Superficial Spreading Cervical Squamous Cell Carcinoma to Endometrium: A Rare Case Report

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Abstract

Introduction: Squamous cell carcinoma (SCC) was the most common variant of cervical cancer with metastases potential to many organs, commonly parametrium and vagina, but in a rare condition can also spread to endometrium. Further evaluations are needed since superficial spreading of cervical SCC are related to poorer outcomes.

Case Presentation: A 62 y.o, post-menstrual, P3A0 women came with complaint of vaginal discharged mixed with blood since 6 months ago. Pap smear result suggestive of malignancy so the patient undergo guided biopsy from endocervix that revealed finding similar to carcinoma intraepithelial (CIN) 3. The patient underwent TAH-BSO operation. Microscopic examination from cervix showed tumor cell with round nuclei, prominent nucleoli, pleomorphic, hyperchromatic, increased nuclear-cytoplasm ratio in whole epithelial layer. Microscopic examination from endometrium showed epithelial squamous cell proliferation in almost 98% endometrial tissue and atypical cell nuclei, consistent with tumor founded in cervix. The final diagnosis was superficial endometrial spreading SCC with moderate differentiation. Immunohistochemistry (IHC) assay with p16 showed positive result in endometrium. Patient then consulted to gynecologist – oncology specialist for further treatment and evaluation.

Conclusion: Superficial spreading of cervical SCC to endometrium was a rare finding. Detection of SCC in endocervix can be considered as predictor for proximal spreading of cervical SCC so further examination like endometrial curretage are suggested to assist the early detection. IHC assay with p16 resulted positive in our patient suggesting that endometrial SCC in this patient was correlated with HPV infection that commonly find in cervical cancer.

Introduction

Cervical cancer is 1 of the 4th most common cancer found globally, squamous cell carcinoma (SCC) accounted for most of the type that were recorded.[1] SCC of the cervix can spread to many organs like parametrium and vagina, but in a rare condition this can also spread to upper genital tract like endometrium and also to

intra-abdominal organs.[2] Superficial spreading of SCC to endometrium was a rare founding, therefore the information regarded this condition are poorly known. This case was reported to improve our knowledge related to superficial spreading of SCC from cervix to endometrium.

Case Description

A 62 years old women came with a complain of vaginal discharge mixed with blood since 6 months ago. This patient already menopause at 55 years old. This patient was married at 24 years old and had 3 child birth via vaginal delivery and had a history of using intrauterine device for 5 years. The patient denied similar complaints before, denied history of cervical cancer screening or cervical procedure, nor history of multisexual partner. Pelvic examination revealed purulent discharge mixed with blood and portio erotions. The transvaginal ultrasonography suggested that there was fluid on uterine cavity, left ovarian cyst size 7.1x6.1cm was observed, the right ovarium and cavum douglas, unremarkable. Blood examination showed microcytic hipochromic anemia, the other blood panel within normal range. Conventional pap smear was conducted on the first doctor visit, intermediate squamous epithelial cell and parabasal was founded with large hiperchromatic, pleomorphic nuclear suggested as malignancy so the patient undergo guided biopsy. Guided biopsy from the endocervix showed squamous epithelial cell with rounded nuclei, pleomorphic, hiperchromatic, coarse chromatin, prominent nucleoli, mitosis was also observed in >1/2 upper epithelial area arranged in pile pattern with impression to the squamous epithelial surface. This finding suggest there was squamous epithelial cell with high-grade dysplasia, similar to cervical intraepithelial neoplasm (CIN) 3. CIN 3 finding in the endocervix was suspected to associate with proximal spreading of SCC so this patient was suggested to underwent the *histerectomy and salphingo-oophorectomy bilateral* (TAH-BSO) procedure by the gynecologist. Post-operative specimen was sent to pathology anatomy laboratorium. The gross examination revealed whitish uterus with rubbery consistency, size 6x6x5cm, cervix and both adnexa was also founded but already separated from the uterus, the cervix size 5x4x3cm, parametrium was not observed. Uterus cutting showed whitish area without clear border (**Figure 1**), then conization procedure was done to the cervix.

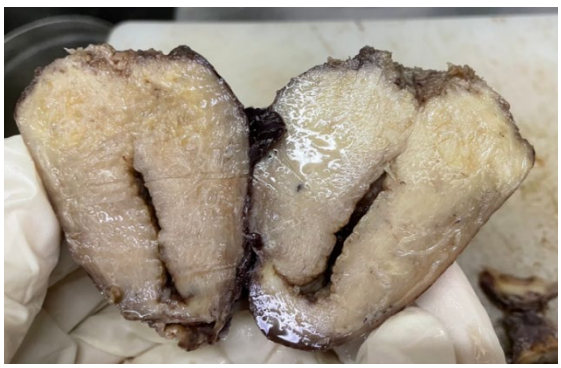

Figure 1. Gross examination of the uterus revealed whitish area without clear border.

Microscopic examination of the cervix showed cell with rounded nuclei, prominent nucleoli, pleomorphic, hiperchromatic, coarse chromatin, mitosis, increased nucleus-to-cytoplasm rasio in almost epithelial layer, part of the tumor cell showed infiltration to fibrous stroma around 3cm of the cervical stromal depth and horizontal spreading >7cm, without penetrating to the serous layer (**Figure 2A)**. Microscopic examination form the endometrium showed minimal surface that still layered by the collumnar epithelial cell, most of the endometrium (± >98%) showed squamous cell proliferation that subtitutes the endometrium stroma, cell with atypic nuclei that similar to the cervical preparation also observed **(Figure 2B)**. The miometrium examination showed tumor cell with infiltration to >1/2 miometrium depth around the smooth muscle cells, but no infiltration to the outer serous layer was founded. Final conclusion from the histopathology examination revealed keratinized squamous cell carcinoma, moderate differentiation with superficial spreading to the endometrium and infiltration to >1/2 miometrium depth (pT1B2). Possible spreading to the vagina or parametrium in this patien cannot be excluded. Immunohistochemisty (IHC) assay found positive p16 marker in the endometrium specimen (**Figure 2C)**. The patient then referred to the gynecologist sub-specialist onkologist for further evaluation and determinaton of the next plan.

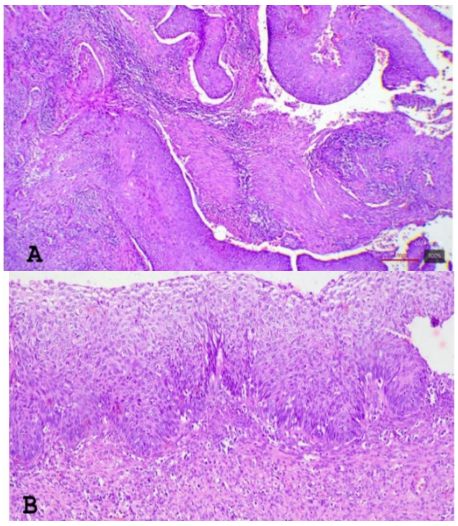

Figure 2A. Microscopic examination from the cervix (HE, 40x). **Fig 2B.** Microscopic examination from the endometrium.
Both suggestive of squamous cell carcinoma (HE, 100x).

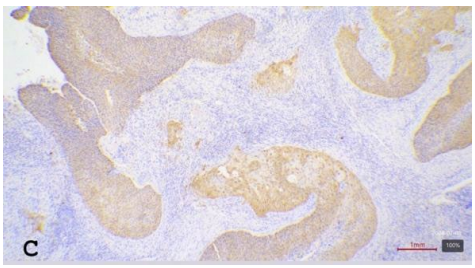

Fig 2C. IHC with p16 showed positive result in endometrium

Discussion

Cervical cancer was malignancy that arise from the cervical cell, including in 1 out of the 4th most common cancer found globally. In Indonesia, cervical cancer occupied the 2nd position as the most common cancer founded in women with estimation of 36,000 new cases each year. Almost 70% of the cases that reported in Indonesia was detected in late stage so the mortality rate related to this case increases.

In 2020, there was 21,000 women died because of cervical cancer, this count was predicted to reach 1.7 million in 2070 and will further increased into 4 million death in 2120 if early intervention was not conducted[1]. Approximately, 70-80% of cervical cancer was squamous cell carcinoma (SCC) variants. SCC of cervix can spread to other organs via direct invasion or lymphatic invasion,[8] most common to the parametrium and vagina, but in a very rare condition this can spread to upper genital tract like endometrium, fallopian tube, ovarium, and can also spread to intraabdominal organs.[\2] Superficial spreading of SCC cervix to the endometrium was a rare condition, marked by cervical SCC spreading superficially to the inner uterus surface followed by replacement of the normal endometrium cells.[3] This rare case was 1st reported in 1900, since that moment few similar cases already reported with prevalence rate around 0.7%.[2] Factor that considered play a role in this SCC spreading to the proximal organ of the cervix was long-term estrogen exposure, vitamin A deficiency, HPV infection, endometrial changes in geriatric, pyometra, radiotherapy, history of cervical procedure, early marriage, and multipara.[2,4] Superficial spreading from cervix to endometrium was thought to happen because of the similar progenitor cell so when both get the same stimulator exposure there will be a cell transformation to malignancy. Genetic factor also thought to have role in this processes, especially the loss of heterozigonity of 6p, 6q, 11p, and 11q chromosomes.[2]

A case reported 65 year-old, P3A0 post-menopausal women, with complain of vaginal discharge and post menopausal bleeding, the patient was known to have *loop electrosurigcal excision procedure* (LEETS) 33 years ago, the biopsy result suggested that there was SCC cervix with keratinization, moderate differentiated. The patient underwent TAH-BSO procedure. Histopatological examinaton reveals SCC cervix in situ with metastasis to endometrial withoud lymph node involvement, the IHC result showed positive p53 and CK 5/6 in the tumor corpus, strongly positive p16 in tumor in situ and tumor which already infiltrating the endometrium, other markers like Ca125, CK7, vimentin, p53, GATA binding protein 3, TTF1, CDX2, ER, PR showed negative result. Patient continued to have adjuvant chemotherapy post-operation and was founded to free of tumor reccurency in 8 months follow-up.[6] Another case reported 66 years-old, post-menopausal multipara women without any clinical symptoms but have atypical squamous cell result suggested malignancy in pap smear examination. The patient underwent hysterectomy. The macroscopic findings show yellowish glandular growth in the ectocervix and superficial surface of the endometrium, this was further examined microscopically with a result that confirmed both lesions as SCC with spreading to the

endometrium. The patient undergo IHC examination with strongly positive result in p16, CK5/6, p63 and high Ki67 index in squamous cell at the endometrium. This case did not mention additional data related to patient follow-up.[7] There's also another case report other than this 2, the reports shows variation in clinical characteristic but usually the superficial SCC spreading to endometrium was associated with women aged >50th years-old with clinical symptoms range from post-menopausal bleeding, vaginal discharge, pyometra, abdominal mass, low abdominal pain,[5,8] or sometimes can be found incidential post-operation.[10] Most patient with superficial spreading had a history of cervical lesions few years before and mostly underwent LEEP procedure, this finding associated with cervical stenosis which predispose to pus accumulation in uterine cavity and help the superficial spreading of SCC to endometrium.[10]

Our case report support the previous studies which state that most cases was found in women aged >55 years-old. Beside structural changes in older patient, multiparity also consider to have role in SCC with superficial spreading. Pap smear was firstly conducted to our patient but the result came with a suggestion to malignancy so our patient underwent guided biopsy from endocervix. The guided biopsy showed CIN3 in the endocervix specimen that suggested the possibility of proximal spreading of cervical SCC to the structure above. Proximal spreading of cervical SCC was a rare case so the patient underwent TAH-BSO procedure as recommended by the gynecologist. Post-operative specimen thent sent to the pathology laboratorium, further examination revealed cervical SCC with superficial spreading to endometrium as suspected by the gynecologist, this result was strengthened by positive p16 marker in IHC assay of the endometrium. p16 marker was commonly associated with cancer related to HPV infection[9] but this marker role in determine SCC origin cells in genital tract malignancy was not clearly explained[4] so we suggest to further evaluate the patient with another IHC panel. Beside supporting examination, SCC in endometrium should underwent evaluation with Fluhmann cirteria to exclude the possibility of primary SCC in endometrium which should fullfil this 3 criteria: 1) No evidence of coexisting endometrium adenocarcinoma or primary SCC of the cervix, 2) There are no associaton between endometrial tumor and squamous epithelial from cervix, 3) There are no association between cervical carcinoma in situ and independent endometrial neoplasm.[9] Our patient cannot be classified as PESSC because all the criteria was founded. Patient was consulted post-operation to the gynecologist sub-specialist onkologist for further evaluation, in 1st month post operation there are no sign of metastasis nor recurrence of the disease. Prognosis and additional therapy consideration for patient with superficial SCC cervix are still barely known due to the

minimal reported case and information about the disease, few studies reported different outcomes due to the minimal follow-up period to this cases, further studies are still needed to improve our knowledge. Minimal information available related to the disease directed us to take more detailed evaluation related to SCC cervix and the possible metastasis to further areas like endometrium, this may help us to early diagnosed and accordially will select the best available therapy to improved patient quality of life.

Conclusion

Superficial spreading of cervical SCC to the endometrium was a rare finding that commonly associate with poor outcomes. SCC founded in the endocervix might raise the possibility for superficial spreading to the endometrium and need further assessment to confirm this suspicion. Due to the rarity of primary SCC in endometrium, we should suspect for possible primary SCC lesion and assess the cancer more thoroughly with possible tools like the Fluhman criteria, in order to give the best therapeutic option for the patient.

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