Superficial spreading cervical squamous cell carcinoma \textit{in situ} involving the endometrium: a case report and review of the literature

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Abstract

Background: The spread of cervical squamous cell carcinoma to the inner surface of the uterus with replacement of the endometrium is rare. Continuity of the lesion must be demonstrated to confirm superficial spread and rule out concomitant endometrial cancer.

Case presentation: We present the case of a 66-year-old white woman with superficial spreading squamous cell carcinoma of the cervix that involved the endometrium. Her relevant past history included conization of the cervix to treat cervical intraepithelial neoplasia III with positive margins. She subsequently had three negative cervical vaginal cytology results, each with a positive high-risk human papillomavirus test. Transvaginal ultrasound showed occupation of the entire uterine cavity by dense material consistent with pyometra in addition to myometrial thinning due to tension and cervical dilation. The patient presented with greenish vaginal discharge of 3 months' duration. The cervix was not visible during speculum examination. Access for endometrial sampling was not possible, raising suspicion of post-conization cervical stenosis. The patient was treated with laparoscopic hysterectomy with double adnexectomy. Histologic examination showed superficial squamous cell carcinoma invading the cervix to a depth of 2.8 mm; superficial spreading squamous cell carcinoma \textit{in situ} was also observed in the lower uterine segment and endometrium. The patient was free of symptoms 12 months after surgery.

Conclusions: Squamous cell carcinoma of the cervix with superficial spread to the endometrium is not included in the 2020 (fifth edition) World Health Organization Classification of Female Genital Tract Tumors or the 2018 International Federation of Gynecology and Obstetrics cervical cancer staging system. More clinical cases are needed to identify other prognostic factors and inform clinical practice guidelines on the management of this disease.

Keywords: Cervical squamous cell carcinoma, Endometrium, Papillomavirus, Superficial spreading, Case report

Background

Squamous cell carcinoma (SCC) accounts for approximately 80% of all cervical cancers and is the fourth most common cancer in women worldwide [1]. Superficial spreading SCC is a form of cervical SCC that extends superficially to the inner surface of the uterus, replacing the endometrium. There are insufficient data to compare superficial spreading SCC of the cervix with other types of cervical cancer. More clinical cases are needed to identify additional prognostic factors and inform clinical practice guidelines on the management of this disease.

Case presentation

The patient was a 66-year-old white woman who had had six pregnancies (four live births via Cesarean delivery and two miscarriages) and reached menopause at age 51 years. She did not smoke tobacco or drink alcohol.
She had a history of hypertension and dyslipidemia and is currently taking enalapril and atorvastatin. She has no remarkable family history. In her country of origin, she had undergone conization of the cervix to treat cervical intraepithelial neoplasia (CIN) III with positive margins in 2011. She did not attend any follow-up appointments. In 2014, she presented for clinical evaluation and had a normal cytology result, but tested positive for high-risk human papillomavirus (HR-HPV); colposcopic examination showed no apparent lesions. The patient visited our clinic for the first time in 2015 and underwent cervical and vaginal cytology. She was asymptomatic at the time. The sample was satisfactory for analysis and tested negative for atypical cells and positive for HR-HPV 16. Co-testing was scheduled for a year later, but the patient did not attend the appointment and was lost to follow-up. She returned in 2020, presenting with greenish vaginal discharge of 3 months’ duration. The cervix was not visible during speculum examination; a point-like orifice consistent with the cervical canal was observed towards the right of the vaginal fornix. It was not possible to gain access for endometrial sampling, and post-conization cervical stenosis was suspected. Transvaginal ultrasound showed occupation of the entire uterine cavity by dense material consistent with pyometra, in addition to myometrial thinning due to tension and cervical dilation. Cervical and vaginal cytology was negative for atypical cells and positive for HPV 16. Contrast-enhanced computed tomography of the abdomen and pelvis (Fig. 1A) confirmed the presence of pyometra (139 mm × 70 mm × 61 mm). The staging study was negative. The patient was treated with laparoscopic hysterectomy with double adnexectomy. Examination of the abdominal cavity showed no abnormal findings. The physical and neurological examination on admission was normal. Upon arrival, her vital signs were blood pressure 130/80 mmHg, pulse rate 80 beats per minute, respiratory rate 20 breaths per minute, and body temperature 36.8 °C. The results of routine blood tests showed a normal blood cell count; hemoglobin (Hgb) 12.1 g/dl, leukocytes (10 × 10³/μl), neutrophils: 7 × 10⁹/L, platelets 250 × 10⁹/L, negative C-reactive protein (CRP; < 0.5 mg/L). Screening for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) serologies were done and found to be negative. Furthermore, liver enzymes, coagulogram, urea and creatinine, and acid–base status of the blood were normal. During admission, intravenous analgesia was prescribed with 1 g of paracetamol every 8 hours. The patient was discharged on clinical day 1 and hemodynamically stable. Oral antiinflammatories were prescribed as needed, and she did not require readmission. Follow-up visits were every 4 months. The patient was symptom free 12 months after surgery.

Histologic examination showed superficial SCC invading the cervix to a depth of 2.8 mm and occupying all quadrants; p16 staining was positive. The diagnosis was HPV-associated SCC. Superficial spreading SCC in situ was also observed in the lower uterine segment and
endometrium (Fig. 1B, C). There were no signs of lymphovascular invasion or infiltration of the fallopian tubes or ovaries. SCC of the cervix with superficial spread to the endometrium is rare. It is not included in the 2020 (fifth edition) World Health Organization (WHO) Classification of Female Genital Tract Tumors or the 2018 FIGO (International Federation of Gynecology and Obstetrics) cervical cancer staging system. Nonetheless, we consider that the patient had stage IA1 (FIGO 2018) pT1a1 (American Joint Committee on Cancer 2018) disease, and as such the treatment was sufficient.

Discussion and conclusions

We present the case of a woman with superficial spreading SCC of the cervix that involved the endometrium. We include ultrasound and microscopy images to perfectly illustrate the clinical case. We review the literature based on 54 cases retrieved by a keyword search in PubMed and Medline in Table 1. This review is the largest to date on this topic. Superficial spreading SCC of the cervix occurs mainly in menopausal women with history of cervical conization. The most common clinical presentation is vaginal bleeding and pyometra.

Carcinoma in situ (preinvasive or CIN III) or invasive carcinoma that is strictly confined to the cervix or extends into the uterine corpus (stage I, FIGO 2018) is by definition a histologic diagnosis. Nevertheless, cervical SCC with superficial spread to the endometrium or upper genital tract is not recognized in the latest FIGO or WHO classification systems. The main site affected by superficially spreading cervical SCC in the cases reported to date has been the endometrium, generally in isolation and without signs of invasive growth (carcinoma in situ). There have, however, been a few reports of unilateral or bilateral involvement of the fallopian tubes and/or ovaries in addition to endometrial extension. There has just been one report of distant metastasis, involving the greater omentum [2].

A genetic study of five patients with superficial spreading cervical SCC showed a single clonal process and frequent loss of heterozygosity at 6p, 6q, 11p, and 11q [3], all loci that are typically lost in cervical SCC. Consistent with our case, superficial spreading cervical SCC stains positively for p16, a surrogate immunohistochemical marker of HPV. HR-HPV infection is known to have a key pathogenic role in cervical SCC [4]. In one of the studies reviewed, all the samples analyzed were HPV 16 positive [4], suggesting that persistent HR-HPV infection is a key factor in the development of superficial spreading cervical SCC. In another study, CD138 was strongly expressed in superficial carcinoma cells in both the cervix and endometrium [5], suggesting that it may also be involved through the regulation of cell–cell interactions.

Conization followed by regular cytology and HPV detection (co-testing) is the standard procedure for CIN III management and follow-up. Cervical stenosis is a late complication of conization [6] and can result in unsatisfactory cytological and colposcopy follow-up and consequently higher false-negative rates and fewer early detections of recurrence [2]. Apart from cervical and vaginal cytology, patients with post-conization cervical stenosis should undergo additional procedures such as endocervical cytology, endometrial biopsy, and/or transvaginal pelvic ultrasound, especially if they have persistent HR-HPV infection.

As superficial spreading SCC of the cervix is so rare, there is limited information on its prognosis or clinical management [7–9]. It is more common in postmenopausal women, and the main presenting signs are vaginal bleeding and discharge (Table 1). HPV genotyping in combination with cervical and vaginal cytology is useful. An important role for local immune intolerance has been postulated. HPV vaccination is probably the only primary prevention measure possible. There have been reports that superficially spreading cervical SCC with endometrial involvement has worse prognosis than standard endometrial SCC [10–13]. Tumor volume and lymphovascular invasion are known risk factors for recurrence in cervical cancer and are also predictive of lymph node metastasis. Cervical stenosis with pyometra [14] and previous radiotherapy [15] can favor superficial spread. It is currently difficult to draw any conclusions regarding optimal treatment. Based on FIGO 2018 recommendations, a simple hysterectomy would be sufficient for SCC in situ or stage IA1 SCC without nodal involvement and an isolated focus of carcinoma in situ in the endometrium.

SCC of cervix is the most common tumor of the female genital tract, accounting for approximately 80% of all cervical cancers. Carcinoma of the cervix generally spreads upwards to the parametrium and through lymphatic invasion to the uterine wall. Although superficial spreading SCC of the cervix is rare, it should be considered in postmenopausal women with past history of cervical conization and persistent HR-HPV infection, as early diagnosis is important. There are insufficient data to compare superficial spreading SCC of the cervix with other types of cervical cancer. More clinical cases are needed to identify additional prognostic factors and inform clinical practice guidelines on the management of this disease.
| Author (year) | Case | Age | Clinical presentation | Cervical lesion | Extension of lesion | Follow-up (months) | Outcome |
|--------------|------|-----|-----------------------|-----------------|---------------------|-------------------|---------|
| Langley et al. (1956) [16] | 1    | 64  | NA                    | Invasive        | Endometrium and bilateral Fallopian tubes | 0             | DED (postsurgical) |
| Friedell et al. (1958) [17]  | 2    | 55  | NA                    | Invasive        | Endometrium (in situ) | 36            | NED      |
|  | 56  | NA  | Invasive              | Endometrium (in situ) | NA               | 36            | NED      |
| Brocheriou et al. (1963) [18] | 1    | 63  | Pyometra              | Invasive        | Endometrium (in situ) | NA           | NA       |
| Kairys et al. (1964) [19]   | 1    | 57  | Pyometra              | Invasive        | Endometrium (in situ) | NA           | NA       |
| Delattre et al. (1965) [20] | 1    | 66  | Cervical stenosis and pyometra | Invasive | Endometrium (in situ) | 12           | NED      |
| Salm et al. (1967) [21]     | 3    | 67  | Pyometra              | Carcinoma in situ | Endometrium (in situ) | 66           | NED      |
|  | 44  | NA  | Abnormal pap smears   | Carcinoma in situ | Endometrium (in situ) | 3            | NED      |
|  | 70  | NA  | Invasive              | Endometrium and vagina (in situ) | NA   | 180          | NED      |
| Weill et al. (1968) [22]    | 1    | 69  | Pyometra              | Carcinoma in situ | Endometrium and left fallopian tube (in situ) | NA           | NA       |
| Hallgimson et al. (1969) [23] | 1   | 54  | Pyometra              | Carcinoma in situ | Endometrium and bilateral Fallopian tubes (in situ) | NA           | NA       |
| Ferenczy et al. (1971) [24] | 1    | 53  | Abnormal pap smears   | Carcinoma in situ | Endometrium (in situ) | 84           | NED      |
| Quizilbash et al. (1975) [25] | 1  | 63  | Vaginal bleeding      | Invasive        | Endometrium and bilateral Fallopian tubes (in situ) | 84           | NED      |
| Kamalian et al. (1977) [26] | 1    | 55  | Vaginal bleeding      | Invasive        | Endometrium (in situ) | NA           | NA       |
| Schmitt et al. (1977) [27]  | 4    | 59  | Abnormal pap smears   | Carcinoma in situ | Endometrium (in situ) | NA           | NA       |
|  | 65  | Abnormal pap smears   | Invasive        | Endometrium (invasive) | NA   | 42          | NED      |
|  | 58  | Cervical stenosis     | Invasive        | Endometrium (invasive) | NA   | 48          | NED      |
|  | 52  | Vaginal bleeding      | Invasive        | Endometrium (in situ) | NA           | NA       |
| Kanbour et al. (1978) [10]  | 5    | 66  | Pyometra              | Carcinoma in situ | Endometrium (in situ, microinvasive foci) | 4            | DOD      |
|  | 58  | Pyometra              | Invasive        | Endometrium (in situ) | 132         | NED      |
|  | 53  | Cervical stenosis and pyometra | Invasive | Endometrium (in situ) | 54           | DOD      |
|  | 61  | Pyometra              | Invasive        | Endometrium (in situ) | 48           | NED      |
|  | 54  | Pyometra              | Invasive        | Endometrium (invasive) | 42           | NED      |
| Gupta et al. (1979) [15]    | 1    | 67  | Vaginal bleeding      | Carcinoma in situ | Endometrium (in situ) | NA           | NA       |
| Punnone et al. (1979) [28]  | 1    | 64  | Abnormal pap smears   | Invasive        | Endometrium and right Fallopian tube (in situ) | NA           | NA       |
| Sandhyamani et al. (1983) [29] | 1  | NA  | Abnormal pap smears   | Invasive        | Endometrium, fallopian tube, and vagina (in situ) | NA           | NA       |
| Daniele et al. (1985) [30]  | 1    | NA  | Abnormal pap smears   | Carcinoma in situ | Endometrium (in situ) | NA           | NA       |
| Motoyama et al. (1988) [31] | 1    | 59  | Vaginal bleeding, lower abdominal mass | Invasive | Endometrium, left Fallopian tube, left ovarian and pelvic lymph nodes (invasive) | 9            | DOD      |
| Teixera et al. (1991) [32]  | 1    | 64  | Pyometra              | Carcinoma in situ | Endometrium (invasive), pelvic lymph nodes (invasive) | NA           | NA       |
| Razquin et al. (1993) [33]  | 1    | 52  | Cervical stenosis and pyometra | Carcinoma in situ | Endometrium and right Fallopian tube (in situ) | 72           | NED      |
| Pins et al. (1997) [34]     | 1    | 55  | Abnormal pap smears   | Carcinoma in situ | Endometrium (in situ), bilateral tubes (in situ), bilateral ovaries (invasive) | 42           | NED      |
| Kushima et al. (2004) [3]   | 5    | 68  | Genital discharge    | Carcinoma in situ | Endometrium (in situ, focal microinvasive), left Fallopian tube (invasive), left ovary (invasive) | 54           | NED      |

Table 1: Reported cases of superficial spreading squamous cell carcinoma of uterine cervix involving the endometrium and upper genital tract.
Abbreviations
CIN: Carcinoma in situ; CRP: C-reactive protein; FIGO: International federation of gynecology and obstetrics; HIV: Human immunodeficiency virus; HR-HPV: Human high-risk papillomavirus; SCC: Squamous cell carcinoma; WHO: World health organization.

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JMV and JBL managed the case and compiled, reviewed, and edited the manuscript; PMB and PCP critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Table 1 (continued)

| Author (year) | Case | Age | Clinical presentation | Cervical lesion | Extension of lesion | Follow-up (months) | Outcome |
|---------------|------|-----|-----------------------|-----------------|---------------------|-------------------|---------|
| Tan et al. (2004) [8] | 1 | 70 | Vaginal bleeding | Microinvasive | Endometrium (in situ) | 6 | NED |
| Agashe et al. (2007) [35] | 1 | NA | NA | Carcinoma in situ | Endometrium, bilateral fallopian tubes and ovaries (in situ) | NA | NA |
| Alder et al. (2007) [36] | 1 | 59 | Lower abdominal mass | Invasive | Endometrium (invasive) | NA | NA |
| Gungor et al. (2011) [7] | 1 | 53 | Vaginal bleeding | Invasive | Endometrium (in situ, focal myometrial involvement), bilateral tubes and ovaries (in situ) | 12 | NED |
| Marwah et al. (2012) [14] | 3 | 65 | Pyometra | Invasive | Endometrium (in situ) | NA | NA |
| | 60 | Vaginal bleeding | Invasive | Endometrium (in situ with small focal microinvasion) | NA | NA |
| | 49 | Vaginal bleeding | Invasive | Endometrium (in situ) | NA | NA |
| Chao et al. (2013) [4] | 1 | 60 | Pyometra | Carcinoma in situ | Endometrium (in situ, foci microinvasive) | – | DOD (2 days) |
| Ishida et al. (2013) [5] | 2 | 64 | Vaginal bleeding | Invasive | Endometrium (in situ) | NA | NA |
| | 59 | Vaginal bleeding | Invasive | Endometrium (in situ) | NA | NA |
| Yang et al. (2014) [37] | 1 | 69 | Hydrometra | Carcinoma in situ | Uterine corpus, vagina, left salpinx (all in situ with multifocal microinvasive) | NA | NA |
| Anthuenis et al. (2016) [38] | 1 | 72 | Hydrometra | Carcinoma in situ | Endometrium (in situ, focal microinvasive) | 24 | NED |
| Neelam et al. (2017) [39] | 2 | 60 | Abdominal mass | Invasive | Endometrium (in situ) | NA | NA |
| | 70 | Abdominal mass | Carcinoma in situ | Endometrium (in situ) | NA | NA |
| Muthusamy et al. (2017) [40] | 1 | 45 | Vaginal bleeding, lower abdominal pain | Carcinoma in situ | Endometrium (in situ) | NA | NA |
| Nakajima et al. (2019) [2] | 1 | 67 | Lower abdominal pain | Carcinoma in situ | Endometrium (in situ), bilateral tubes (in situ), both ovaries (invasive), greater omentum (invasive) | 24 | NED |
| Du et al. (2019) [41] | 1 | 66 | Abnormal pap smears | Carcinoma in situ | Endometrium (in situ, foci microinvasive) | 43 | NED |
| Current study | 1 | 66 | Abnormal pap smears, pyometra | Invasive | Endometrium (in situ) | 6 | NED |

SCC: squamous cell carcinoma, NA not available, NED: no evidence of disease, DOD: died of disease
Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the fundamental principles of the Declaration of Helsinki.

Consent for publication
Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

Competing interests
None of the authors have any potential conflicts of interest relevant to this article.

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