Primary squamous cell carcinoma of the endometrium. A report of 3 cases

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Summary

Primary squamous cell carcinoma of the endometrium (PSCCE) is a rare disease of unknown etiology. Diagnosis is based on the identification of squamous cell carcinoma in the endometrium with no coexisting analogous cervical component or endometrial adenocarcinoma. There must also be no connection between the endometrial tumour and the squamous epithelium of the cervix. Although the majority of patients are classified as stage I disease, prognosis is rather dismal.

We report two new cases of primary squamous cell carcinoma of the endometrium which fulfill all the above criteria and we discuss another interesting case of squamous cell carcinoma of questionable endometrial origin.

Management by abdominal hysterectomy and adjuvant pelvic irradiation resulted in long-term survival of our patients.

Key words: Primary Squamous Cell Carcinoma of the Endometrium; Adenocarcinoma of the Endometrium; Squamous Cell Carcinoma of the Cervix.

Introduction

Primary squamous cell carcinoma of the endometrium (PSCCE) is rarely reported in the literature. Since 1928 when Fluhman first reported the issue and established the criteria for diagnosis of PSCCE, 50 cases of the disease have been reported and reviewed.

Diagnosis of PSCCE is based on the following criteria: 1) No coexisting endometrial adenocarcinoma, 2) no coexisting cervical squamous cell carcinoma (SCC) and 3) no connection between endometrial SCC and the squamous epithelium of the cervix [1-3]. To these criteria described by Fluhman, the World Health Organization (WHO) added that "there must be clear evidence of squamous differentiation in terms of intracellular bridges and/or keratin" [4, 5].

Prognosis of primary SCC of the endometrium is reported as poor compared to endometrial adenocarcinoma [6].

Management of PSCCE is basically surgical with abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH & BSO) as the most frequently used procedures. Radical hysterectomy with pelvic lymphadenectomy (PLND) is also reported as the treatment of choice in some cases [2, 6]. Adjuvant irradiation in terms of intravaginal brachytherapy to the vaginal surface and/or external beam irradiation to the pelvic area is usually given to prolong survival with ambiguous results [2, 6, 7].

In the present study we add three cases of SCCE and we report our experience with emphasis on the strict diagnostic criteria and disease prognosis.

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Case Reports

Three cases of PSCCE are reported. These cases were found out of a total 1,422 patients with endometrial carcinoma (0.2%) who were managed at the Gynecologic Oncology Unit of the 1st Department of Obstetrics and Gynecology of the University of Athens in Alexandra Hospital during the years 1985 to 1996.

The histories of these three cases are outlined below along with the management of the disease and the available follow-up.

Case 1

A 68-year-old woman, G.E., gravida 4, para 2, menopause at the age of 49, complained of lower abdominal pain and high fever. Gynecologic examination showed an enlarged and painful uterus. The patient was admitted to the Gynecologic Oncology Unit of Alexandra Hospital where she underwent a diagnostic work-up. An upper and lower abdominal CT-scan was negative but there was an enlarged uterine body inconclusive of the primary origin. The examination under anaesthesia (EUA) showed an enlarged mobile uterus with no parametrial infiltration or shortening. A fractional D & C revealed an ESCC restricted to the endometrial fraction. The patient was classified as stage I by FIGO guidelines.

An abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Histopathology showed a Grade II endometrial squamous cell carcinoma (Figures Ia, Ib). The tumour was in an exophytic form in the endometrial cavity with dimensions of 4x4x2.5 cm invading the myometrium. Intercellular bridges and keratinization were present and no connection of the tumour with the squamous epithelium of the cervix was found. There was no evidence of adenocarcinoma of the uterine body (with dimensions of 11x8x4.5 cm). Multiple sections from the cervix showed no tumour and both ovaries and fallopian tubes were also free of disease. Cytologic sampling from intraperitoneal washings was negative. Postoperative adjuvant external beam irradiation was given to the pelvic area (up to 5,000 rads).

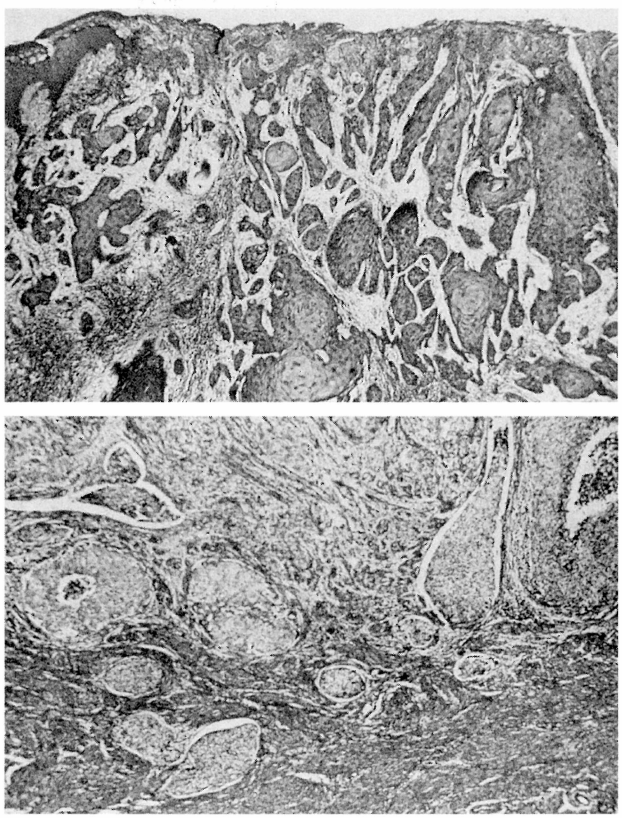
The patient was put on regular follow-up every three months and has been alive and free of disease for 54 months (since June 1995).

Case 2

A 61-year-old woman, P.A., gravida 1, nulliparous with a history of one induced abortion, menopause at the age of 50, was refferered to our hospital due to profused postmenopausal bleeding. The patient's history was free from serious diseases and her pap smear history was reported as normal – even the last smear taken one month before. A fractional D & C showed fragments of a moderately to poorly differentiated SCC restricted to the endometrial fraction. Endocervical scrapings were negative. The uterus (EUA) was partially mobile with left parametrial shortening. The patient was assigned to FIGO stage I. A radical (type II) hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy was performed. Histopathological examination showed a poorly differentiated keratinizing endometrial squamous cell carcinoma, invading the myometrium with capillary-like space involvement (Figure 2). Normal atrophic endometrium was found with no evidence of adenocarcinoma. Intracellular bridges and keratinization were also present. The cervix and both ovaries and tubes showed no tumour. All 34 pelvic lymph nodes resected (21 from the left and 13 from the right parametrium) showed no evidence of metastatic disease. External beam irradiation to a dose of 5,000 rads was administered to the pelvis as adjuvant treatment. The patient was put on regular follow-up every three months and is alive and free of disease 36 months after the completion of the primary treatment (since December 1996).

Case 3

A 70-year-old woman, S.A., gravida 6, para 5, 19 years postmenopausal was referred to our Unit because of an enlarged uterus found on ultrasound after she had experienced lower abdominal pain for two months.



A

B

Figures 1a-1b. — Endometrial squamous cell carcinoma - Case 1.

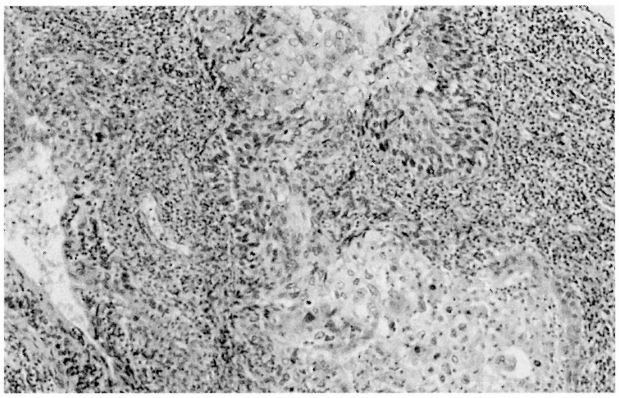


Figure 2. — Endometrial squamous cell carcinoma - Case 2.

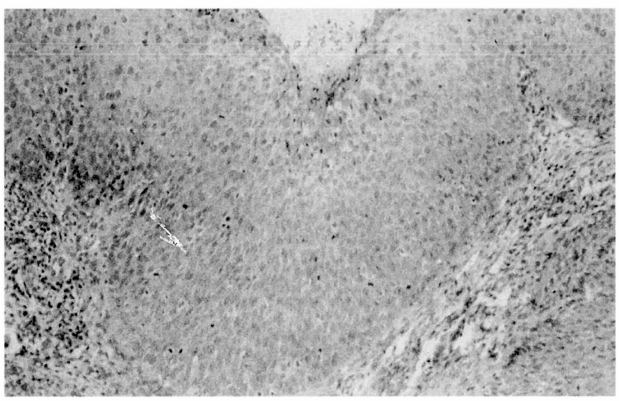


Figure 3. — In situ squamous cell carcinoma of the endometrium - Case 3.

D & C was unable to be performed due to an obliteration of the external cervical os. There was no parametrial involvement and the lower and upper abdominal CT-scan was negative. The patient underwent a wide abdominal hysterectomy with bilateral salpingo-oophorectomy and she had an uneventful postoperative course. Histopathological gross examination showed a uterus measuring 9x5x3.5 cm with an adjacent vaginal rim of 0.9 cm. The cervix measured 2x2x1 cm. The endometrial cavity measured 4x2.5 cm and had a polypoid nodule of 2 cm in diameter. Both adnexae were normal. Microscopic examination revealed moderately-differentiated squamous cell carcinoma of the cervix invading 2/3 of the depth of cervical tissue with no extension to the isthmus.

The endometrial cavity in two separate positions (on the endometrial polyp and fundus, respectively) was replaced by an in situ squamous cell carcinoma, a non-keratinizing large cell-type (Figure 3). There was no myometrial or capillary-like space involvement and the in situ component was not in connection with the cervical carcinoma with normal atrophic endometrial mucosa in between. There was no tumour involving the fallopian tubes or ovaries.

The patient received postoperative adjuvant radiotherapy with external beam irradiation and brachytherapy to the vaginal vault (up to 6,500 rads).

Follow-up was negative for 18 months when the patient was admitted to hospital with a large pelvic recurrence infiltrating the pelvic wall and developing a left ureteral obstruction requiring a stent catheterization. The patient died two months later from a large bowel obstruction.

Discussion

The etiology of primary squamous cell carcinoma of the endometrium is unknown. These tumours are considered as primary only in cases where a squamous cervical lesion is ruled out [8, 9, 10]. Squamous cell carcinoma of the endometrium either intraepithelial or invasive is also very rare.

In the past two possible histogenetic mechanisms were implicated. Thus a primary cervical lesion extending upward to the endometrium or a transformation of omnipotent reserve cells lying beneath the columnar epithelium could give rise to a SCCE [11-13].

Currently the possibility of malignant transformation of endometrial squamous metaplasia is also being investigated [11, 14]. Operability is a prerequisite to establish diagnosis in ESCC whereas in patients treated by irradiation either preoperatively or as a sole modality it is impossible to confirm the histology set by the D & C. Thus, if no tumour is left in the hysterectomy specimen after irradiation or in inoperable tumours, documentation of ESCC is impossible because a squamous cell carcinoma of cervical origin can not be excluded. Analogous diagnostic difficulties have arisen in cases of a presumed stage II ESCC where infiltration of the upper part of the cervix could not be differentiated from a primary SCC of the cervix [4, 14-16]. All these cases where diagnosis is difficult or impossible to be established are usually excluded from articles reviewing the reported cases of PSCC of the endometrium.

In contrast preoperative diagnosis of squamous cell carcinoma of the endometrium may be difficult since curettage specimens may show only well differentiated squamous epithelium [17].

Out of the three cases reported in the present study, only the first two fulfill all the Flushman criteria. Thus, in the two cases there was no malignant tumour of the cervix found nor an adenocarcinoma of the endometrium. Intracellular mucin was not found in any case whereas keratinization and intracellular bridges were present in both tumours.

In the third case of our report both the cervix and the endometrium were involved with SCC. Such cases are in the literature and the most likely diagnosis is considered to be primary SCC of the cervix [4, 15, 16, 18]. In our case there was no correlation of the two neoplasms and intervening normal atrophic glandular epithelium was present inbetween. Additionally D & C did not precede the final histology, thus this uterine histologic evaluation accurately showed the presumed natural process of the disease. The presence of an intraepithelial squamous component in two different sites on the endometrium could be considered either a missed metastatic cervical lesion or a second primary endometrial disease.

The average age of our three cases was 66.3 years (range from 61 to 70) compared to an average of 63.3 years in previously reported cases (range 47 to 86) [19]. Postmenopausal bleeding reported as the most common presenting symptom seen in 71% of ESCC cases, was associated with one of our cases [19]. Pyometra has also been reported in the literature as a common symptom found in 29-31% of cases [3, 20-24]. In our report two patients presented with pyometra or uterine enlargement.

The relationship between squamous metaplasia of the endometrium and ESCC remains controversial. Squamous metaplasia in the endometrium coexisting with some of the reported cases of ESCC has been considered as a precancerous lesion of the disease [11, 22, 25-29]. Thus some conditions associated with ESCC such as vitamin A deficiency, presence of chemicals in the uterus, curettage, as well as pyometra or uterine inversion, and irradiation to the pelvis could cause squamous metaplasia of the endometrium, a potential precursor of squamous cell carcinoma [3, 11, 14]. Squamous metaplasia was not found in any of our cases.

Estrogen deficiency associated with squamous changes of the endometrium have also been found in ESCC cases [12]. All our cases were postmenopausal and the estrogen deficiency resulted in an atrophic endometrium.

Previous radiation therapy, considered as a cause of squamous metaplasia, has been reported to increase the risk of a second malignancy from the bladder, ovaries and endometrium [3, 30, 31]. However radiation treatment did not precede the diagnosis of ESCC in any of our cases.

Considering the extent of the disease it has been reported that myometrial invasion was noted in 85% of ESCC cases, with more than 50% invasion of the myometrium in 66% of cases [19]. In two of our cases where invasive ESCC was diagnosed, the disease invaded the myometrium only superficially in one and was restricted to an exophytic endometrial polypoid tumour in the second case. Deep myometrial involvement was not found in any case.

Optimal management of primary SCCE is difficult to determine due to the rarity of the disease, the lack of treatment protocols and the great variety of modalities used.

Although total abdominal hysterectomy is reported as the mainstay of management (in 53% of cases), combined treatment approaches consisting of surgery and radiotherapy either pre- or postoperative (in 38% of cases), surgery, radiotherapy and chemotherapy or surgery and adjuvant chemoradiation have been reported in the past [32-36].

In all of our cases adjuvant radiation was offered and prognosis was rather good for both primary ESCC cases, whereas prognosis of the third case with a cervical squamous cell carcinoma was dismal.

The precise 5-year survival rate of ESCC is difficult to determine due to inadequate follow-up and the advanced age of the patients. Both our primary ESCC cases were alive 54 and 36 months post-diagnosis, respectively, with no evidence of metastatic disease, whereas the third case with intraepithelial endometrial and invasive cervical disease died 20 months after the operation.

The rather good prognosis of our primary SCCE cases could be because of the lack of myometrial invasion and the adjuvant radiation offered to these patients. The third case with a cervical squamous cell carcinoma component

had a spread pattern and site of recurrence resembling cervical rather than endometrial carcinoma.

In summary by reporting our experience and reviewing previous reports, primary endometrial squamous cell carcinoma is a rare disease of unknown etiology with no well established treatment strategies. Early stage disease and aggressive management by combined surgery and irradiation seem, at least in our two cases, adequate to control the disease. Although additional irradiation has not improved prognosis in previous reports, prognosis does seem to be dependent on the presence of deep myometrial invasion and metastases rather than on the adjuvant treatment component [11, 12, 14, 18, 27, 37, 38].

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