negative for CD117 and S-100 protein. ACC component was immunoreactive for CD117 and S-100 protein, but p63 showed only focal positivity. Both components showed diffuse, strong positivity for p16 immunostaining (**Figure 3**). Final pathologic diagnosis was coexisting invasive SCC and ACC of the uterine cervix. HPV DNA chip study showed positivity for high risk HPV 16. Perineural invasion was identified, but lymphovascular tumor emboli were not observed. Postoperative adjuvant radiotherapy was planned due to deep stromal invasion and microscopic parametrial extension. The patient refused to receive any further therapy. During the period of follow-up management, MRI revealed a newly appeared 2.2 × 2.3 cm sized mass with heterogeneous signal intensity located at left side of vaginal vault, 14 months after surgery. Then concurrent chemoradiotherapy (CCRT) consisting of 50.4 Gray whole pelvis irradiation in 28 fractions and six weeks of cisplatin (40 mg/m^2/week) administration was initiated. Two months after completion of CCRT, positron emission tomography-computed tomography (PET-CT) still revealed a hypermetabolic mass on the vaginal stump, suggesting poor response to radiotherapy. Subsequently, 3 courses of paclitaxel (135 mg/m^2), cisplatin (50 mg/m^2), and bevacizumab (15 mg/kg) were

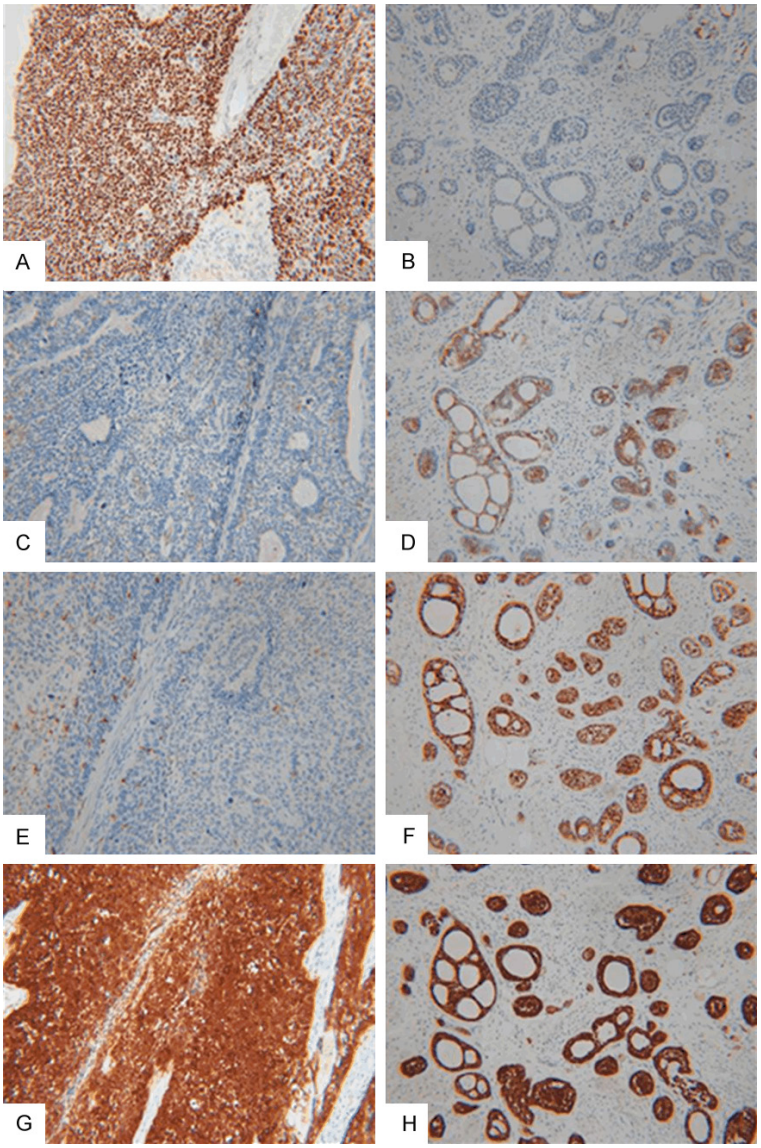

Figure 3. Immunohistochemical findings. P63 positivity is diffusely seen in SCC (A), but focally in ACC (B). Expression of CD117 and S-100 protein are not identified in SCC (C and E), but seen in ACC (D and F). The tumor cells are strongly positive for p16 in SCC (G) and ACC (H) areas.

administered, and finally, subsequent MRI revealed no evidence of residual disease.

Discussion

Adenoid cystic carcinoma (ACC) occurs mainly in the salivary gland and respiratory tract, but it may occur in a variety of other sites. In the female genital tract, it occurs most commonly in the Bartholin gland and rarely in the cervix [2]. ACC of the uterine cervix is a rare malignant neoplasm and accounts for only 1% of all cases of cervical adenocarcinoma [3].

There are few reports of coexisting ACC and SCC of the uterine cervix. In the literature to date, Shi et al. [4] reviewed 27 cases of cervical ACC associated with SCC including the 3 cases reported in their study and Rais et al. [5] added 2 cases of coexisting carcinoma recently (**Table 1**). The tumors are mostly seen in postmenopausal women, but rarely 3 cases developed in premenopausal women. The median age of the patients with this coexisting carcinoma was 62 (ranged 24-80 years of age) [4, 5]. Among all prior reports, postmenopausal bleeding was a predominant presenting symptom. Clinical and radiological characteristics, along with gross features of the surgical specimens, of ACC of the cervix are similar to those usually seen in ordinary SCC of the cervix [6].

The proper identification of ACC is very important for the prediction of prognosis, appropriate adjuvant therapy, and careful clinical follow up. The differential diagnosis includes adenoid basal carcinoma (ABC) and basaloid squamous cell carcinoma (SCC). These conditions can be distinguished by morphology and immunohistochemical staining. ACC can be distinguished from SCC by immunohistochemistry. ACC seems to be more aggressive than SCC in the cervix and to have a higher tendency to recurrence and metastasis even in the earlier stages [7, 8]. ACC is considered to have indolent character and benign clinical behavior. Cytokeratin and myoepithelial immunohistochemical markers, such as, p63, CD117 and S-100, have been suggested to be helpful in distinguishing ACC from SCC [4, 5]. Strong and diffuse nuclear staining of p63 is a valuable marker in SCC; and myoepithelial markers, such as SMA, S-100 or calponin, are characteristically expressed in ACC [4]. The SCC component was diffusely posi-

tive for p63 but negative for CD117 and S-100 protein in the present case. The ACC component was immunoreactive for CD117 and S-100 protein, but p63 showed only focal positivity in the ACC component (**Figure 3**). ACC can be distinguished from ABC morphologically. ACC typically exhibits following pathologic features: cellular pleomorphism, mitoses, necrosis and stromal hyalinization [4]. ACC is often associated with perineurial invasion, as shown in our case. In contrast, tumor cells in ABC have less pleomorphic nuclei and less mitotic activity [5].

The synchronous occurrence of ACC and SCC suggests a common origin of histogenesis, but studies on the histogenesis of ACC have not been fully reported. Among the theories, HPV association is the one that has been most considered. The association between HPV and SCC and adenocarcinoma in the cervix has been well documented, but the relationship between HPV and ACC of the cervix has been not fully investigated. Shi et al. demonstrated that HPV might play a significant role in tumor pathogenesis of these coexisting carcinomas [4]. In their study, P16, a surrogate marker for the presence of HPV infection, exhibited strong, diffuse nuclear and cytoplasmic reactivity in both the ACC and SCC components in all 3 cases, and HPV DNA in situ hybridization signals were present in the two components in all 3 cases. In the present case, the tumor cells also were strongly positive for p16 in SCC and ACC areas (**Figure 3G**, **3H**), suggesting that high risk HPV infection may contribute to the pathogenesis of this coexisting disease.

To date, no standard treatment of these coexisting carcinomas has yet been proposed due to the rarity of the disease. Combined treatment (surgery, radiotherapy and chemotherapy) could be recommended for achieving a long-term remission for ACC. These co-existing carcinomas of the cervix were treated similar to other conventional histology. Surgery and radiation therapy have been used in the treatment of coexisting ACC and SCC of the cervix (**Table 1**). Chemotherapy has very little role in the management of these tumors but has been used for advanced, recurrent, or metastatic cancer [9]. In our case, further chemotherapy has been required after CCRT because of relative radioresistance. Our case is inconsistent with the previous observation in that ACC of the cervix is a radiosensitive tumor.

In conclusion, we present a rapidly progressive case of synchronous ACC and SCC of the uterine cervix. P16 immunostaining was detected in both ACC and SCC, suggesting a common causative agent of this coexisting disease. Clinicians should report more cases of co-existing ACC and SCC in order to explore the histogenesis and optimal management.

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Disclosure of conflict of interest

None.

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