

Primary Endometrial Squamous Cell Carcinoma: A Case Report and Review of Relevant Literature on Korean Women

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Primary endometrial squamous cell carcinoma (PESCC) is an extremely rare tumor with unclear pathogenesis. A 54-year-old postmenopausal woman presented with a 6-month history of vaginal bleeding. The patient was provisionally diagnosed with uterine submucosal leiomyoma. This was followed by total hysterectomy with a bilateral salpingo-oophorectomy under the laparoscopic guidance. Histopathologically, the tumor was PESCC which was accompanied by a lack of the tumor in the uterine cervix. The tumor showed positive immunoreactivity for p16^{INK4a}. But there was no evidence of human papillomavirus (HPV) on *in situ* hybridization and HPV DNA chip analysis. We also present a review of the relevant literature on Korean women.

Key Words: Endometrium; Carcinoma, squamous cell; Human papillomavirus; *In situ* hybridization; Genes, p16

Primary endometrial squamous cell carcinoma (PESCC) is an extremely rare tumor, and its pathogenesis remains unclear. It was first reported by Gebhard in 1892.¹ Its diagnostic criteria were established in 1928 by Fluhmann,² and are as follows: 1) no coexistence of endometrial adenocarcinoma; 2) no connection between the endometrial tumor and the squamous epithelium of the cervix; and 3) no primary cervical squamous cell carcinoma (SCC). In 1975, the World Health Organization (WHO) added two other criteria: presence of intercellular bridges and keratinization.³ Here, we present a case of PESCC satisfying the WHO criteria with positive p16^{INK4a} immunoreactivity and having no evidence of human papillomavirus (HPV).

CASE REPORT

A 54-year-old woman with gravidity 3 and parity 1, who had been postmenopausal for two years, presented with a 6-month history of vaginal bleeding and general weakness. The patient looked generally anemic and fatigued, and had no past history of taking estrogen replacement therapy. In addition, the patient had a body mass index of 24.5 kg/m² and a blood cancer anti-

gen 125 level of 24.2 U/mL (normal range, 0 to 35 U/mL). The patient had a normal Papanicolaou smear but no notable gynecological history. Pelvic examination revealed an enlarged uterus without palpable ovaries. Transvaginal ultrasound showed a 7-cm protruding mass in the endometrial cavity with an endometrial thickness of 22.3 mm. In addition, the mass was surrounded by echogenic blood flow and it showed an ill-defined margin with the myometrium.

The patient underwent total hysterectomy with a bilateral salpingo-oophorectomy under the laparoscopic guidance under a provisional diagnosis of submucosal leiomyoma. The tumor did not involve the serosal surface of the uterus or the abdominal cavity. The cervix, adnexa and vagina appeared normal. Grossly, there was an ill-defined, relatively solid endometrial mass with a spotty necrosis, measuring 7×6×5 cm. In addition, it involved the myometrium at the fundus and body but not its serosal tissue. Following a careful examination, the endometrial mass was divided into 12 sections in total. There were no notable findings in the uterine cervix and both adnexae. The entire uterine cervix was divided into 12 sections in total from the 12 o'clock position.

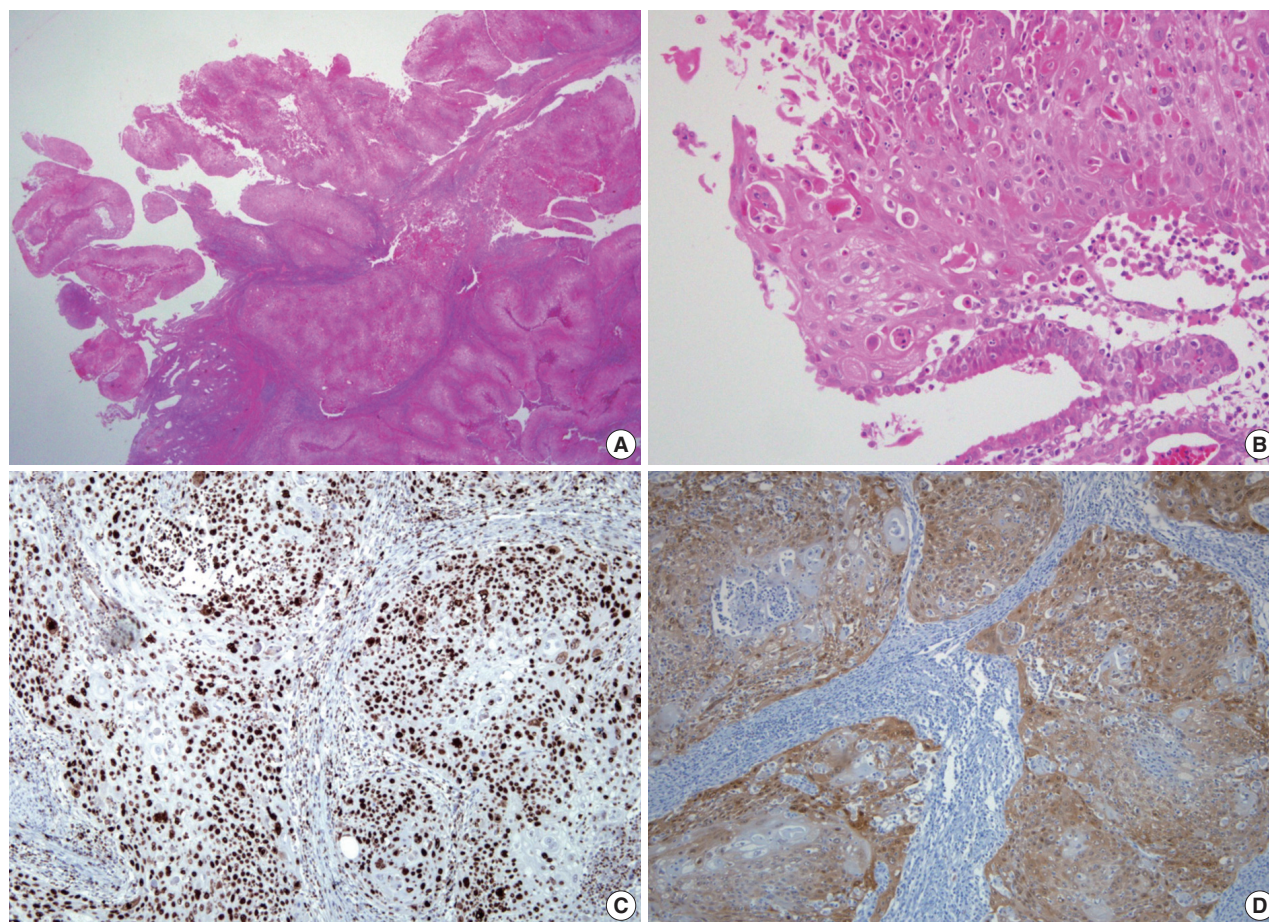


Fig. 1. The solid tumor consists of nests of varying size with a squamous differentiation (A) including distinct intercellular bridges and abortive keratinization (B). Immunohistochemically, the tumor cells are immunoreactive for p63 (C) and p16 (D).

Microscopically, the tumor showed a clear evidence of squamous differentiation, such as presence of intercellular bridges and keratinization (Fig. 1A, B), thus confirming a well-differentiated, invasive SCC of the endometrium. The tumor involved more than 80% of the myometrial thickness and it showed a vascular invasion to the myometrium. In the adjacent non-neoplastic endometrium, there were glands with both a pseudostratification and a ciliary change and their stroma was infiltrated by inflammatory cells, plasma cells and neutrophils in particular (Fig. 1B). There were no evidences demonstrating the presence of squamous metaplasia of the endometrium, endometrial adenocarcinoma, cervical SCC and a connection between the endometrial tumor and the squamous epithelium of the cervix. Both fallopian tubes and ovaries were normal. Moreover, there was no evidence of SCC at other sites. These findings confirmed the diagnosis of PESCC rather than submucosal leiomyoma. On immunohistochemistry, there was a positive immunoreactivity for cytokeratin 7, p63 (Fig. 1C), and p16^{INK4a} (Fig. 1D), but not for

cytokeratin 20 and estrogen receptor (ER) and progesterone receptor (PR). Ki-67 was stained in 80% of the tumor cells. But HPV was not detected on either *in situ* hybridization (ISH) or HPV DNA chip analysis. The patient underwent radiotherapy for two months. The patient showed a disease-free course during a 13-month follow-up period.

DISCUSSION

It is generally known that endometrial SCC originates from the uterine cervix. The connection between the endometrium and the cervix should therefore be ruled out in making a diagnosis of PESCC. Squamous differentiation of an endometrioid adenocarcinoma must also be excluded.²

Several theories regarding the cellular origin of PESCC have been proposed: 1) reserve or stem cells located between the glandular basement membrane and the endometrial columnar cell layer;⁴ 2) squamous metaplasia of the normal endometri-

Table 1. General characteristics of Korean women with PESCC

Case No.	Authors	Age (yr)	Gravidity/Parity	Symptom	Preoperative diagnosis	Cytology	HPV analysis	PLNM	Operation	Stage	Adjuvant therapy	Follow-up (mo)
1	Jung <i>et al.</i> ¹⁴	66	G7P7	Vaginal bleeding	CIS	HSIL	HPV 16/18(+) in cervix and (-) in endometrium by ISH and PCR	(+)	TH+BSO	IIc	CT+RT	AWD (12)
2	Chung and Lee ¹⁵	68	G6P5	Vaginal discharge	Myoma uteri	NA	HPV16/18(-) in endometrium by PCR	NA	TH+BSO	Ia	None	AWD (6)
3	Seo <i>et al.</i> ¹⁸	62	G6P5	Vaginal bleeding	Myoma uteri	ASCUS	NA	(-)	RH+BSO	Ic	RT	AWD (2)
4	Kim <i>et al.</i> ¹⁹	65	G12P7	Vaginal bleeding	Myoma uteri	HSIL	NA	(+)	RH+BSO	IIc	CT	AWD (12)
5	Tong <i>et al.</i> ²⁰	57	G6P3	Vaginal bleeding	Cervical cancer	SCC	HPV(-)	(-)	RH+BSO	Ia	RT	AWD (9)
6	Present report	54	G3P1	Vaginal bleeding	Myoma uteri	Normal	HPV(-) in endometrium by ISH and DNA chip analysis	(-)	TH+BSO	Ib	RT	AWD (13)

PESCC, primary endometrial squamous cell carcinoma; HPV, human papillomavirus; PLNM, pelvic lymph node metastasis; CIS, carcinoma *in situ* of the cervix; HSIL, high-grade squamous intraepithelial lesion; ISH, *in situ* hybridization; PCR, polymerase chain reaction; TH, total hysterectomy; BSO, bilateral salpingo-oophorectomy; CT, chemotherapy; RT, radiation therapy; AWD, alive with the disease; NA, unknown; ASCUS, atypical squamous cells of undetermined significance; RH, radical hysterectomy; SCC, squamous cell carcinoma.

um;⁵ and 3) heterotopic cervical tissue.⁶ It has been reported that vitamin A deficiency, anti-estrogen treatment, pyometra, chronic infection, uterine prolapse, myoma, intrauterine device, history of pelvic irradiation and curettage are associated with squamous metaplasia of the endometrium.^{2,5,7,8}

HPV infection plays a key role in the pathogenesis of squamous neoplasms of the uterine cervix,⁹ whose role in that of PESCC remains controversial. Of note, Kataoka *et al.*¹⁰ demonstrated the presence of HPV type 31 by the polymerase chain reaction (PCR) in one patient with PESCC. But there were no other reports demonstrating a clear association between HPV and PESCC.¹¹⁻¹³ Horn *et al.*¹¹ performed an HPV analysis with general primers and HPV typing in eight patients with PESCC. These authors noted that there was only one positive case for HPV type 16. Giordano *et al.*¹² failed to detect HPV DNA by PCR in one patient with PESCC. In addition, Im *et al.*¹³ could not detect HPV by ISH in three patients with PESCC. According to review of literatures about five Korean women with PESCC (Table 1), there were one positive case for HPV 16/18 in the cervix but not the endometrium by ISH and PCR assay¹⁴ and another negative case for HPV 16/18 by PCR assay.¹⁵ Moreover, we did not find any evidence of HPV in our patient. We therefore suggest that HPV may not be the primary causative factor for PESCC.

A cyclin-dependent kinase-4 inhibitor involved in the pRb pathway, p16^{INK4a} is a surrogate marker for HPV infection in cervical neoplasms.⁹ It has been reported that p16^{INK4a} is expressed in some cases of endometrial carcinoma.^{11,16} To date, however, fewer attempts have been made to evaluate both the HPV status and p16^{INK4a} expression. Ansari-Lari *et al.*¹⁶ reported that p16^{INK4a} expression is moderate to strong and diffuse in endocervical adenocarcinoma and weak and patchy in endometrial adenocarcinoma. These findings suggest that p16^{INK4a} im-

munohistochemistry may be helpful for distinguishing endocervical adenocarcinoma from endometrial adenocarcinoma. According to Horn *et al.*,¹¹ 50% of the cases showed a positive p16^{INK4a} immunoreactivity but there was only one positive case for HPV. These reports suggest that alterations of the p16^{INK4a} pathway may play a role in the pathogenesis of some cases of PESCC, if any, without an HPV involvement. Similarly, our case showed weak and patchy p16^{INK4a} expression and negative results for HPV by both ISH and DNA chip analysis. Our case therefore indicates that p16^{INK4a} overexpression may be involved in the development of PESCC with no respect to HPV infection.

The clinical applicability of the ER and PR status as a prognostic indicator of PESCC is still uncertain. Considering that most patients are postmenopausal, however, a loss of estrogen cannot be completely ruled out as an etiologic factor. This is not only because most cases of PESCC occur in postmenopausal women but also because one of the most frequent presenting symptoms is vaginal bleeding. The average duration of symptoms before diagnosis is 11.5 months.⁸

Total hysterectomy with a bilateral salpingo-oophorectomy is the first line of choice for menopausal women. The effectiveness of radiotherapy and chemotherapy as adjuvant treatments remains highly controversial.^{7,8} PESCC has a poor prognosis compared with endometrial adenocarcinoma. That is, it is well documented that the 5-year survival rates in endometrial adenocarcinoma at stages I, II, III, and IV are 89.1%, 78.8%, 57.8%, and 22.8%, respectively.¹⁷ However, the 5-year survival rate of PESCC is difficult to assess because of its rarity. With a survival period ranging from 14 to 36 months, it has been reported that the 1-year survival rates in PESCC at stages I, III, and IV are 80%, 20%, and 0%, respectively.^{7,8}

The mean age of the six Korean patients (Table 1), including our case, was 62 years (range, 54 to 68 years), all of whom were

postmenopausal.^{14,15,18-20} Most of the Korean women with PESCC are multiparous, which is contradictory to the report, by Goodman *et al.*,⁸ made from nulliparous women. In addition, vaginal bleeding is one of the typical symptoms that occur in Korean women.

In summary, there was positive p16^{INK4a} immunoreactivity with no evidence of HPV by ISH and DNA chip analysis in our case. Our case highlights the significant role of p16^{INK4a} overexpression, regardless of the HPV status in the pathogenesis of PESCC. Henceforth, however, further large-scale studies are warranted to gain a deeper insight into its characteristics of PESCC.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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