

Superficial spreading squamous cell carcinoma of the cervix involving the endometrium: A case report and literature review

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Abstract. Superficial spreading cervical squamous cell carcinoma (SCC) constitutes a relatively uncommon subtype of cervical cancer, distinguished by the replacement of the endometrium and, in some instances, the epithelial lining of the fallopian tubes with cervical SCC cells that are contiguous with the primary cervical lesion. The present study describes a case involving a 76-year-old patient who primarily exhibited symptoms of abdominal pain and pyometra. During a routine cervical ThinPrep cytologic test, which was conducted while the patient was undergoing anti-infective treatment, high-grade squamous intraepithelial lesion of the cervix was detected. Following the surgical procedure of total hysterectomy with bilateral salpingo-oophorectomy, pathological examination indicated a diagnosis of superficial spreading SCC of the cervix, with extensive involvement of the endometrial lining and the mucosal layer of the interstitial portions of both fallopian tubes. This rare case is a reminder that in elderly patients with pyometra where cervical biopsy only indicates cervical intraepithelial neoplasia, merely administering anti-infective treatment or performing cervical conization may lead to a missed diagnosis of superficial spreading cervical SCC. Currently, there are no standardized diagnostic and therapeutic approaches for superficial spreading cervical SCC. In the present case, radiotherapy was administered to the patient to delay recurrence. Large-sample studies are crucial for improving the understanding of this tumor and facilitating advancements in precision medicine treatments.

Introduction

Cervical cancer (CC) ranks as the fourth most common cancer and the fourth leading cause of cancer-related mortality among women globally (1). For high-grade squamous intraepithelial lesions of the cervix, cold knife conization, laser conization or loop electrosurgical excision procedures are standard treatment methods, while for elderly patients unsuitable for cervical conization, a total hysterectomy with bilateral salpingectomy serves as an alternative approach (2). According to the National Comprehensive Cancer Network guidelines (NCCN) guidelines (3), patients with stage IA1 cervical cancer who do not require fertility preservation may undergo a total hysterectomy, while those with fertility preservation needs may undergo cervical conization. The subsequent treatment plan is determined based on the presence or absence of lymphovascular space invasion in the postoperative pathology. For cervical carcinoma in situ, the 5-year survival rate after standard treatment reaches 93%, and for stage I CC confined to the cervix, it's 80% (4). However, superficial spreading cervical squamous cell carcinoma (SCC) is a form of cervical SCC that superficially extends to the inner surface of the uterus, replacing the endometrium and the epithelium fallopian tubes, and spreads to the ovarian surface. Due to its low incidence, information on the diagnosis, treatment and prognosis of superficial spreading cervical SCC is incomplete. In the present case report, a case of superficial spreading cervical SCC with microinvasion (<1 mm) extending to the endometrium and interstitial portions of the fallopian tubes is presented, along with a review of the relevant literature.

Case report

A 76-year-old patient was admitted to West China Second Hospital (Chengdu, China) in September 2024 with lower abdominal pain lasting for >1 month. At 2 weeks prior to admission, the patient underwent an ultrasound examination at another hospital, which revealed pyometra in the uterine cavity. After undergoing antibiotic treatment (ceftriaxone + tinidazole) at that hospital, the condition of the patient improved. A cervical ThinPrep cytologic test was conducted, which revealed high-grade squamous intraepithelial lesion

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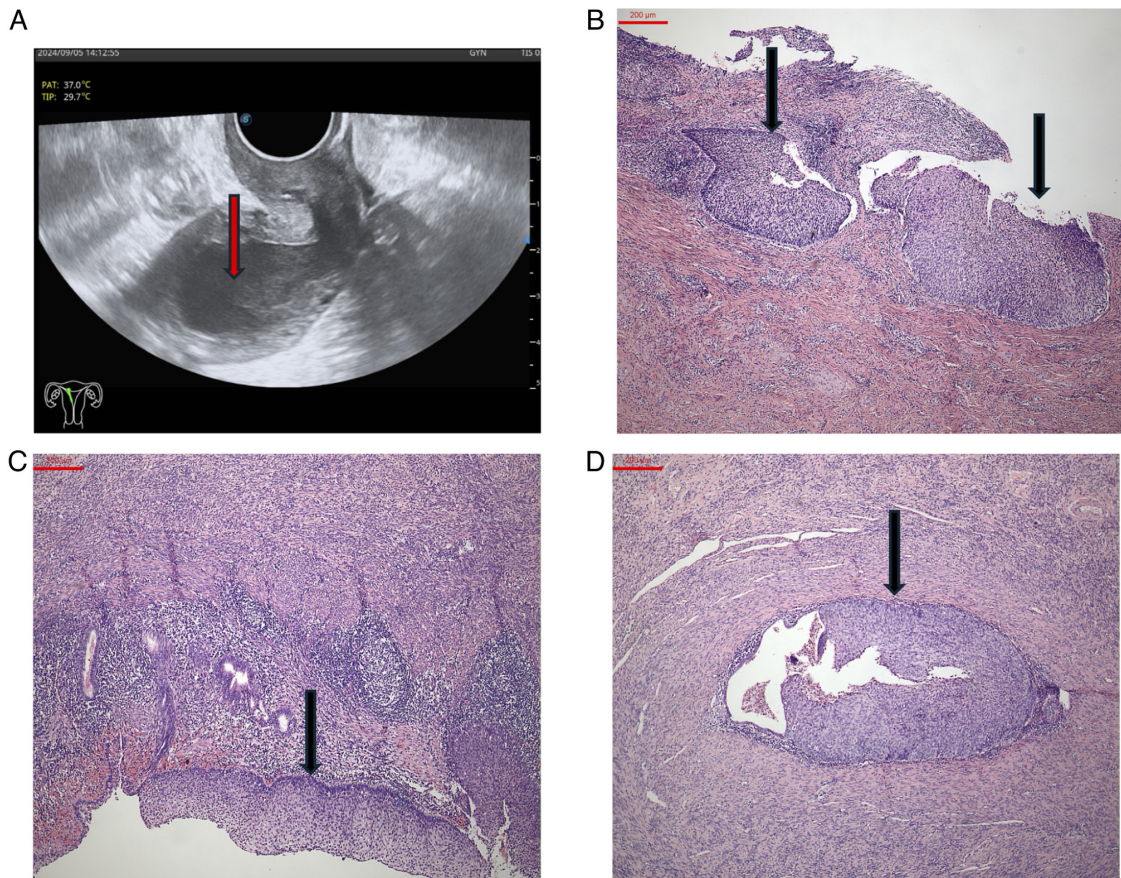


Figure 1. (A) Ultrasound image, with a red arrow indicating the uterine cavity. (B) H&E staining of cervical squamous cell carcinoma *in situ* (magnification, x40). (C) SCC of the endometrium *in situ* (H&E; magnification, x40). (D) SCC *in situ* of the interstitial region of the fallopian tubes (H&E; magnification, x40). Scale bars, 200 μ m. Black arrows indicate the lesion. SCC, squamous cell carcinoma.

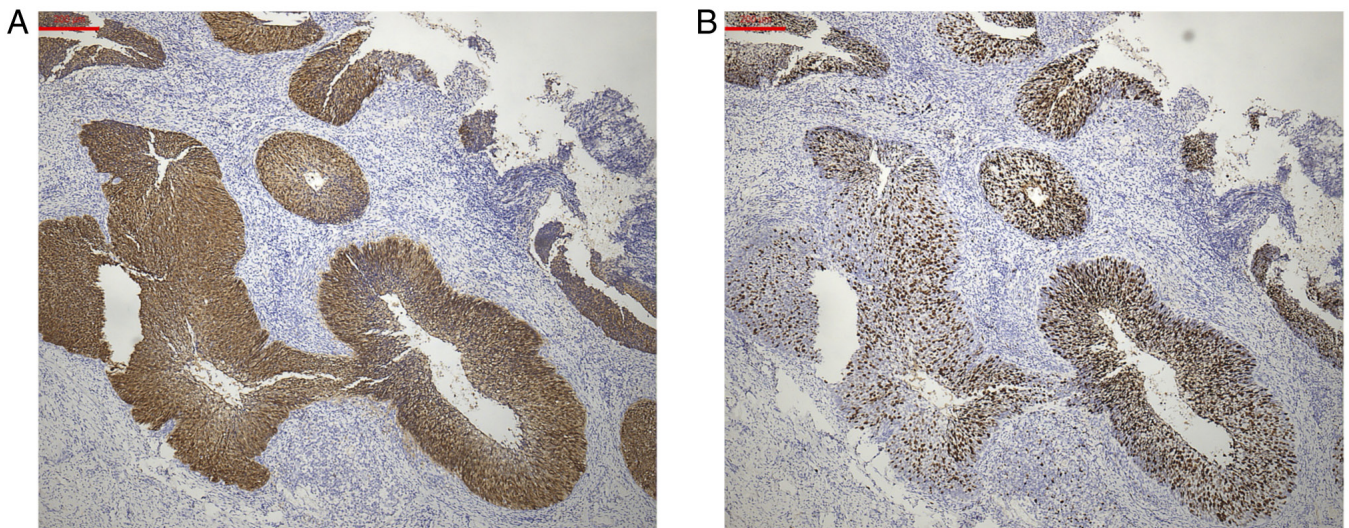


Figure 2. Immunohistochemical staining for (A) p16 and (B) Ki-67 in the cervix. Scale bar, 200 μ m.

with human papillomavirus (HPV)16 positivity. Subsequently, a cervical biopsy was performed, and the pathological report results were sent to West China Second Hospital for consultation. The consultation results indicated: At the 3 and 6 o'clock positions of the cervix, it was determined that chronic inflammation, cervical intraepithelial neoplasia (CIN) I and CIN II

were present. At the 9 and 12 o'clock positions, chronic cervicitis with focal CIN I and CIN II was diagnosed. Free squamous epithelia in the cervical canal showed moderate to severe atypical hyperplasia. The B-scan ultrasonography results upon admission revealed the following (Fig. 1A): The endometrial monolayer measured ~ 0.1 cm in thickness, with a uterine

Table I. Reported cases of squamous cell carcinoma in the literature.

First author, year	Age, years	Clinical presentation	HPV	Cervical lesion	Extension of lesion	Adjuvant therapy	Follow-up period, months	Outcome after follow-up	(Refs.)
Razquin <i>et al</i> , 1993	52	Cervical stenosis and pyometra	NA	<i>In situ</i>	Endometrium (<i>in situ</i>), right fallopian tube (<i>in situ</i>)	Radiotherapy	72	Disease free	(11)
Pins <i>et al</i> , 1997	55	Abnormal cervical smear	16+	<i>In situ</i>	Endometrium (<i>in situ</i>), bilateral fallopian tubes (<i>in situ</i>), bilateral ovaries (<i>in situ</i>), bilateral ovaries (<i>in situ</i>)	Radiotherapy	42	Disease free	(12)
Kushima <i>et al</i> , 2001	68	Excessive vaginal discharge	NA	<i>In situ</i>	Endometrium (microinvasive), left fallopian tube (invasive), left ovary (invasive)	NA	54	Disease free	(13)
Tan <i>et al</i> , 2004	72	Hematometra	NA	<i>In situ</i>	Endometrium (<i>in situ</i>)	NA	30	Disease free	(14)
Anthuenis <i>et al</i> , 2016	70	Vaginal discharge	NA	Microinvasive	Endometrium (microinvasive)	-	6	Disease free	(15)
Anthuenis <i>et al</i> , 2016	72	Distended abdomen	NA	Microinvasive	Endometrium (<i>in situ</i>)	-	24	Disease free	(15)
Nakajima <i>et al</i> , 2019	67	Pain in the lower abdomen	+	<i>In situ</i>	Endometrium (<i>in situ</i> , focal myometrial involvement) bilateral tubes and ovaries (<i>in situ</i>), omentum (invasive), transverse colon (invasive)	Chemotherapy	40	Disease free	(16)
Wang <i>et al</i> , 2021	53	Pyometra	+	<i>In situ</i>	Endometrium (<i>in situ</i>)	-	6	Disease free	(17)
Martín-Vallejo <i>et al</i> , 2022	61	Pyometra and vaginal discharge	16+	Microinvasive	Endometrium (<i>in situ</i>)	-	12	Disease free	(18)
Shu <i>et al</i> , 2022	57	Pyometra	16+	<i>In situ</i>	Endometrium (<i>in situ</i>)	Radiotherapy	12	Disease free	(19)

HPV, human papillomavirus; NA, not available/reported; -, no adjuvant therapy.

cavity separation of 0.3 cm, within which multiple flocculent hypochoic areas were observed, thus indicating pyometra of the uterine cavity. As the preoperative cervical biopsy did not indicate invasive carcinoma, no magnetic resonance imaging (MRI) examination was performed. Subsequently, an experienced professor of gynecology conducted a triple examination on the patient, and no parametrial infiltration was palpated. Due to severe cervical atrophy in the patient, it was not possible to perform a cervical cone biopsy and instead the patient directly underwent a laparoscopic total hysterectomy with bilateral salpingo-oophorectomy. Upon postoperative examination of the uterus, pyometra was observed in the uterine cavity, but no obvious masses were seen in the cervix or endometrium. Pathological examinations were performed on the resected specimens, including hematoxylin and eosin (H&E) staining and immunohistochemical (IHC) testing. The uterine and bilateral salpingo-oophorectomy tissue samples were fixed in 10% neutral-buffered formalin at room temperature (~22°C) for 24 h. The fixed tissues were then processed and embedded in paraffin. Sections were cut at a 4- μ m thickness using a microtome. Conventional H&E staining was performed at room temperature with hematoxylin for 5 min and eosin for 2 min. As for IHC testing, the paraffin sections were dewaxed by placing them in a 67°C oven for 2 h and then removing the glass. The sections were dehydrated with graded ethanol (95, 85 and 75%). The antigens were repaired twice using antigen retrieval solution (0.01M sodium citrate buffer, pH 6.0) and washed three times with PBS. The sections were then immunolabeled with anti-p16 (cat. no. MAB-0673; Fuzhou Maixin Biotechnology Development Co., Ltd.) and anti-Ki-67 (cat. no. RMA-0542; Fuzhou Maixin Biotechnology Development Co., Ltd.) antibodies overnight at 4°C. After thoroughly washing with PBS, the sections were incubated with secondary antibody (cat. no. A4416; MilliporeSigma). The staining was visualized using the peroxide substrate solution diaminobenzidine and counterstaining with haematoxylin. Observation was conducted under a light microscope (Olympus BX53; Olympus Corporation). The postoperative pathological results indicated superficial spreading cervical SCC *in situ* (Fig. 1B), extensively involving the endometrium (Fig. 1C) and the mucosa of the interstitial portions of both fallopian tubes (Fig. 1D). The carcinoma demonstrated multiple foci of vertical infiltration in the cervix and uterine body on the basis of extensive horizontal spread, with infiltration depths all <1 mm. No cancer involvement was observed in the bilateral parametria, bilateral pelvic sidewall resection margins or bilateral ovaries. The immunohistochemistry results demonstrated p16+++ (Fig. 2A), with Ki-67+ consistent with the range of p16 positivity (Fig. 2B).

The patient began radiotherapy 6 weeks after surgery, consisting of 6 weeks of external beam pelvic radiotherapy [with a dosage of clinical target volume (CTV) 1.8 Gy per fraction for 25 fractions, and gross tumor volume 2.2 Gy per fraction for 25 fractions]. After external beam pelvic radiotherapy, the patient received two sessions of three-dimensional intracavitary brachytherapy within 3 days (with a dosage of CTV 6.0 Gy per fraction for 2 fractions). During the follow-up period extending up to 10 months after the surgery, the patient had multiple physical examinations, along with pelvic enhanced MRI and serum SCC antigen tests, none of which indicated recurrence or metastasis.

Discussion

CC is a common gynecological tumor, with the mode of metastasis often involving direct extension and lymphatic spread (5). SCC of the cervix with superficial spread to the endometrium, fallopian tubes or even ovaries is relatively rare (6). Symptoms in elderly patients with cervical lesions are often atypical. In the present case, the primary symptoms were lower abdominal pain and pyometra, underscoring that cervical cancer screening is necessary for elderly women presenting with lower abdominal pain or pyometra, regardless of whether cervical lesions are visually detectable.

In 1967, Hallgrímsson (7) first reported a case of SCC *in situ* simultaneously affecting the cervix, endometrium and fallopian tubes; however, the author was unable to determine whether the lesion originated from the cervix or the endometrium. In 1969, Salm (8) first proposed that cervical carcinoma *in situ* could superficially spread to the endometrium. A 44-year-old woman underwent a total hysterectomy due to a preoperative diagnosis of CIN. Postoperative pathology revealed that the cervical SCC *in situ* extended upwards, replacing part of the endometrium. Additionally, part of the endometrium exhibited a bilayer appearance, with a lower layer of normal endometrium and an upper layer of SCC *in situ*.

PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) was searched for all reports of superficial spreading cervical SCC published after 1967 and excluded those where the primary cervical lesion was an invasive cancer, as CC above stage IA1 exhibits significantly increased lymphatic metastasis rates, potentially spreading to the endometrium and other organs via lymphatic routes or other mechanisms (9,10). The case reports with follow-up data are listed in Table I (11-19), it was determined that all patients with superficial spreading cervical SCC were postmenopausal women. The most common symptoms were pyometra and vaginal discharge, and half of the patients had undergone conization due to CIN3/carcinoma *in situ*. All patients were diagnosed with superficial spreading cervical SCC postoperatively, and 90% of them did not undergo pelvic lymph node dissection. None of the cervical lesions showed vascular infiltration. In the retrieved case series, over one-half of patients with superficial spreading cervical SCC presented with pyometra, indicating that cervical conization alone may lead to underdiagnosis of endometrial lesions in postmenopausal women with cervical squamous cell carcinoma *in situ* who exhibit pyometra or abnormal vaginal discharge. The overall prognosis for patients with this type of CC was relatively good. Four patients did not receive additional treatment after surgery and had no recurrence during the 6-24 months of follow-up; three patients received supplementary radiotherapy and had no recurrence during the 12-72 months of follow-up; one patient received supplementary chemotherapy and had no recurrence after 40 months of follow-up. For the remaining two patients, it was not mentioned whether they received supplementary radiotherapy or chemotherapy, but they also had no recurrence during the 30-54 months of follow-up. Since radiotherapy is the preferred adjuvant treatment for cervical SCC, in order to avoid recurrence, adjuvant radiotherapy was administered in the present case. A recently published article reported that

for intermediate-risk CC, adding chemotherapy to radiotherapy does not improve overall survival (20); therefore, radiotherapy alone may be sufficient for such patients. Thus far, after 10 months of follow-up, there has been no evidence of metastasis or recurrence for the present patient.

Regarding the etiology of superficial spreading cervical SCC, Ishida and Okabe (21) analyzed two cases of superficial spreading CC and found that the intraepithelial component of the cervical invasive cancer and the endometrial component were strongly positive for CD138, while the invasive component beyond the epithelium had minimal expression of CD138, suggesting that high expression of CD138 may be associated with the direct spread of SCC to the endometrium. Kushima *et al* (13) conducted a preliminary analysis of chromosomal heterogeneity in patients and suggested that superficial spreading cervical SCC undergo a single clonal process with frequent loss of heterozygosity on chromosomes 6p, 6q, 11p and 11q. Due to the rarity of cases, the metastatic mechanism of superficial spreading cervical SCC has not been thoroughly studied at present.

The upregulation of p16 is typically associated with HPV infection, whereas high expression of Ki-67 reflects the proliferative activity of tumors. In the present case, the expression pattern of p16 was consistent with that of Ki-67, suggesting that HPV infection may be associated with this type of CC. It was reported in 1993 by Pins *et al* (12) that this type of CC may be associated with HPV infection. More recently, Zhang *et al* (22) reported a case of SCC of the cervix with superficial spread to the endometrium, fallopian tubes and ovaries, in which all lesions tested positive for HPV. The association between HPV and endometrial malignancies has been reported previously; a large-scale observational clinical trial among Taiwanese women conducted by Wu *et al* (23) found that HPV infection increases the incidence of endometrial cancer among women (HR 1.88, 95% CI 1.335-1.888). Darre *et al* (24) also reported a case of SCC of the endometrium that was positive for HPV16/18. Jiang *et al* (25) reported 15 cases of CC involving the endometrium, all of which were positive for HPV16. The findings in the present case suggest that HPV16 may be associated with superficial spreading CC.

In clinical practice, the staging and treatment of CC are often based on the International Federation of Gynecology and Obstetrics (FIGO) staging system, which focuses on the depth of invasion of the cancer lesion, its size and the local extent of involvement. For patients with cervical invasive carcinoma where the lesion has spread to the endometrium, the decision to administer adjuvant chemoradiotherapy postoperatively can be made according to the FIGO guidelines or NCCN guidelines (3,26). However, for patients whose cervix shows only carcinoma *in situ* or microinvasive carcinoma with the lesion extending to the endometrium, there are currently no corresponding guidelines available. Nakajima *et al* (16) reported a case of a patient with cervical carcinoma *in situ*, in which the tumor superficially disseminated to the endometrium, the surfaces of both fallopian tubes, both ovaries, transverse colon and implanted on the greater omentum, forming an invasive carcinoma. After undergoing a radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy and transverse colectomy, the patient received six cycles of chemotherapy with

paclitaxel and carboplatin. Following a 40-month follow-up period the patient showed no signs of recurrence. This report indicates that supplementary chemotherapy may be beneficial to the prognosis of CC with superficial dissemination to the ovaries. Nevertheless, due to the scarcity of cases, large-scale controlled trials cannot be conducted, and it remains uncertain whether postoperative adjuvant chemoradiotherapy is beneficial for prognosis.

In conclusion, superficial spreading SCC of the cervix currently lacks standardized diagnostic and treatment methods. It was the aim of the present report to highlight that for elderly patients with pyometra whose cervical cytology only indicates CIN and does not suggest cervical invasive carcinoma, merely administering anti-infective treatment or performing a cervical conization might lead to a missed diagnosis of superficial spreading cervical SCC. For such patients, fractional curettage should minimally be performed concurrent with cervical conization. Due to the limited number of cases, conducting molecular or histopathological studies at present would not yield statistically significant results; therefore, more cases of superficial spreading cervical SCC should be collected to investigate the molecular mechanisms underlying its pathogenesis, particularly the role of specific HPV genotypes in its development. Additionally, these patients should be followed up over a prolonged period to assess their prognosis and explore whether adjuvant chemoradiotherapy is beneficial for improving outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XH conceived the case report. SS and HZ collected and analyzed the data. SS and HZ wrote and revised the manuscript. XH and SS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was provided by the patient for the case report to be published.

Competing interests

The authors declare that they have no competing interests.

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