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Case Report

Superficial spreading squamous cell carcinoma in situ of the cervix involving the endometrium: a rare case presentation and review of literature

Jing Du[1], Xuhui Liao[2]

[1]Faculty of Medicine and Health, Lishui University, Lishui, China; [2]Department of Pathology, Lishui People's Hospital, Lishui, China

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Abstract: Objective: Squamous cell carcinoma in situ of the cervix rarely can spread superficially to the inner surface of the uterus replacing the endometrium. Case: We report a case of cervical squamous cell carcinoma in situ (CIS) in a 66-year-old female with contiguous extension to the endometrium with small foci of microinvasion. Immunohistochemistry revealed that these tumor cells were positive for p16, p63, and ck5/6 with a high Ki-67 labelling index. It is an extremely unusual phenomenon for cervical CIS superficial to spread to the endometrium. Conclusion: Cervical CIS can also spread superficially upward, and replace the endometrial lining. The detection of immunohistochemical expression of p16, p63 and CK5/6 in the lesions of cervix and the endometrium suggest that these two lesions are etiologically related, favoring the possibility of the endometrium SCC secondary to cervical SCC in situ, and reveal that HPV is a causative factor for superficial spreading SCC.

Keywords: Squamous cell cervical carcinoma, endometrium, superficial spreading

Introduction

Squamous cell carcinoma (SCC) is the most common malignant tumor of the cervix, comprising 70-80% of cervical malignancies. Cervical SCC generally invades directly into the uterine wall with or without parametrial involvement. Cervical SCC that spreads superficially to the inner surface of the uterus and replaces the endometrium with carcinoma cells is called superficial spreading SCC. Superficial spreading SCC is a very rare phenomenon [1-3]. In this report we describe an unusual case of squamous cell carcinoma in situ (CIS) of the cervix with extension to the endometrium with microinvasion. We reviewed all the literature include by PubMed from 1971 to now, reporting 31 cases in English literature over the last 48 years.

Case report

A 66-year-old multiparous, postmenopausal woman's Pap smear revealed features of atypical squamous cells. A cervical biopsy was performed, which on histological examination showed cervical intraepithelial neoplasia III. A wide abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. On gross examination, the uterus measured 9 cm × 5 cm × 4 cm with a granular and yellowish appearance of the ectocervix. Most of the endometrial surface was thin and smooth, but a superficial yellowish growth measuring 0.7 cm × 0.5 cm × 0.2 cm was seen on the endometrial surface of the uterine body (**Figure 1A**). The fallopian tubes and the ovaries were grossly unremarkable. Frozen sections demonstrated that the specimen was CIS.

Microscopic examination of hysterectomy specimens showed squamous cell carcinoma in situ (CIS) of the cervix (**Figure 1B**). There was contiguous extension of the cervical CIS into the lower uterine segment replacing part of the endometrium (**Figure 1C**). Microscopically, the superficial yellowish growth was squamous CIS. Some of the endometrial glands were partially or completely obliterated by the spread of in situ, malignant, squamous epithelium. In a few

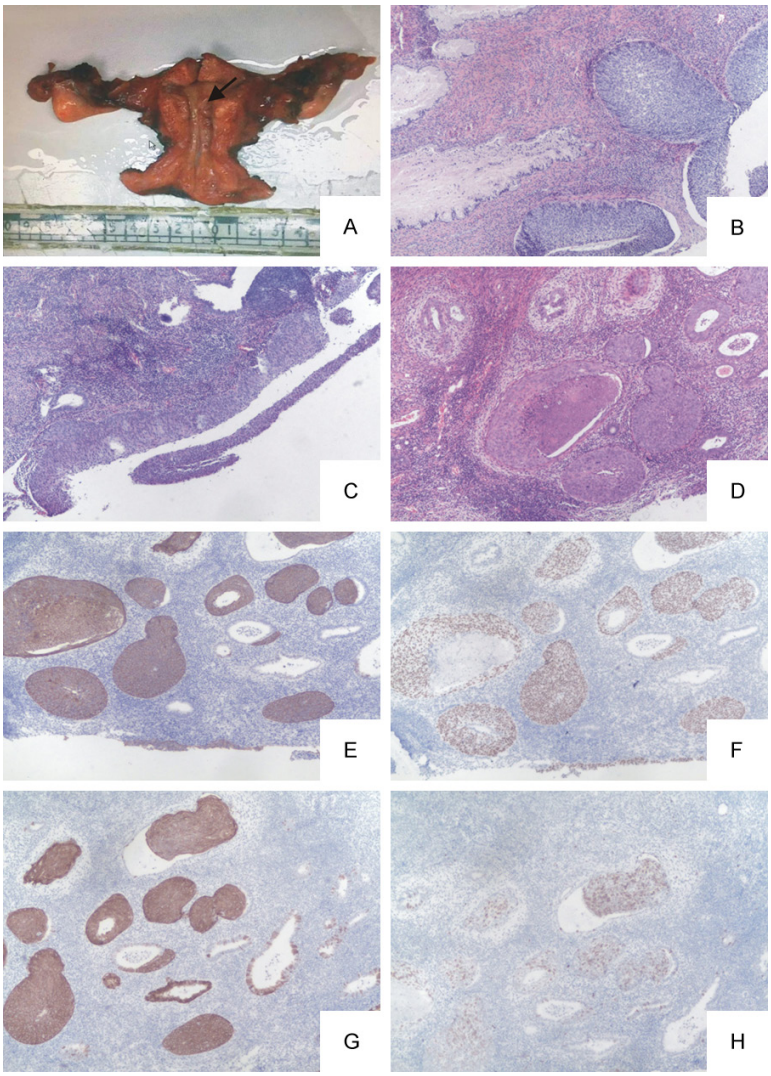

Figure 1. Histopathological and immunohistochemical features of the case. (A) Uterine specimen showing granular and yellowish appearance of ectocervix and the superficial yellowish growth (black arrow) measuring 0.7 cm × 0.5 cm × 0.2 cm of the endometrial surface. (B) Cervical squamous cell carcinoma in situ lesion (H&E, × 40). (C) Superficial spreading squamous cell carcinoma of the uterine cervix in situ involving the endometrium, with continuity of the endometrium lesion with cervix was observed (H&E, × 40). (D) Involvement of the endometrial glands by in situ, malignant, squamous epithelium focal microinvasion can be observed in the endometrial squamous cell carcinoma in situ lesion. Nests of squamous cell carcinoma elicit a stromal response (H&E, × 100). Dysplastic cells of endometrial squamous cell carcinoma in situ lesion are immunohistochemically strongly positive for CK5/6 (E), p63 (F), p16 (G), and had a high Ki67 labelling index (H).

ages 45 to 78 years (mean, 61.3 years). The main clinical manifestations of superficial spreading SCC of the uterine cervix involving the endometrium were vaginal bleeding (11/31, 35%), pyometra (6/31, 19%), abdominal mass (3/31, 9%), lower abdominal pain (2/31, 6%), abnormal pap smears (3/31, 9%), hematometra (2/31, 6%), and excessive genital discharge (1/31, 3%). The current patient was admitted to our hospital because pap smear revealed features of atypical squamous cells, did not show any above mentioned clinical manifestations.

As seen from the **Table 1**, the pathology of the cervical neoplasia was ranging from SCC in situ (15/31, 48%), invasive SCC (15/31, 48%). foci, there was evidence of microinvasion (less than 1 mm in depth) from the endometrial glands into the surrounding stroma (**Figure 1D**). Uninvolved foci of endometrial surface were seen as occasional glandlike clefts lined by residual columnar epithelium (**Figure 1D**). Leiomyoma was identified in the myometrium.

Immunohistochemical analysis demonstrated strong p16 (Dako) (**Figure 1G**) expression, noted in the dysplastic and carcinoma in situ cells arising from the endometrium. CK5/6 and p63 (Dako) were strong positive (**Figure 1E** and **1F**), and Ki-67 (Dako) index was 60% (**Figure 1H**).

Discussion

Superficial spreading SCC of the uterine cervix involving the endometrium is an extremely rare entity. We reviewed all the English literature include by PubMed from 1971 to now and found that 31 cases of superficial spreading squamous cell carcinoma of the cervix were reported. The clinicopathologic features of the cases are shown in **Table 1** [4-19].

Here, we present a rare clinical case of superficial spreading SCC in situ of the cervix extending to the endometrium, which occurred in a 66-year-old patient of postmenopausal age. The neoplasm occurs in menopausal and postmenopausal women,

Table 1. Clinicopathological features of reported cases of superficial spreading squamous cell carcinoma of uterine cervix involving the endometrium

No	Reference	Case	Age	Clinical presentation	Extension of lesion	Follow-up
1	Takahiko N et al. [4] 2019	1	67	Lower abdominal pain	Cervix (in situ), endometrium (in situ), bilateral tubal (in situ), both ovaries (invasive) the greater omentum (invasive)	40 months
2	Rajeshwari K et al. [5] 2017	1	45	Lower abdominal pain, vaginam bleeding	Cervix (in situ), endometrium (in situ)	NA
3	Neelam S et al. [6] 2017	2	60	Abdominal mass	Cervix (invasive), endometrium (in situ)	NA
			70	Abdominal mass	Cervix (in situ), endometrium (in situ)	NA
4	Anthuenis J et al. [7] 2016	1	72	Hydrometra	Cervix (in situ), entire endometrium (generally in situ, focal microinvasive)	2 years
5	Yang SW et al. [8] 2014	1	69	Hydrometra	cervix, entire uterine corpus, vagina, left Salpinx (all in situ, with multifocal microinvasive)	NA
6	Ishida M et al. [9] 2013	2	64	Postmenopausal vaginal bleeding	cervix (invasive), endometrium (in situ)	NA
			59	postmenopausal vaginal bleeding	cervix (invasive), endometrium (in situ)	NA
7	Chao A et al. [10] 2013	1	60	Pyometra	Cervix (in situ), endometrium (generally in situ, foci invasive), bilateral fallopian tube (in situ)	died 2 days later
8	Marwah N et al. [11] 2012	3	65	Pyometra	cervix (invasive), endometrium (in situ)	NA
			60	Vaginal bleeding and discharge	cervix (invasive), endometrium (in situ with small focal microinvasion)	NA
			49	Postmenopausal vaginal bleeding	cervix (invasive), endometrium (in situ)	NA
9	Gungor T et al. [1] 2011	1	53	Postmenopausal vaginal bleeding	cervix (invasive), Endometrium (in situ, focal myometrial involvement), bilateral tubes and ovaries (in situ)	1 year
10	Tan GC et al. [2] 2004	1	70	Postmenopausal spotting	Cervix (microinvasive), endometrium (in situ)	6 months
11	Kushima M et al. [3] 2004	5	68	Excessive genital discharge	Cervix (in situ), endometrium (generally in situ, focal microinvasive), left fallopian tube (invasive), left ovary (invasive)	4.5 years
			58	NA	cervix (in situ), endometrium (single focus of microinvasion, <1 mm in depth)	NA
			72	Abdominal mass, hematometra	Cervix (in situ), endometrium (in situ)	2.5 years
			78	Vaginal bleeding	Cervix (invasive, papillary), endometrium (invasive), vagina (in situ)	
			59	Lower abdominal mass, vaginal bleeding	Cervix (invasive), endometrium (in situ with endometrial stroma sarcoma), left fallopian tube, left ovary, vagina (in situ), vulva (in situ)	NA
12	Pins MR et al. [12] 1997	1	55	Abnormal pap smears	Cervix (in situ), Endometrium (in situ), bilateral tubes (in situ), bilateral ovaries (invasive)	3.5 years
13	Razquin S et al. [13] 1993	1	52	Vaginal stenosis and pyometra	Cervix (in situ), endometrium (in situ)	6 months
14	Teixeira M et al. [14] 1991	1	64	pyometra	Cervix (in situ), endometrium (invasive)	NA
15	Punnone R et al. [15] 1979	1	64	Abnormal pap smears	Cervix (invasive), endometrium (in situ)	NA
16	Gupta S et al. [16] 1979	1	67	spotty bleeding per vaginum	Cervix (in situ), endometrium (in situ)	NA
17	Kanbour AI et al. [17] 1978	5	66	pyometra	Cervix (invasive), endometrium (in situ, foci of microinvasive)	4 months
			58	vaginal bleeding, abdominal pain	Cervix (invasive), endometrium (in situ)	11 years
			53	stenosis and pyometra	Cervix (invasive), endometrium (in situ)	4.5 years
			61	Abnormal pap smears	Cervix (invasive), endometrium (in situ)	3 years
			54	vaginal bleeding	Cervix (invasive), endometrium (in situ)	2 years
18	Kamalian N et al. [18] 1977	1	55	Vaginal bleeding and discharge	Cervix (invasive), endometrium (in situ, focal microinvasive)	NA
19	Ferenczy A et al. [19] 1971	1	53	Abnormal pap smears	Cervix (in situ), endometrium (in situ)	7 years

NA not available.

Microinvasive SCC [2] (1/31, 3%). The pattern of 15 cases of cervical SCC in situ spread in the endometrium was in situ (13/15, 87%), invasive (2/15, 13%). The pattern of 15 cases of cervical SCC invasive spread in the endometrium was in situ SCC, 3 cases with focal microinvasion, and 1 case with endometrial stroma sarcoma [3]. The pattern of 1 case of microinvasive SCC spread in the endometrium was also in situ [2]. 6 cases reported spread of tumor to the fallopian tube or ovaries as well [1, 3, 4, 10, 12], 1 case disseminated to the omentum [4].

HPV is known to be the main cause of cervical cancer, but its role in superficial spreading SCC in the endometrium remains unclear. p16, a surrogate marker for HPV infection, is positive in HPV associated cervical SCCs [20]. We observed p16 positivity in these superficial spreading and glandular involvement of atypical squamous cells in our case. We found signs of HPV in our patient, thus supporting the idea that HPV is a causative factor for superficial spreading SCC. In addition, immunohistochemical analysis showed a high Ki67 labelling index (80%) in the present case, in accord with the aggressive and malignant nature of the lesion.

Kushima et al. [3] described five cases of similarly unusual superficial spread of cervical squamous cell carcinoma and showed that genetic analysis suggested a single clonal process for these tumors with frequent loss of heterozygosity of 6p, 6q, 11p and 11q. Thus, they indicated that these tumors originated from the cervix and extended superficially to the upper genital tract. In our patient, detection of immunohistochemical expression of p16, p63 and CK5/6 in the cervix and the endometrium in our case suggest that these two lesions were etiologically related, favoring the possibility of the endometrial SCC secondary to cervical SCC in situ. Furthermore the present case showed the endometrium lined with malignant squamous epithelium, with foci of microinvasion into the surrounding stroma. The demonstration of continuity of the lesion suggested a superficial spread.

The diagnosis of superficial spreading SCC of the uterine cervix involving the endometrium requires careful examination of the uterine body and the cervix to rule out primary endometrial squamous cell carcinomas (PESCCs). It is essential to differentiate endometrial SCC involvement from PESCC based on the following strict pathological criteria recommended by Fluhmann [21]: (1) no evidence of a coexisting endometrial adenocarcinoma or primary cervical SCC; (2) no connection between the endometrial tumour and squamous epithelium of the cervix; or (3) no connection between any existing cervical in situ carcinoma and the independent endometrial neoplasm. In the present case, the entire cervix and endometrium had to be sampled entirely and showed a connection between the SCC in the corpus and in situ SCC of the cervix. We observed that cervical lesion superficially spread to the endometrium (**Figure 1C**), which did not conform to Fluhmann's criteria and demonstrated of continuity of the lesion suggested a superficial spread squamous cell carcinoma of the cervix involving the endometrium of uterus.

Survival data for superficial spreading SCC are poor. In our reviewed cases, the follow-up time ranged from 2 days to 11 years. Follow-up data were not available in 15 cases. Our patient was alive without evidence of the disease after a follow-up time of 3.6 years. Although total abdominal hysterectomy with bilateral salpingo-oophorectomy is the optimal therapy for superficial spreading SCC, the available data are insufficient to evaluate additional radiotherapy or chemotherapy.

Conclusion

Superficial spreading SCC in situ of the cervix to the endometrium is a rare phenomenon, with few cases reported in the literature. The World Health Organization in its classification of tumors of the cervix has not described such an event. The prognostic significance is also lacking because of limited data. The current case report indicated that not only invasive SCC of the cervix can spread to the endometrium, but also in situ SCC of cervix can also spread superficially upward, and replaced the endometrial lining, and we suggest that endometrium should be inspected and evaluated carefully, even if CIS diagnosed in cervical biopsy. More cases of superficial spreading SCC of the cervix are needed to determine management guidelines and prognosis.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Du, Faculty of Medicine and Health, Lishui University, Lishui, China. E-mail: 3582749663@qq.com

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