Case report

Primary endometrial squamous cell carcinoma with synchronous early stage Fallopian adenocarcinoma: A case report and review of diagnostic and treatment considerations

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A B S T R A C T

Background: Primary endometrial squamous cell carcinoma (PESCC) remains a rare subtype of endometrial cancer. This case is especially unique due to the incidental finding of early stage Fallopian adenocarcinoma. This report adds to the literature of this rare condition and discusses its etiology, clinical course, and treatment regimen.

Case: 65 year old postmenopausal female presented with postmenopausal bleeding. Dilation and curettage revealed endometrial highly atypical squamous epithelial proliferation. Staging procedure showed FIGO stage IB squamous cell carcinoma of the endometrium, without evidence of cervical involvement. A small focus of incidental poorly differentiated FIGO stage IA adenocarcinoma of the left Fallopian tube was discovered. She underwent six cycles of Paclitaxel and Cisplatin, and has remained disease free for two years.

Conclusion: Primary endometrial squamous cell carcinoma is a poorly understood entity. Early diagnosis is critical due to the strong correlation between initial stage and survival. Biopsy of the cervix and endometrium should be considered in cases of abnormal uterine sampling. The case presented is a prototypical example of PESCC, both in presentation, pathology, and course. It is especially unique due to synchronous high grade Fallopian adenocarcinoma.

1. Introduction

Primary endometrial squamous cell carcinoma (PESCC) is an exceedingly rare tumor. First reported in 1892 by Gebhard, it accounts for less than 1% of all malignancies of the corpus uteri. (Gebhard, 1892; Bogani et al., 2014) Herein, we report the first case of PESCC with synchronous high-grade adenocarcinoma of the Fallopian tube.

2 Case

A 65-year-old postmenopausal female initially presented to her primary gynecologist for postmenopausal bleeding. Her PAP smear demonstrated high-grade cytologic atypia and a transvaginal ultrasound showed an abnormal uterus with a 12 mm endometrial lining and myometrium with diffusely inhomogeneous texture. Subsequent colposcopy and biopsies were obtained that showed atypical squamous cells, suspicious for carcinoma. The patient was referred to gynecologic oncology for further evaluation. Physical examination was notable for an enlarged uterus on bimanual exam. Her medical history was non-contributory and her surgical history was significant for four prior Cesarean sections and bilateral tubal ligation. The patient was a former smoker, with a four-pack-year history. She underwent menarche at 12 years old and menopause at 50 years old with no postmenopausal bleeding prior to her recent symptoms.

Hysteroscopy, dilation, and curettage with cervical conization were performed. Curettage pathology showed highly atypical squamous epithelial proliferation of the endometrium, with benign tissue obtained from conization. Multiple differential diagnoses were suggested by pathology, which included primary squamous cell carcinoma of the endometrium, squamous metaplastic change in an endometrioid adenocarcinoma with pauci-glandular proliferation, and metastatic squamous cell carcinoma to the endometrium either from a distant site or extending from the uterine cervix. P16 stain by immunohistochemistry was negative, which essentially excluded a primary squamous cell carcinoma of cervical origin (Fig. 1). The endocervical curettage only showed p16 negative atypical squamous cells. The case was discussed at...
a multi-disciplinary tumor board and surgical treatment and staging were recommended. Given the negative cervical conization, type II endometrial carcinoma was the leading differential diagnosis, and thus open cytoreduction was recommended, and radical hysterectomy was deferred. She underwent an uncomplicated exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, and omental biopsy. Her postoperative course was complicated by ileus and acute kidney injury that resolved with supportive measures. Patient was discharged on postoperative day ten. At her postoperative visit, the patient was diagnosed with a superficial wound infection that ultimately required operative debridement on postoperative day 26.

Final pathology demonstrated a 7 cm, high-grade squamous cell carcinoma of the endometrium invading the entire myometrium with extensive lymphovascular space invasion (LVSI), with no serosal involvement (FIGO stage IB). Lower uterine segment involvement was identified, but no tumor was found in the cervix. Pelvic and para-aortic lymph nodes were negative for malignancy. The wall of the left Fallopian tube had an independent, incidental 6 mm focus of poorly differentiated adenocarcinoma, favoring endometrioid type (FIGO stage IA). The fallopian tube tumor was positive for CK7, P53 (mutant type), focally positive for WT1 and PAX8, and negative for CK20, ER, PR and P16 (Fig. 2). The right Fallopian tube was benign. Brenner tumors were found in both ovaries.

Her case was discussed again at a multi-disciplinary tumor board. It was recommended for the patient to receive adjuvant treatment with six cycles of chemotherapy due to the aggressive histology involving both the uterus and Fallopian tube. The patient received six cycles of Paclitaxel 175 mg/m² and Cisplatin 75 mg/m², starting 9 weeks after surgery due to infection and delayed wound healing. She experienced a reaction to Paclitaxel during cycle 4. Docetaxel 75 mg/m² was substituted for cycles 5 and 6. On day 1 of cycle 6, after receiving her treatment, patient

Fig. 1. Highly atypical squamous epithelium in endometrial curettage. The endometrium is replaced with nests of highly atypical squamous epithelium resembling conventional squamous cell carcinoma.

Fig. 2. Primary endometrial squamous cell carcinoma and independent high-grade adenocarcinoma of the fallopian tube. The cervix is benign with reactive changes (A). The endometrium is involved by malignant squamous epithelium resembling squamous cell carcinoma of other organs with no malignant glandular component (B). An incidental adenocarcinoma of the fallopian tube (C) which is strongly positive for P53 (D) has been identified.
developed an incarcerated hernia requiring emergency surgery with small bowel resection and primary reanastomosis. A CT scan of the chest, abdomen and pelvis was obtained 1 month after completing chemotherapy and demonstrated no evidence of disease. Patient is currently being evaluated every 3 months for surveillance visits and remains free of disease at time of report.

2. Discussion

Primary endometrial squamous cell carcinoma remains a rare histologic sub-type of endometrial cancer and its description is mostly confined to case reports. The most common clinical presentations include postmenopausal bleeding or vaginal discharge. The diagnosis of PESCC was established in 1928 with clinical criteria that required exclusion of cervical carcinoma extending into the endometrium, coexistent endometrial adenocarcinoma, and contiguity between the endometrial cancer and the squamous cervical epithelium. (Bogani et al., 2014; Fluhmann, 1928) Establishing the diagnosis prior to surgical management is difficult due to the inability to distinguish the borders of the lesion based on biopsies. One of the largest case and literature reviews of PESCC, with over 60 cases included, noted an average treatment delay of 11.5 months. (Goodman et al., 1996) Despite most patients receiving multiple exams and biopsies prior to hysterectomy, only 50 % of women had a preoperative diagnosis of PESCC. (Goodman et al., 1996) Interestingly, approximately half of the patients studied had abnormal Pap smears, but only 17 % of these were actually diagnostic of carcinoma. (Goodman et al., 1996) Given the rarity of PESCC, any atypical squamous proliferation obtained on an endometrial sampling, whether via endometrial biopsy or curettage, could be reasonably assumed to be contamination from a cervical primary. This case was atypical due to the endometrial and cervical sampling prior to surgery, which demonstrated a discrepancy that suggested PESCC. In such an atypical situation, thorough evaluation of the endometrial cavity in addition to sampling of the cervix enabled adequate tissue to assist in an accurate preoperative pathologic diagnosis. Determining the correct primary site is crucial to provide appropriate and timely treatment for this rare entity. Given the significant difference in treatment approach between cervical and uterine carcinoma, the importance of determining the primary site cannot be overstated.

The etiology of PESCC is largely unknown, however there are a few hypotheses. First noted in 1885, many researchers suggest a hypothesis of ichthyosis uterus, wherein uterine irritation leads to total squamous differentiation of the endometrium. (Bogani et al., 2014; Murhekar et al., 2008) This irritation can be iatrogenic (radiation), inflammatory (e.g. pelvic inflammatory disease, cervical stenosis), or from other chronic conditions (e.g. vitamin A deficiency, senile involution). (Bogani et al., 2014; Murhekar et al., 2008; Patton et al., 1962) Though some hypothesize a shared pathway with cervical cancer, there is limited data to support this. (Bogani et al., 2014; Goodman et al., 1996; Wu et al., 2018; Thomakos et al., 2008; Katoaka et al., 1997) Notably, many risk factors associated with endometrioid adenocarcinoma of the uterus, such as obesity and hyperestrogenism, do not appear to correlate with PESCC. (Goodman et al., 1996) Published reports consistently agree that age is a significant risk factor for the development of PESCC, with the average age of diagnosis 65 years old or above.

The overall prognosis for PESCC is generally poor. Despite surgery and radiation, the survival rates are worse than uterine adenocarcinomas, making early diagnosis and treatment paramount. (Bogani et al., 2014; Goodman et al., 1996) Though rarely discovered, early stage PESCC has a better prognosis, with an 80 % survival rate with a median follow-up time of 32 months. (Goodman et al., 1996) Late-stage disease is almost uniformly fatal within one year of diagnosis. (Goodman et al., 1996).

Due to the scarcity of cases, there has yet to be a consensus regarding treatment options for patients with PESCC and treatment is typically individualized. Most reported cases describe primary surgical treatment with total hysterectomy and bilateral salpingo-oophorectomy. (Goodman et al., 1996) Method of surgical approach is not consistent among reported cases. In our case, the patient underwent an open staging procedure without a radical hysterectomy. The choice of open versus minimally invasive surgery was chosen due to the high presurgical suspicion for an endometrial primary site. Laparotomy is the preferred method of cytoreduction of type II endometrial carcinoma at our institution. The negative pathology obtained from cervical conization allowed the avoidance of radical hysterectomy. There are no consistent recommendations regarding the inclusion of pelvic lymph node dissection (PLND) along with primary surgical treatment. Though commentary on this decision was not included, it is notable that only 4 of the 49 cases available for review included PLND. (Goodman et al., 1996; Kennedy et al., 1995) Reported cases typically provide adjuvant platinum-based chemotherapy and/or radiation, with varying efficacy. (Bogani et al., 2014; Im et al., 1995; Goodrich et al., 2012; Kennedy et al., 1995) Our patient received adjuvant treatment with 6 cycles of Cisplatin and Paclitaxel without radiation, and has remained without evidence of disease for two years since diagnosis. Choice of chemotherapy regimen was based upon the mixed pathology found in this case, with paclitaxel added to cisplatin in deference to the incidental finding of Fallopian tube carcinoma. Radiation was deferred, as all lymph nodes were negative and there was no evidence of cervical involvement.

Interestingly this case had two incidental pathologic findings, stage IA high-grade Mullerian adenocarcinoma confined to the left Fallopian tube, as well as bilateral ovarian Brenner tumors. Synchronous tumors of the upper female genital tract occur in approximately 1 % of gynecologic malignancies, with coexistent ovarian and endometrial carcinomas compromising approximately half of these cases. (Eisner et al., 1989; Gungor et al., 2009) To the best of our knowledge, this is on the only report of synchronous PESCC and Fallopian adenocarcinoma. Luckily for this patient, the Fallopian adenocarcinoma discovered was only FIGO stage IA, but a taxane was added to this patient’s chemotherapy regimen due to its presence on pathology. While the Brenner tumor was less clinically significant, this is only the second recorded case of PESCC found along with a Brenner tumor. (Goodrich et al., 2012; Adhya and Mohanty, 2019) There have been a few recorded incidents of Brenner tumors associated with cervical squamous cell carcinoma (SCC), and prior case reports have shown ovarian SCC arising within Brenner tumors. (Goodrich et al., 2012; Adhya and Mohanty, 2019).

3. Conclusion

Primary endometrial squamous cell carcinoma is a rare entity. Though the pathogenesis is unknown, there is increased incidence in older, postmenopausal patients. The case presented herein is an excellent prototypical example of PESCC, both in presentation and pathology. Strict adherence to diagnostic criteria and utilization of ancillary studies are necessary to differentiate PESCC from cervical SCC. This patient required several procedures before receiving definitive surgery, but her diagnosis was not significantly delayed when compared to the reported delay in treatment published by other authors. Early diagnosis is critical due to the strong correlation between the stage of PESCC and survival, and sampling of both the endometrium and cervix should be considered when endometrial sampling is suggestive of squamous neoplasia. Treatment with primary total hysterectomy and bilateral salpingooophorectomy is typical with consideration given to adjuvant therapy based on clinical factors and multidisciplinary review. As the aging population grows, there may be an increased incidence of this condition. Given the rarity of this disease, more information is needed to clarify and define the etiology, clinical course, and treatment regimen for these patients.

CRediT authorship contribution statement

Margaret Caulkins: Conceptualization, Investigation, Resources,
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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