

CASE REPORT

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Superficial spreading cervical squamous cell carcinoma *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 *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.

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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 ($10 \times 10^3/\mu\text{l}$), neutrophils: $7 \times 10^9/\text{L}$, platelets $250 \times 10^9/\text{L}$, 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

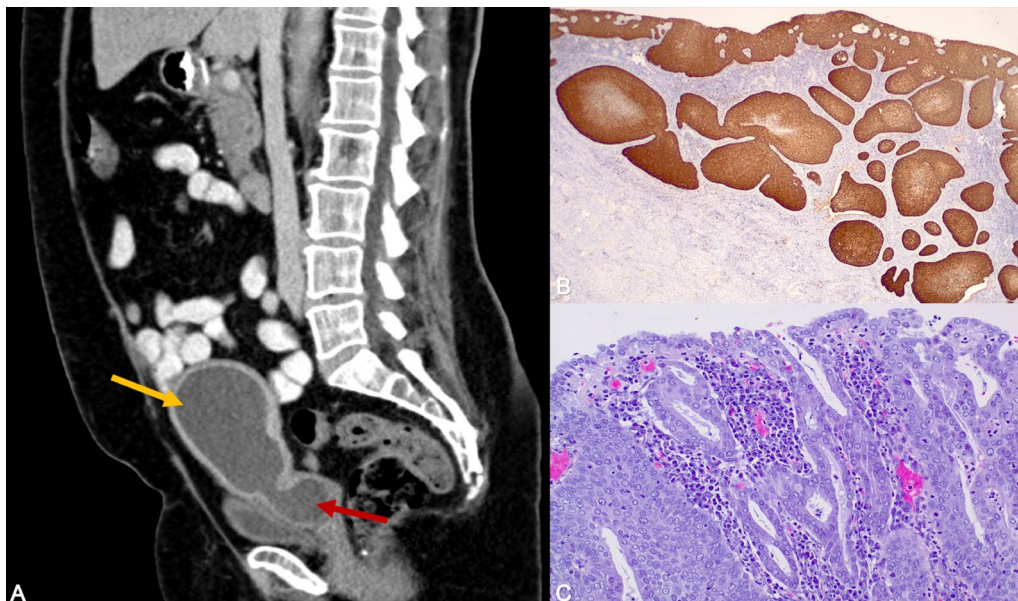


Fig. 1 **A** Contrast-enhanced computed tomography scan. Marked distension of the uterine cavity (yellow arrow) and cervical canal (red arrow). Presence of dense material consistent with pyometra. **B** Squamous cell carcinoma with superficial invasion (2.8 mm). Staining for p16 × 250. **C** Note the large number of endometrial glands in the tumor. Hematoxylin–eosin × 100

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.

Table 1 Reported cases of superficial spreading squamous cell carcinoma of uterine cervix involving the endometrium and upper genital tract

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 (<i>in situ</i>)	36	NED
		56	NA	Invasive	Endometrium (<i>in situ</i>)	36	NED
Brocheriou et al. (1963) [18]	1	63	Pyometra	Invasive	Endometrium (<i>in situ</i>)	NA	NA
Kairys et al. (1964) [19]	1	57	Pyometra	Invasive	Endometrium (<i>in situ</i>)	NA	NA
Delattre et al. (1965) [20]	1	66	Cervical stenosis and pyometra	Invasive	Endometrium (<i>in situ</i>)	12	NED
Salm et al. (1967) [21]	3	67	Pyometra	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	66	NED
		44	NA	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	3	NED
		70	NA	Invasive	Endometrium and vagina (<i>in situ</i>)	180	NED
Weill et al. (1968) [22]	1	69	Pyometra	Carcinoma <i>in situ</i>	Endometrium and left fallopian tube (<i>in situ</i>)	NA	NA
Hallgímson et al. (1969) [23]	1	54	Pyometra	Carcinoma <i>in situ</i>	Endometrium and bilateral fallopian tubes (<i>in situ</i>)	NA	NA
Ferenczy et al. (1971) [24]	1	53	Abnormal pap smears	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	84	NED
Quizilbash et al. (1975) [25]	1	63	Vaginal bleeding	Invasive	Endometrium and bilateral fallopian tubes (<i>in situ</i>)		
Kamalian et al. (1977) [26]	1	55	Vaginal bleeding	Invasive	Endometrium (<i>in situ</i>)	NA	NA
Schmitt et al. (1977) [27]	4	59	Abnormal pap smears	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	NA	NA
		65	Abnormal pap smears	Invasive	Endometrium (invasive)	NA	NA
		58	Cervical stenosis	Invasive	Endometrium (invasive)	NA	NA
		52	Vaginal bleeding	Invasive	Endometrium (<i>in situ</i>)	NA	NA
Kanbour et al. (1978) [10]	5	66	Pyometra	Invasive	Endometrium (<i>in situ</i> , microinvasive foci)	4	DOD
		58	Pyometra	Invasive	Endometrium (<i>in situ</i>)	132	NED
		53	Cervical stenosis and pyometra	Invasive	Endometrium (<i>in situ</i>)	54	DOD
		61	Pyometra	Invasive	Endometrium (<i>in situ</i>)	48	NED
		54	Pyometra	Invasive	Endometrium (invasive)	42	NED
Gupta et al. (1979) [15]	1	67	Vaginal bleeding	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	NA	NA
Punnone et al. (1979) [28]	1	64	Abnormal pap smears	Invasive	Endometrium and right fallopian tube (<i>in situ</i>)	NA	NA
Sandhyamani et al. (1983) [29]	1	NA	NA	Invasive	Endometrium, fallopian tube, and vagina (<i>in situ</i>)	NA	NA
Daniele et al. (1985) [30]	1	NA	NA	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	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 <i>in situ</i>	Endometrium (invasive), pelvic lymph nodes (invasive)	NA	NA
Razquin et al. (1993) [33]	1	52	Cervical stenosis and pyometra	Carcinoma <i>in situ</i>	Endometrium and right fallopian tube (<i>in situ</i>)	72	NED
Pins et al. (1997) [34]	1	55	Abnormal pap smears	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>), bilateral tubes (<i>in situ</i>), bilateral ovaries (invasive)	42	NED
Kushima et al. (2004) [3]	5	68	Genital discharge	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i> , focal microinvasive), left fallopian tube (invasive), left ovary (invasive)	54	NED

Table 1 (continued)

Author (year)	Case	Age	Clinical presentation	Cervical lesion	Extension of lesion	Follow-up (months)	Outcome
		58	NA	Carcinoma <i>in situ</i>	Endometrium (single focus of microinvasion, <1 mm in depth)	NA	NA
		72	Hematometra	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	30	NED
		78	Vaginal bleeding	Invasive	Endometrium (invasive), vagina (<i>in situ</i>)	NA	NA
		59	Vaginal bleeding, lower abdominal mass	Invasive	Endometrium (<i>in situ</i> with endometrial stroma sarcoma), left fallopian tube, left ovary, vagina (<i>in situ</i>), vulva (<i>in situ</i>)	NA	NA
Tan et al. (2004) [8]	1	70	Vaginal bleeding	Microinvasive	Endometrium (<i>in situ</i>)	6	NED
Agashe et al. (2007) [35]	1	NA	NA	Carcinoma <i>in situ</i>	Endometrium, bilateral fallopian tubes and ovaries (<i>in situ</i>)	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 (<i>in situ</i> , focal myometrial involvement), bilateral tubes and ovaries (<i>in situ</i>)	12	NED
Marwah et al. (2012) [14]	3	65	Pyometra	Invasive	Endometrium (<i>in situ</i>)	NA	NA
		60	Vaginal bleeding	Invasive	Endometrium (<i>in situ</i> with small focal microinvasion)	NA	NA
		49	Vaginal bleeding	Invasive	Endometrium (<i>in situ</i>)	NA	NA
Chao et al. (2013) [4]	1	60	Pyometra	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i> , foci microinvasive)	–	DOD (2 days)
Ishida et al. (2013) [5]	2	64	Vaginal bleeding	Invasive	Endometrium (<i>in situ</i>)	NA	NA
		59	Vaginal bleeding	Invasive	Endometrium (<i>in situ</i>)	NA	NA
Yang et al. (2014) [37]	1	69	Hydrometra	Carcinoma <i>in situ</i>	Uterine corpus, vagina, left salpinx (all <i>in situ</i> with multifocal microinvasive)	NA	NA
Anthuenis et al. (2016) [38]	1	72	Hydrometra	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i> , focal microinvasive)	24	NED
Neelam et al. (2017) [39]	2	60	Abdominal mass	Invasive	Endometrium (<i>in situ</i>)	NA	NA
		70	Abdominal mass	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	NA	NA
Muthusamy et al. (2017) [40]	1	45	Vaginal bleeding, lower abdominal pain	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>)	NA	NA
Nakajima et al. (2019) [2]	1	67	Lower abdominal pain	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i>), bilateral tubes (<i>in situ</i>), both ovaries (invasive), greater omentum (invasive)		
Du et al. (2019) [41]	1	66	Abnormal pap smears	Carcinoma <i>in situ</i>	Endometrium (<i>in situ</i> , foci microinvasive)	43	NED
Current study	1	66	Abnormal pap smears, pyometra	Invasive	Endometrium (<i>in situ</i>)	6	NED

SCC squamous cell carcinoma, NA not available, NED no evidence of disease, DOD died of disease

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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Availability of data and materials

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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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