

# Primary squamous cell carcinoma of the endometrium: A rare case report

Sigit Purbadi, PhD<sup>1</sup>, Kade Yudi Saspriyana, MD<sup>2</sup>, Tantri Hellyanti, MD<sup>3</sup>

<sup>1</sup>Gynecology Oncology Division, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Dr Cipto Mangunkusumo National Referral Hospital, <sup>2</sup>Fellowship Gynecology Oncology Trainee, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Dr Cipto Mangunkusumo National Referral Hospital, <sup>3</sup>Department of Pathology Anatomy, Faculty of Medicine, Universitas Indonesia, Dr Cipto Mangunkusumo National Referral Hospital

## SUMMARY

**Primary endometrial squamous cell carcinomas (PESCC) occur sporadically. It is defined as a primary carcinoma of the endometrium composed of squamous cells of varying degrees of differentiation. A 57-year-old female patient was referred to the gynaecological clinic of Faculty of Medicine, Universitas Indonesia, Dr Cipto Mangunkusumo National Referral Hospital because of abdominal enlargement with pain. Total hysterectomy and bilateral salpingectomy were performed. Histopathological examination confirmed a moderately differentiated squamous cell carcinoma, with lymph-vascular invasion. Two weeks after the operation, the patient complained of a mass on her left supraclavicular area. Fine needle aspiration biopsy revealed squamous cell carcinoma metastatic in nature. The recommended treatment was paclitaxel (175mg/m<sup>2</sup>) and carboplatin (AUC-6), combined with pelvic radiotherapy.**

## INTRODUCTION

Globally, endometrial cancer accounted for an estimated 382,069 new cases and 89,929 deaths in 2018. This disease ranks as the sixth most frequently diagnosed cancer in women.<sup>1</sup> Primary endometrial squamous cell carcinomas (PESCCs) are sporadic in occurrence, although the exact prevalence is not yet known. The majority of squamous cell carcinoma (SCC) cases represent an extension from the cervix, where SCC spreads superficially to the inner surface of the endometrium and replaced by carcinoma cells.<sup>2</sup> However, either primary or secondary, endometrial SCC is rare and PESCC *in situ* is even rarer. Thus far about 70 cases have been reported, according to the WHO blue book. It is defined as a primary carcinoma of the endometrium composed of squamous cells of varying degrees of differentiation.<sup>3</sup> Recently, case reports of endometrial SCC have been published sporadically. Here we report a rare case endometrial SCC.

## CASE REPORT

The patient was a 57-year old woman, para-3, was referred to the gynaecological Of Faculty of Medicine, Universitas Indonesia, Dr Cipto Mangunkusumo National Referral Hospital because of abdominal enlargement with pain. Her medical history dated back to the age of 54 years when she

had moderate dysplasia of her cervix and endometritis based on cold knife conization and endometrial curettage (figure 1a, 1b). At that time, Human Papillomavirus Deoxyribonucleic acid (HPV DNA) examination was also performed, resulting in positive for high-risk HPV type 66 and 68. The gynaecologist suggested to do a total hysterectomy, but she refused. She had been menopause for ten years.

Gynaecologic examination revealed vagina and cervix that were normal. The uterus was enlarged, corresponding to the size of a 4-month-pregnant uterus. Gynaecologic ultrasonography confirmed that the uterus was enlarged, and there was a cystic mass in the uterine cavity sized 77x150mm. Endometrial area was regular, and endocervix was normal (Figure 1c). HPV genotyping was positive for HPV DNA; however, the subtypes are not included in the 33 subtypes detected in our lab (used DiagCor® GenoFlow HPV Array Test). The chest X-ray of the patient revealed no radiologic abnormality. Endometrial biopsy (EB) and CT scan were not performed, diagnosis based on clinical data three years before as moderate dysplasia of the cervix and suspected hydrometra according to latest ultrasound examination. The general gynaecologist did not consider performing EB at that time, due to clinical and imaging finding as a benign condition.

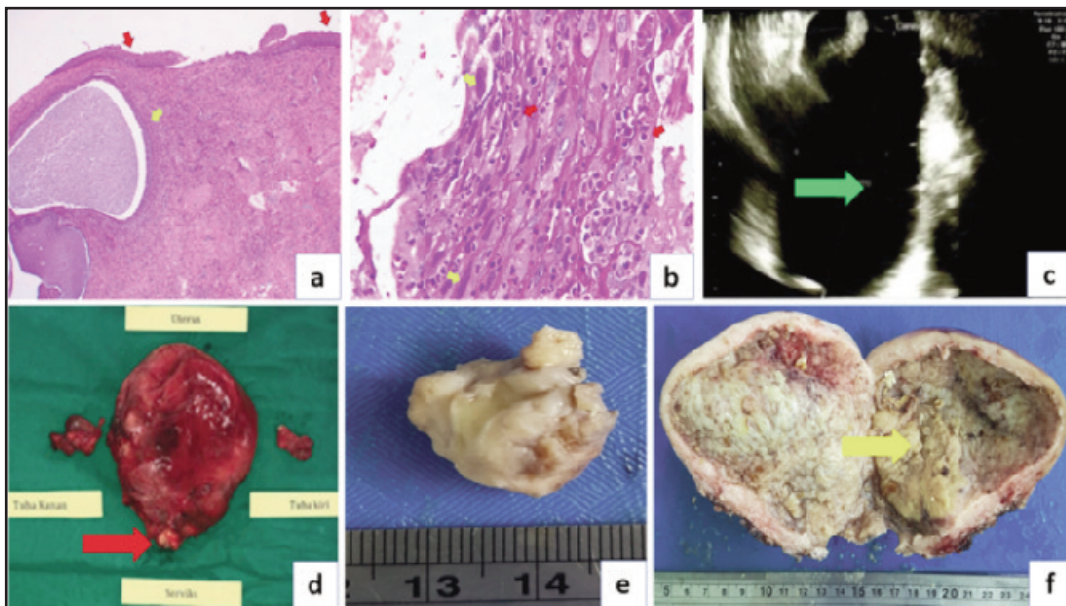
The patient underwent a total hysterectomy and bilateral salpingectomy on April 2019 by the gynaecologist, without any consideration of pelvic lymph node dissection. During the operation, 1200ml of hydrometra was found. Both ovaries were normal. Macroscopically, the uterus measured 10x10x3cm, and the cervix was 2x1x0.7cm long with an outer diameter of 2.5cm (Figure 1d, 1e). The uterine cavity was enlarged, contained necrotic materials, and endomyometrial thickness was 0.5-1.3cm (Figure 1.f). The areas of the uterus from where the histology sections were taken are marked in Figure 2a. The gynaecologist decided to keep both ovaries, because they were macroscopically normal and uterine condition was suspected as a benign condition.

Histopathological examination confirmed a moderately differentiated squamous cell carcinoma of endometrium, with lymph-vascular invasion (figure 2b). Entire endometrial lining had been replaced by atypical squamous cells with marked pleomorphism. Tumour invasion was more than half

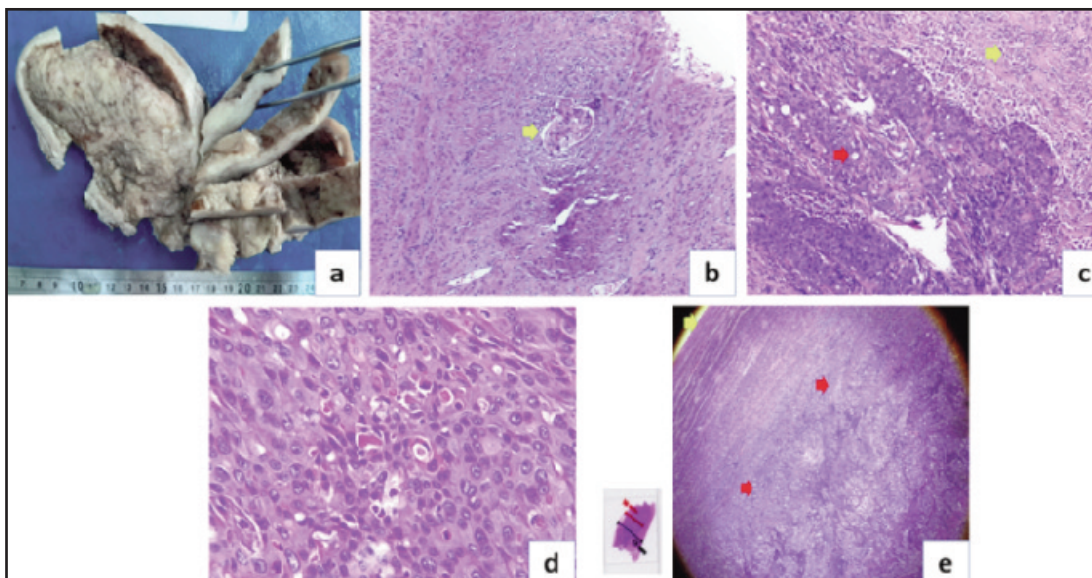
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*Corresponding Author: Sigit Purbadi*

*Email: spurbadi@gmail.com*



**Fig. 1:** a. Histopathology of cervix conization. HE x100: moderate dysplasia in superficial squamous epithelium (red arrow) and squamous metaplasia accompanied by extension of moderate dysplasia to glandular components (yellow arrow); b. Histopathology of endometrial curettage. HE x400: intense inflammation in the endometrium (red arrow). This condition had a high possibility to becoming abundant squamous metaplasia on the endometrial surface. This picture also revealed dysplasia process (yellow arrow); c. Preoperative ultrasound examination: cystic area intrauterine cavity (green arrow); d. Operation specimen: uterine cervix (red arrow); e. Macroscopic detail of cervix: 2x1x0.7cm long; f. Macroscopic feature of uterus with massive necrotic area: yellow arrow points out malignant growth of the endometrium and no normal endometrial tissue was found.



**Fig. 2:** a. Histology section of the uterine area; b. Histopathology of uterus. HE x100: lymph-vascular invasion; c. Histopathology of uterus. HE x100: tumour mass (red arrow), necrotic area in the uterine cavity (yellow arrow); d. Histopathology of uterus. HE x400: tumour cell with intense pleomorphic, coarse chromatin, eosinophilic cytoplasm, and dyskeratosis individual cell; e. Histopathology of the uterus, HE x25: tumour invades more than half myometrial thickness: deepest invasion reached 10mm from 13mm myometrial thickness (red arrow: invasion to myometrium; yellow arrow: serous layer of the uterus).

myometrial thickness (figure 2c, 2d, 2e). The lymph vascular emboli of the tumour metastasized into bilateral fallopian tube and on cervical surface. The cervix showed high grade squamous intraepithelial lesion, but there was no invasive cancer as yet. Based on these histologic finding, this patient was in stage IIIA endometrial cancer (FIGO 2009). She was then referred to onco-gynaecology Division.

Two weeks after the operation, the patient complained of mass on her left supraclavicular area. Physical examination found a mass on left supraclavicular lymph nodes sized 2cm. Squamous cell carcinoma metastatic was the result of fine-needle aspiration biopsy. The patient was diagnosed with stage IVB endometrial squamous cell carcinoma. The recommended treatment was paclitaxel (175mg/m<sup>2</sup>) and

carboplatin (AUC-6) for sixth series, combined with pelvic radiotherapy. She was sensitive to chemotherapy and developed bone marrow suppression, nausea and vomiting and hair loss, but her liver and kidney function were unaffected. The patient was followed-up regularly and remained in good condition. The patient provided written informed consent for participation in and for publication of this case report.

## DISCUSSION

Our case has many errors, especially in preoperative diagnosis and treatment. To begin with the patient was treated by a general gynaecologist, who was not aware of her previous history and was confident that it was a benign condition. The diagnosis was made only by clinical examination, imaging, and history of pathology reports. Hence, this case had a poor preoperative workup. So, the management did not perform lymph node evaluation. Intraoperative, 1200 ml hydrometra came out and it caused difficulty in identification of the atrophic post conization cervix. The uterine body was taken out, followed by the remnant of the cervix.

The most common histological type of endometrial cancer is adenocarcinoma, followed by adenosquamous carcinoma, while PESCC is very rare. PESCC usually occurs in older or postmenopausal women, with similar clinical manifestations to adenocarcinoma.<sup>4</sup> PESCC, based on the strict criteria set forth by Fluhmann, is a rare entity with fewer than 100 cases being reported in the literature. The Fluhmann criteria, established in 1928, include<sup>1</sup> no coexisting glandular carcinoma in the endometrium,<sup>2</sup> no connection between the tumour in the endometrium and the squamous epithelium of the cervix, and<sup>3</sup> no primary squamous cell carcinoma of the uterus.<sup>5</sup> Our case fulfilled Fluhmann's criteria with the presence of changes of dysplasia and carcinoma-*in-situ* without any signs of an invasive primary cervical squamous cell carcinoma even on extensive sampling.

PESCC have been found in association with pyometra, cervical stenosis, chronic inflammation, multiparity and ichthyosis uteri in postmenopausal women. PESCC can arise from endometrial stem cell, squamous metaplasia of the normal endometrium or heterotopic cervical tissue. It is essential to exclude cervical SCC extension into the endometrium and squamous differentiation of an endometrioid adenocarcinoma.<sup>4,5</sup>

The pathogenesis of primary SCC of the endometrium is unknown. Several possibilities exist. First, the SCC is a complete malignant squamous differentiation of endometrioid adenocarcinoma. Second, HPV is involved in the pathogenesis of primary SCC of the endometrium. Thirdly, squamous metaplasia-dysplasia SCC sequence is included in the pathogenesis of primary SCC of the endometrium. Finally, primary SCC of the endometrium may develop from ectopic cervical tissue in the endometrium.<sup>3</sup> In our case, along with the conization on 2016 (3 years before hysterectomy), endometrial curettage specimen was sent to the laboratory. The endometrium showed intense inflammation, which triggered squamous metaplasia on the surface of the endometrium. At that time, we did not know whether ichthyosis uteri had occurred on the entire surface of

the endometrium because EB was not performed before the total hysterectomy. Therefore, we could not make a direct association with ichthyosis uteri and development of PESCC in this case.

A study by Kataoka et al., demonstrated HPV 31 in one patient with PESCC by polymerase chain reaction, HPV analysis of published PESCC case reports failed to find any evidence of HPV.<sup>6</sup> This patient had a history of positive HPV type 66 and 68 in the past three years. Theoretically, HPV may intervene in the pre-existing ichthyosis, leading the transformation to squamous cell carcinoma. However, in our case, EB was not performed before the hysterectomy, and by the limited reported case of PESCC, it is difficult to establish correlation between HPV status and PESCC.

PESCC has a high malignancy grade and poor prognosis, with a 5-year survival rate of zero.<sup>4</sup> Our patient had stage IV endometrial squamous cell carcinoma and was treated with surgery, pelvic radiotherapy, and chemotherapy. The chemotherapy reduced the size of the lymph node metastases in the left supraclavicular, and imaging showed no recurrence of the pelvic lesions. Nevertheless, the effects of postoperative radio chemotherapy are better in patients with stage IV squamous cell carcinoma of the endometrium should be followed-up for a prolonged period.

From this case, a valuable lesson was learned on how to build a good preoperative workup and make an appropriate diagnosis. All of these are important in the prompt treatment of our patient

## CONCLUSION

PESCC is an extremely rare malignancy of the corpus uteri. Diagnosis of this rare entity is based on careful pathologic review of the hysterectomy specimen. More studies are needed to address the concern about the extension of primary surgical treatment and the efficacy of adjuvant therapy for this disease.

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