Primary endometrial squamous cell carcinoma with endometrial atypical hyperplasia in elderly women: a case report

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Background: Primary endometrial squamous cell carcinoma (PESCC) is a rare entity with poorly understood pathogenesis. Given the difficulty of pathological diagnosis, we report a case of postmenopausal PESCC to highlight the complexity of its immunohistochemical findings.

Case Description: A 66-year-old woman presented with lower abdominal discomfort and pain. Endometrial biopsy showed a papillary hyperplasia and squamous differentiation of the endometrium. Transvaginal ultrasound and pelvic enhanced computed tomography (CT) scan confirmed a mass in the uterus, and enlarged lymph nodes around the right foramen ovale and bilateral iliac vessels, suggesting a uterine malignancy. Radical hysterectomy, bilateral salpingo-oophorectomy, large omental appendectomy, sigmoid colectomy, ileostomy and intestinal anastomosis were performed. The definitive diagnosis was primary endometrial squamous carcinoma with lymph node and intestinal metastasis (stage IVB). Immunohistochemistry of tumor cells showed positive for cytokeratin 5/6, p63 and HPV16, and 30–50% of tumor cells were reactive for Ki-67. Wilms tumor 1 (WT-1) as well as estrogen and progesterone receptor were negative. Nine months after surgery, the patient died at home due to cancer progression.

Conclusions: The diagnosis of PESCC is based on careful pathological examination of hysterectomy specimens by pathologists and its differential diagnosis from squamous cell carcinoma of cervical origin and endometrioid carcinoma with extensive squamous differentiation is particularly important. The pathogenesis of PESCC and its pathological phenotype are complex, further studies of a large number of cases are needed.

Keywords: Primary endometrial squamous cell carcinoma (PESCC); human papillomavirus; immunohistochemical staining; case report

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Introduction

Primary endometrial squamous cell carcinoma (PESCC) is an exceedingly rare tumor of the uterus, accounting for less than 5% of all endometrial malignancies (1). It is being defined as a primary carcinoma of the endometrium consisting of squamous cells with variable degrees of differentiation (2). The diagnostic criteria for PESCC were elaborated by Fluhmann in 1928 (3) and have been used ever since. According to this criteria, endometrial adenocarcinoma with squamous differentiation and squamous cell carcinoma (SCC) of the cervix with endometrial spreading must be excluded; in addition, there must be no association between the endometrial tumor and the squamous epithelium of the cervix (3). In view of the fact that little is known about the pathogenesis of PESCC and the difficulty of its pathological diagnosis, we report a case of postmenopausal PESCC, which was diagnosed by carefully analyzing the complex immunohistochemical staining results and differentiated from squamous carcinoma of cervical origin and endometrial adenocarcinoma with predominant squamous differentiation. We present the following case in accordance with the CARE reporting

checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-9/rc).

Case presentation

The patient was a 66-year-old postmenopausal woman who presented to the Department of Gynecology of the West China Second Hospital on December 10, 2018 because of lower abdominal discomfort with pain. Her medical history dated back to 3 months earlier when she first noticed a slight pain in her lower abdomen. Two months ago, based on an endometrial curettage performed at a local hospital, she was shown to have papillary hyperplasia and squamous differentiation of the endometrium, and subsequently she was referred to our hospital. Thirty-four years ago, she had a tubal ligation and became menopausal about 20 years ago. She was found to have hypertension a year ago and was using amlodipine to control her blood pressure, which was 133/73 mmHg on admission. The patient had no record of tobacco or alcohol consumption and no family history of cancer.

The gynecological examination showed an irregularly enlarged uterus resembling the size of 16 weeks of pregnancy, with a hard texture, poor mobility, and unclear borders. The cervix was atrophic with no obvious lesions or contact bleeding, and there was no tenderness on palpation of the adnexa bilaterally. A Pap smear and a human papillomavirus deoxyribonucleic acid (HPV DNA) examination were also performed and showed negative results. Transvaginal ultrasound revealed an enlarged uterus (7.7 cm × 7.5 cm × 10.1 cm) with a slightly echogenic intrauterine occupancy (6.2 cm × 2.5 cm × 5.5 cm) and two weakly echogenic masses with abundant blood flow signal (2.0 cm × 2.0 cm × 2.7 cm and 2.7 cm × 1.9 cm × 3.0 cm). A subsequent pelvic enhanced computed tomography (CT) scan confirmed a mass in the uterus, and enlarged lymph nodes around the right foramen ovale and bilateral iliac vessels, suggesting a uterine malignancy. The serum level of cancer antigen 125 (CA125) was 53 U/mL (normal range: 0–34 U/mL), the carcinoembryonic antigen (CEA) was 5.8 ng/mL (normal range: 0–2.5 ng/mL) and squamous cell carcinoma antigen was 3. 9 ng/mL (normal range: 0–1.5 ng/mL). Other serum tumor markers namely alpha-fetoprotein (AFP) and CA19-9 were within normal range. The preoperative tests, including measurement of the blood routine, coagulation routine, liver and kidney function, urinalysis, chest X-ray, electrocardiography, and cardiac evaluation, were all normal.

First, dilatation and curettage (D&C) was performed and pathology showed degenerative necrotic tissue with inflammatory cells and epithelial cells, with no obvious atypical cells. Then the patient underwent an exploratory laparotomy with a transabdominal longitudinal incision. There is no ascites found in the abdominal cavity. Macroscopically, the uterus measured approximately 8 cm × 7 cm × 10 cm, and the fundus of uterus was penetrated by a lesion that invaded the junction of the rectum and the sigmoid colon. Two neoplastic nodules of 3 cm × 4 cm and 3 cm × 3 cm were seen on the sigmoid colon. Some brittle nodules were found on the colonic haustra, the mesenteric root and the surface of the appendix. There was also a large amount of pus moss in the pelvis. Frozen sections obtained during surgery showed malignant tumor cells detected in nodules on the surface of the uterus and appendix as well as squamous carcinoma cells in nodules on the surface of the intestine. Lymph node dissection was not performed because of severe inflammatory edema and massive pus diffusion in the pelvic tissue. Finally, on the recommendation of the gastroenterologist, the patient underwent radical hysterectomy, bilateral salpingo-oophorectomy, large omental appendectomy, and colectomy, followed by ileostomy and intestinal anastomosis. Grossly, the excised uterus had a hard armor-like texture and the endometrial cancer occupied the entire uterine cavity, with the largest lesion (4 cm × 4 cm) located in the posterior wall of the uterus. Moreover, there was a tumor measuring 2 cm × 2 cm at the junction of the lower uterine segment and endocervix. Longitudinal incision of the intestinal cavity revealed that the tumor had infiltrated into the muscular layer (*Figure 1*).

Immunohistochemical (IHC) stains, including HPV16, Ki-67, cytokeratin 5/6 (CK5/6), CK7, CA125, estrogen receptor (ER), progesterone receptor (PR), p63, p53, CEA, vimentin (VIM), Wilms tumor 1 (WT-1) were performed. Immunoreactivity of endometrial cancer cells for CK5/6(+++), p63(+), HPV16(+) was evidenced, and Ki-67 stained about 30–50% (*Figure 2*). Metastatic carcinoma of the right fallopian tube was HPV16(+), CK5/6(+++), and Ki-67 stained about 45%. Cancer of the uterine body–cervical junction (the lower uterine segment/endocervix) was VIM(+++/–), CA125(+++/–), p53(–/++), WT–1(–/–), p63(–/+++), CK7(+++/–), CK5/6(+++/+++), CEA(+++/+), HPV16(–/–), ER(–/–), PR(–/–). On the basis of these microscopic findings, the definitive diagnosis was endometrial squamous cell carcinoma with endometrial atypical hyperplasia, FIGO (International Federation of

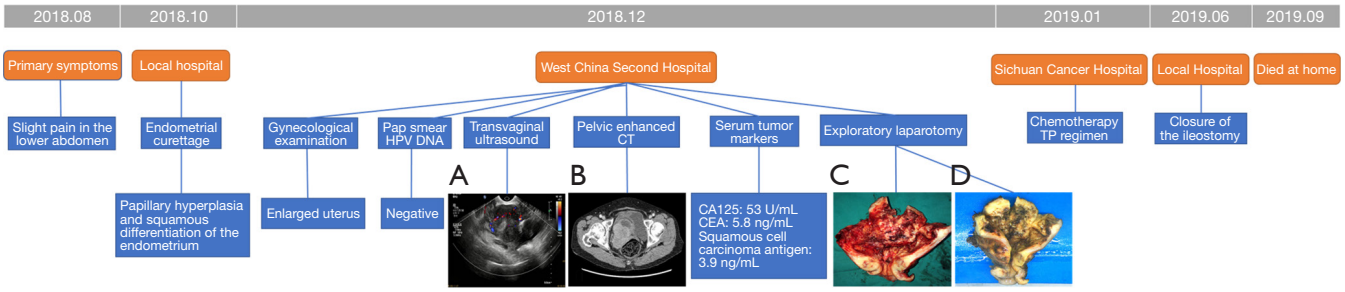

Figure 1 Timeline of disease progression. This timeline describes the entire process from the patient felt discomfort to the time she was admitted to the hospital and finally died of progressive disease. The four pictures are diagnostic testing and important clinical findings. (A) Preoperative ultrasound examination; (B) preoperative enhanced CT scan; (C) operation specimen: uterine cervix; (D) macroscopic feature of uterus with massive necrotic area: malignant growths of the endometrium can be seen internally. CT, computed tomography; CA125, cancer antigen 125; CEA, carcinoembryonic antigen; TP, paclitaxel and cisplatin.

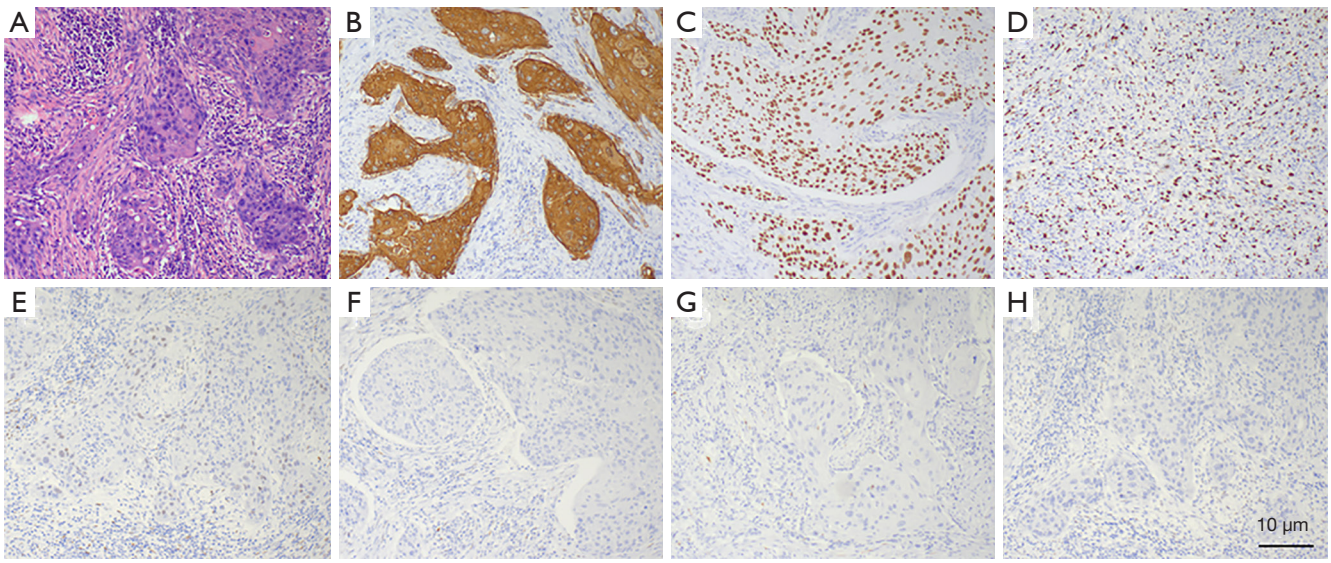

Figure 2 HE and IHC staining of endometrial cancer cells. (A) Microphotograph presenting HE stained specimens of endometrial cancer cells (100×). (B-E) Tumor markers of CK5/6, p63, Ki67 and HPV16 were positive in specimens of endometrial squamous cell carcinoma (100×). (F-H) Tumor markers of PR, ER and WT-1 were negative in endometrial cancer cells (100×). HE, hematoxylin-eosin; IHC, immunohistochemical; CK5/6, cytokeratin 5/6; PR, progesterone receptor; ER, estrogen receptor; WT-1, Wilms tumor 1.

Gynecology and Obstetrics) stage IVB (pT4NXM1).

Chemotherapy was started one month after surgery in the Sichuan Cancer Hospital & Institute, as the patient had a severe pelvic infection and received postoperative anti-infective treatment. The patient underwent a PET-CT scan prior to chemotherapy, which revealed partial peritoneal and omental thickening and increased nodular radioactive uptake in the right peritoneal space of the lower abdomen. The lymph nodes in the right pelvis and parietal abdominal aorta also showed higher nodal radioactive uptake. Due to financial constraints, the patient received only one cycle of TP (paclitaxel, 180 mg, ivgtt, D1 and cisplatin 30 mg, ivgtt, D1-D3) chemotherapy combined with pelvic radiotherapy. The patient was sensitive to chemotherapy and experienced nausea, vomiting, hair loss and bone marrow suppression, but her liver function and kidney function were normal. Six months after surgery, the patient underwent closure of the ileostomy at a local hospital and gradually regained bowel

function. Nine months later, the patient died at home.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

There are only sporadic cases of PESCC reported since the first case reported in 1892 (4). Patients with PESCC ranged in age from 28 to 87 years, but mostly occur in perimenopausal, postmenopausal and nulliparous women, being associated with HPV infection (5), pelvic chronic inflammation (6), radiation therapy, pyometra, and ichthyosis (7,8). However, its etiology and pathogenesis remain unclear. The clinical manifestations of PESCC are similar to adenocarcinoma of uterus. But it is more malignant and is prone to deep myometrial infiltration, vascular space invasion, and lymphatic metastasis even though the intrauterine lesions are small. The 5-year survival rate of PESCC is very low, except in isolated cases (5). This post-menopausal patient was asymptomatic except for lower abdominal discomfort and thus was in the advanced stage of cancer at the time of consultation.

The preoperative diagnosis of PESCC is challenging because cervical or vaginal smear status has been reported to be abnormal in only about half of cases, and many patients have undergone multiple gynecologic examinations and curettage prior to surgery (9). In our case, the patient's first curettage at the local hospital showed papillary hyperplasia and squamous differentiation of the endometrium. However, the histological findings of the preoperative curettage showed no obvious atypical cells, only degenerated necrotic tissue with inflammatory cells and epithelial cells. A combination of tumor marker testing and imaging (e.g., transvaginal ultrasound and enhanced CT) is needed to highly suspect a malignant lesion.

The immunophenotype of PESCC is heterogeneous as it is a rare entity and our knowledge is largely dependent on limited number of cases. Notably, immunocytochemical staining using CK5/6 labeling confirmed the squamous origin of the endothelial tumor cells in this patient. We also detected mutant p63 expression in our patient which was in line with reports by Jetley *et al.* and Lee *et al.* (10,11). CK5/6 and p63 are markers of basal and squamous differentiation in some normal epithelial cells and human tumors (12). The strong positive expression of CK5/6 in endometrial cancer cells and the diffuse distribution of p63-positive cells were the main diagnostic basis, and the specificity of these two markers was higher than that of CEA expression in the lower segment of the uterine body (12). HPV16-positive endometrial tumor cells and metastatic carcinoma of the right fallopian tube might explain the observed pathogenesis of PESCC, as tumor cells at the junction of the uterine body and the cervix are HPV16 negative; however, we were unable to confirm this possibility. High-risk HPV infection has a major role in the development of cervical squamous neoplasia, but its contribution in PESCC remains controversial (13,14). The detection of ER and PR provides some guidance for the treatment of endometrial cancer, but their role as indicators of prognosis remains uncertain (15). Moreover, the WT-1 was negative in both metastatic carcinoma of the right fallopian tube and cancer of junction of body and cervix of uterus. Unfortunately, this patient already had intestinal and lymphatic metastases at the time of surgery and combined with severe pelvic inflammation, so lymph node dissection was not done; the patient had only one radiotherapy-chemotherapy session after surgery for personal reasons and did not complete the standard treatment regimen, which also contributed to her poor prognosis.

In conclusion, PESCC is a rare cancer with a high degree of malignancy and a poor prognosis. The clinical manifestations could be asymptomatic. The diagnosis of PESCC is based on careful pathological examination of hysterectomy specimens by pathologists and its differential diagnosis from squamous cell carcinoma of cervical origin and endometrioid carcinoma with predominant squamous differentiation. The therapeutic regimen for PESCC remains controversial while surgery combined with radio-chemotherapy was considered to be the optimal treatment. To understand the pathogenesis and pathological features, we need more high-quality experimental studies.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-9/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-9/coif). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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