Primary squamous cell carcinoma of the endometrium: a case report

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Summary

Purpose of investigation: Primary squamous cell carcinoma of the endometrium (PSCCE) is an extremely rare entity. *Methods:* We present the clinical and pathological findings of a 90-year-old patient with International Federation of Gynecologists and Obstetricians Stage 1C primary squamous cell carcinoma of the endometrium who was treated with hysterectomy and bilateral salpingo-oophorectomy. *Results:* The patient declined adjuvant therapy and continues on progestin therapy. She was free of disease at a one-year follow-up visit. In addition, the current literature is discussed in this report. *Conclusions:* Since primary squamous cell carcinoma of the endometrium is so infrequent, it is difficult to evaluate the efficacy of adjuvant therapy. Although the prognosis historically has been reported as poor compared to endometrial adenocarcinoma, the prognosis does seem to be dependent on the surgical stage at diagnosis rather than on the adjuvant treatment component.

Key words: Endometrial cancer; Squamous epithelium; Primary squamous cell carcinoma of the endometrium; HPV; Treatment; Follow-up.

Introduction

Squamous epithelium in the uterine cavity has been reported in association with benign uterine pathologies, but occasionally it may be found in relation to malignancy of the endometrium, appearing as a benign component in adenoacanthoma or as a malignant component of an adenosquamous carcinoma [1]. Although up to 30% of endometrial carcinomas present with squamous cell differentiation [2], primary squamous cell carcinoma of the endometrium (PSCCE) is extremely rare and represents less than 1% of endometrial carcinoma cases [3]. Gebhard described the first substantiated case in 1892 [4]. Furthermore, in 1928, Fluhmann [5] proposed three criteria to determine with precision that a squamous carcinoma is a primary neoplasia of the endometrium: 1) A coexistant adenocarcinoma of the endometrium must not be present. 2) There should be no connection between the tumor and the squamous epithelium of the cervix. 3) Absence of primary squamous cell carcinoma of the cervix. In 1975, the WHO extended Fluhmann's criteria and added a fourth criterion: There must be clear evidence of squamous differentiation in the tumor such as intercellular bridges and/or keratin [3, 6]. The diagnosis demands meticulous histological examination, especially with regard to the microscopic appearance of the cervical area [7]. Since Gebhard's initial report in 1892 [4], the literature contains less than 100 cases fulfilling the previously cited four criteria.

The management of PSCCE is mainly surgical with abdominal hysterectomy and bilateral salpingo-oophorectomy as the most frequently used procedures [8, 9]. Radical hysterectomy with pelvic lymphadenectomy has also been reported as the treatment of choice in some cases [8]. Postoperative adjuvant chemoradiation has been used in selected cases. However, since the condition occurs so infrequently, it is difficult to evaluate the efficacy of this additional therapy [9]. Although historically the prognosis of PSCCE has been reported as poor compared to endometrial adenocarcinoma [9], the prognosis does seem to be dependent on tumor stage emphasizing that early diagnosis and treatment are imperative.

The purpose of this case study is to report the clinicopathological features of a recent case of PSCCE and to discuss the current literature.

Case Report

A 90-year-old multiparous 60 kg Caucasian female presented with a 5-day history of postmenopausal bleeding. She did not have a history of abnormal pap smears or hormone replacement therapy use. A CT of the abdomen/pelvis was performed showing the endometrial cavity to be fluid-filled with thickened uterine walls. No focal uterine or adnexal masses or lymphadenopathy were apparent. A pelvic ultrasound measured the uterus to be 10.5 cm x 5.4 cm x 6 cm with an endometrial stripe of 2.2 cm and atrophic adnexa. An endometrial biopsy was reported as poorly differentiated squamous cell carcinoma.

The patient was referred to our institution for additional evaluation and management. The patient was counseled on her options in view of her age and associated comorbidities including definitive surgical management, radiation therapy or continued observation with progestin therapy. She underwent exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy without complications. Intraoperative findings showed a normal upper abdomen and no palpable lymph nodes.

Cytologic examination from pelvic washings was negative. Grossly, the uterine cavity showed a 5 cm x 4.5 cm exophytic

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Fig. 1

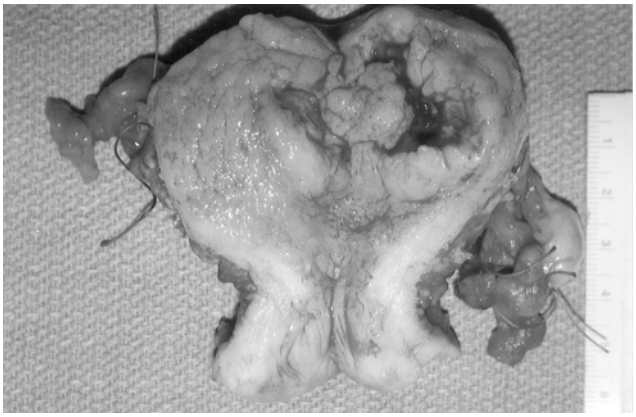

Fig. 2

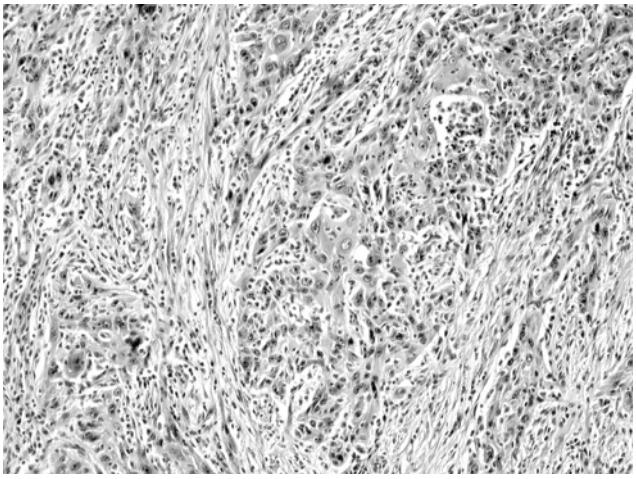

Fig. 3

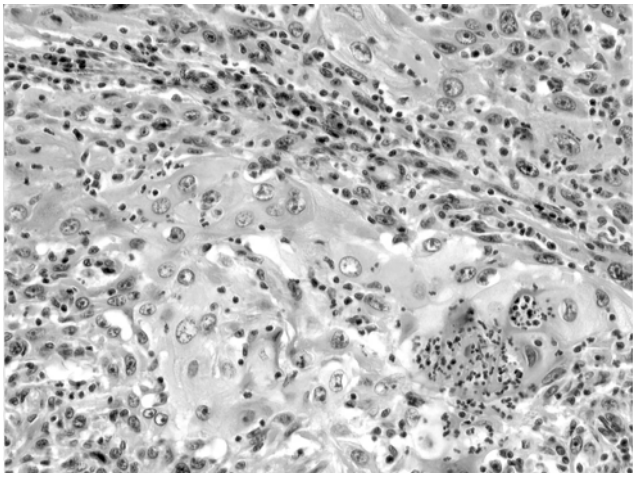

Figure 1. — Gross picture of the uterus with endometrial cavity filled by a vegetating friable mass.

Figure 2. — Microscopic examination of the mass showing the tumor is composed of spindle cells infiltrating through the entire thickness of the myometrium.

Figure 3. — Higher magnification of the tumor showing tumor cells exhibiting keratin pearls with extensive neutrophilic infiltrates.

mass filling the uterine cavity (Figure 1). Histological examination showed an invasive poorly differentiated squamous cell carcinoma of the endometrium with 98% myometrial thickness invasion (13.8/14mm) and extension to the lower uterine segment (Figure 2). There were frequent keratin pearls throughout the tumor (Figure 3). Extensive tumoral neutrophilic infiltrates were also present. The cervical mucosa was unremarkable. Both adnexes were unremarkable. Immunohistochemistry studies for estrogen and progesterone receptors were negative and tumor cells were focally positive for p16.

The patient was discharged home on the seventh postoperative day. Further treatment options were reviewed with the patient and she declined radiation or chemotherapy treatment at that time. She continues on oral progestin therapy and was doing well at her 12-month follow-up visit.

Discussion

The pathogenesis of squamous cell carcinoma of the endometrium continues to be controversial. Two theories have been offered to explain the pathogenesis of PSCCE: the vertical field theory and the squamous metaplasia theory [6, 10, 11]. The vertical field theory implies a local mechanism within the uterine corpus arising from an abnormal population of reverse cells adjacent to the basement membrane. Radical growth eventually replaces normal endometrium by neoplasia and vertical growth invades the myometrium [6, 10]. The squamous metaplasia theory suggests that endometrial squamous metaplasia is a potential precursor of squamous cell carcinoma [6, 11]. Indeed, some investigators claim that squamous metaplasia is always a pathological process, and may be a precursor to the development of squamous cell carcinoma [11]. Factors implicated in the development of squamous metaplasia include various infectious and foreign irritants including pyometra and intrauterine devices, fibromyoma, vitamin A deficiency, hormonal disturbances (deficiency as well as excess of estrogen hormones), uterine prolapse or inversion, pelvic irradiation, and chemical agents [11]. However, in a review of 34 cases of PSCCE, squamous metaplasia was documented clearly in only 11 cases, suggesting that endometrial squamous metaplasia is not a definitive precursor of PSCCE [12]. Several other factors have been discussed as being influential in the development of PSCCE. HPV has been implicated strongly in squamous neoplasms of the lower genital tract and has also been identified in the squamous component of endometrial adenocarcinoma [6, 10]. In case reports using DNA primers for HPV and in situ hybridization, HPV was not detected and appears to be an unlikely carcinogenic factor in the development of PSCCE [2, 6, 10, 12-13]. The expression of p16, p14, p53, cyclin D1, and steroid hormone receptors (estrogen, progesterone, and androgen) has also been examined immunohistochemically in eight PSCCE cases [14]. All

but one case was negative for HPV analysis. One case was positive for estrogen receptors, four cases were positive for progesterone receptors, and none of the cases showed androgen receptor immunostaining. The results of that study suggest that alterations of the p16 pathway may play an etiologic role in at least a proportion of PSCCE, but without any association to HPV infection [14]. In our case, p16 was focally positive and estrogen/progesterone receptors were negative.

In a comprehensive review of the literature, Goodman *et al.* described the clinical characteristics of 64 patients with PSCCE [9]. As described in the case above, most cases of PSCCE present in postmenopausal women with an average age of 67 years (older than most patients with corpus carcinoma). Eighty-eight percent (37/42) of the cases reviewed were recorded as Caucasian and the average weight in their six cases was 136 pounds. Of the 48 patients whose parity was known, 17 (35%) were nulliparous. Nulliparity, presumed to be secondary to chronic anovulation, has been cited as a risk factor for carcinoma of the endometrium in general, with frequencies ranging from 18 to 40% [11]. In seven of 41 cases in which information was available, the patient was recorded to have taken estrogens (17%); in one additional case tamoxifen was used. Six patients had previous cancers: three breast carcinomas, two colon carcinomas, and one concurrent ovarian carcinoma. In addition, a review of these 64 cases for predisposing factors revealed that 20 patients presented with pyometra [9]. The etiology of a pyometra has been described by Yamashina and Robara and attributed to the tendency of PSCCE to undergo necrosis; a relatively late discovery of PSCCEs; and poor drainage due to polyploidy growth of tumors and a nulligravida state of the patient [15]. It also has been suggested that pyometra and chronic infection may be the result rather than the cause of the disease [2, 9]. In addition, three patients had uterine inversion or prolapse and five had a history of pelvic radiation. Cervical stenosis was stated to be present in four patients [9]. In our case, we could not identify any risk factor. The presenting signs and symptoms in these 64 cases were postmenopausal bleeding (68%), vaginal discharge (28%), pain (17%), weight loss (6%), pelvic mass (6%), brain metastases (1.5%), and more than one sign/symptom (39%) [9]. Cervical or vaginal smear status was known in 32 cases of which 15 were abnormal [9].

The diagnosis of PSCCE should be considered in postmenopausal women whose smears show abnormal squamous cells and in whom there is a negative cervical biopsy [1, 9]. It is suggested that cytology permits earlier and more accurate diagnosis [1, 9]. However, the final diagnosis of PSCCE should be made on the hysterectomy specimen. Hysterectomy with bilateral salpingo-oophorectomy was the primary treatment in 62 of the 64 cases [9]. Although it is difficult to evaluate the efficacy of additional therapy, postoperative adjuvant chemoradiation has been used in selected cases [9, 10].

Although historically the prognosis has been reported as worse than for the more common adenocarcinoma, adenocanthoma, and adenosquamous carcinoma, Goodman *et al.* reported the evaluable outcome data in 42 of their 64 cases presented [9]. All the patients with surgical Stage I tumors (8/8) survived with a median survival of 45 months (range 14-114 months), suggesting that a tumor that is confined to the uterus, regardless of the grade and depth of myometrial invasion, has a good prognosis [9]. Similar to other types of endometrial cancer, vascular space invasion appears to be a risk factor for recurrence. In contrast, all six patients with Stage IV disease (median time to death 17 months, range 5-18 months), and 80% (8/10) with Stage III disease, died despite adjuvant therapy [9]. Our patient had Stage I disease and we can speculate a good survival rate despite her decline to undergo adjuvant therapy.

Conclusion

Vaginal bleeding and discharge, pyometra, abnormal squamous cytologic findings, or combinations thereof that are unexplained after thorough evaluation of the cervix require further investigation. Cytology seems to permit earlier and more accurate diagnosis. Therefore, abundant benign-appearing squamous epithelium on a curettage specimen obtained from the endometrial cavity in a postmenopausal patient usually warrants a hysterectomy because of the possibility of carcinoma [9]. After definitive surgical therapy, postoperative adjuvant chemoradiation has been used in selected cases. However, since PSCCE is so infrequent, it is difficult to evaluate the efficacy of this additional therapy [9, 10] Although the prognosis of PSCCE historically has been reported as poor compared to endometrial adenocarcinoma, the prognosis does seem to be dependent on the surgical stage at diagnosis rather than on the adjuvant treatment component [8, 9, 11].

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