

A review and case report of enigmatic superficial endometrial spread of cancer of the uterine cervix: Need for vigilance in the primary care setting

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ABSTRACT

Cervical cancer is a leading cause of cancer-related morbidity and mortality. It usually spreads via direct invasion and lymphatics. Few cases with superficial spread to the uterine endometrium, fallopian tubes, and ovaries have been observed. The staging of these cases, as well as management, is not yet clear due to limited data. The Federation of Gynecology and Obstetrics (FIGO) staging disregards uterine spread to upstage the disease, and it also fails to provide clear guidelines regarding the superficial extension to the ovaries and tubes which is not uncommon in these cases. A 63-year-old female with postmenopausal bleeding was diagnosed with squamous cell carcinoma on a pap smear. Ultrasound and magnetic resonance imaging revealed a predominant endometrial lesion. Histopathology after Wertheim's hysterectomy revealed a squamous cell carcinoma of the endocervix, stage 1B2, that had spread superficially to the endometrium. A total of 48 cases of cervical cancer with superficial spread were identified. The commonest complaint was postmenopausal bleed in 39.39%. In 50% of the cases, the disease was carcinoma *in situ*, and 70.45% of the women had disease of stage 1B or less. In many cases, the disease had reached the tubes, 36.66%, and ovaries 23.33%. All women with stage 2A or lesser disease except for one were alive at 6 months after surgery. Superficial spread of cervical cancer is a distinct entity. Endometrial pathology must be ruled out before planning management in these women, especially when managing early-stage disease with conservative therapy.

Keyword: Cervical cancer, endometrial extension, gynecologic oncology, oncology, superficial spread

Introduction

Cervical cancer is one of the prime causes of cancer-related morbidity and mortality in Indian women.^[1] The primary routes of spread are by direct extension to the surrounding structures and lymphatic invasion. Superficial spread to the endometrium

is very rare with few cases reported in the literature. Historically, Cullen gave the first description in the year 1900, of a 65-year-old patient that had a squamous cell carcinoma that had an extension into the vagina and invaded into the lower uterine body but demonstrated a superficial spread to the rest of the endometrium forming multiple cell layers.^[2]

The revised 2018 Federation of Gynecology and Obstetrics (FIGO) classification^[3] focuses on the size of the tumor and the depth of stromal invasion. FIGO stage I clearly defines it as cancer strictly confined to the cervix and extension

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to the uterine corpus is disregarded. It further sub-classifies stage I based on the depth of invasion and tumor size in the cervix. The staging disregards the presence of cancer in the endometrium, fallopian tubes, and superficial spread to the ovaries. However, it is not uncommon for a superficial spreading of cervical cancer to reach these areas. It is undetermined if this kind of superficial spread changes the stage, management, and prognosis. The literature on this entity is limited. The primary care physician may be the first point of contact for women with cancer cervix. Hence, they need to be aware of this condition. We present a case of squamous cell cancer of the cervix that had extensive superficial endometrial spread with a review of available literature.

Case Description

After due patient consent and approval from the institutional ethical committee, we present the following report:

A 63-year-old old woman, menopausal since 20 years presented at the Gynecology OPD at All India Institute of Medical Sciences, Raipur, with a chief complaint of discharge per vaginum since 6 months. Per speculum examination revealed a cervix flushed with vagina and friable tissue at the external os. There was a 2.5 cm × 2 cm firm mass in the posterior fornix confirmed on per rectal examination. Bilateral parametria and rectal mucosa were free from tumor. Pap smear and biopsy revealed a squamous cell carcinoma. Ultrasound reported a uterus of size 6.8 × 3.2 cm. The endometrial cavity was distended with echogenic content and minimal fluid. Both ovaries were normal suggesting a diagnosis of “asymmetrical hetero echoic thickening of the endometrium with collection in the endometrial cavity, suspected carcinoma endometrium.” Magnetic resonance imaging (MRI) abdomen and pelvis [Figure 1] revealed a fluid-filled endometrial cavity, an irregular, circumferentially thick, intermediate to high signal intensity endometrium surrounded by thin hypointense rim seen in the fundus, body, and lower uterine segment. The

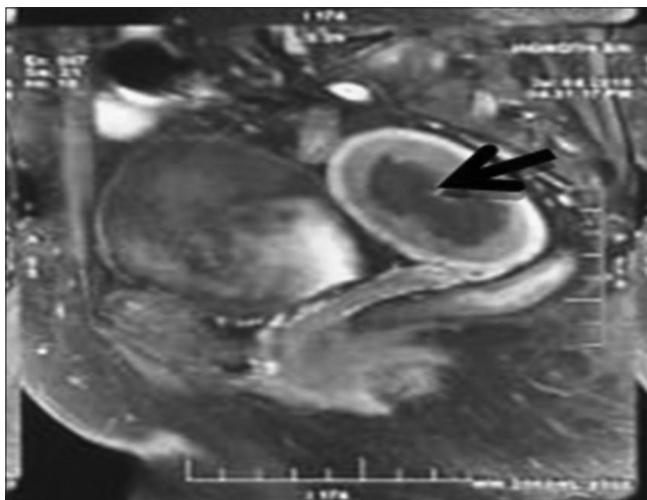


Figure 1: Image shows a mildly bulky uterus with fluid filled endometrial cavity. Endometrium is irregular and thickened intermediate to high signal intensity surrounded by thin hypointense rim

endo-myometrial junction was mildly obscured, and the visualized myometrium was normal in signal intensity. The lesion was seen extending into the cervical canal reaching just proximal to the external os, and the internal os was seen mildly widened by the lesion. A small nodule was noted in the stroma of the anterior cervical wall with signal characteristics similar to the endometrial lesion, and it was suggested to represent local spread. The uterine serosa, parametrium, mesorectal fascia, urinary bladder, and lymph nodes were not involved. Bilateral adnexa was reported normal.

There was a “diagnostic dilemma” given findings of cervical malignancy on biopsy but predominant endometrial lesion on imaging studies.

A Type III Radical Hysterectomy with bilateral pelvic lymphadenectomy was performed keeping a clinical diagnosis of carcinoma cervix stage 1B2 (revised FIGO staging). On the gross cut section, the entire endometrium was filled with friable tissue admixed with gelatinous mucoid material. A small friable mass was seen in the endocervical canal [Figure 2]. Histopathology revealed a squamous cell carcinoma, nonkeratinizing, moderately differentiated, grade 2, depth of invasion 16 mm, closest resected margins uninvolved, all lymph nodes were negative, parametrium and paracervical tissue uninvolved, and the tumor had spread superficially to the endometrium. Bilaterally, the tubes and ovaries were uninvolved. Human papillomavirus (HPV) DNA was positive for serotype 16. At follow-up, the patient was alive at 6 months after surgery.

Review and Discussion

Search methodology

We performed a PubMed, ResearchGate, Google search using the mesh terms, “cervical and carcinoma and superficial and/cephalad and/endometrial/ium, uterine and spread/extension. We searched all articles and cross-searched the references in these articles as of 14 June 2021. The mesh terms were used in different combinations, and the maximum number of results retrieved were 69 articles for a single search. The results from each search were analyzed by two independent researchers, and the articles where abstract or title was not related to the superficial spread of cervical cancer were primarily excluded. After removing duplicates, 32 articles remained. Of these, we could not retrieve 4 articles as they were too old and unable to access. The final analysis included 28 articles with 48 cases that reported superficial spreading cervical cancer lesions involving the endometrium, fallopian tube, and rarely the ovaries. These were included in our review. In most of these cases, the entire endometrium was found to be replaced by squamous cell cancer with primary in the cervix. Out of all these cases, eight cases were from India.

Findings: [Table 1]

Age profile

The age of these women varied from 38 years to 78 years [Table 1]. Most of the women were 46 to 65 years (89.19%) including our

Table 1: Demographic profile, clinical findings, histopathology, surgery and staging

	Number	Percentage
Age		
n=37		
35-45	3	8.11
46-55	11	29.73
56-65	10	27.03
65-75	12	32.43
75	1	2.70
Clinical profile		
n=33 (one women may have more than one complaint)		
Post-menopausal bleed	13	39.39
Lump in abdomen or distension	7	21.21
Pain	7	21.21
Vaginal discharge	4	12.12
Routine pap	7	21.21
Referred	1	3.03
Vaginal bleed	1	3.03
Urinary complaints	1	3.03
Histological subtype		
n=45		
Squamous cell carcinoma	41	91.11
Adenoid	1	2.22
Adenocarcinoma	1	2.22
Adenosquamous	1	2.22
Verrucous	1	2.22
Stage		
n=44		
CIS	23	50.00
1a	1	2.27
1b	8	18.18
2a	3	6.82
2b	5	11.36
Invasive	5	9.09
HSIL [†]	1	2.27
Involvement of tubes		
n=30		
Involved	11	44.44
Not involved	20	55.60
Ovarian involvement		
n=30		
Involved	7	25.93
Not involved	23	70.37
Surgery		
n=37		
TAH [‡]	2	5.41
TAH BSO [§]	6	16.22
Conization than TAH BSO	4	10.81
Conization than Wertheim's after 16 years	1	2.7
Radical Vaginal hysterectomy	1	2.7
Emergency subtotal hysterectomy	1	2.7
Wertheim's	21	56.76
Wertheim's with vulvectomy	1	2.7

^{*}CIS=carcinoma in situ, [†]HSIL=High grade squamous intraepithelial lesion, [‡]TAH=total abdominal hysterectomy, [§]TAH BSO=Total abdominal hysterectomy with bilateral salpingo oophorectomy

case. The youngest reported woman, 38 years, was also positive for HIV, hepatitis B, and C.^[4]

Clinical profile

The commonest symptom was postmenopausal bleed (39.39%) followed by a lump in the abdomen or distension of the abdomen (21.21%). The pain was the presenting feature

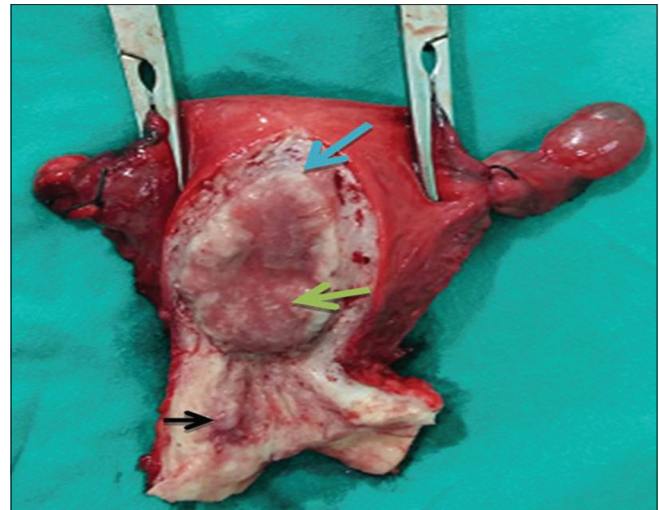


Figure 2: The bulky uterus is filled with heterogeneous pale pink gelatinous material (green arrow). The endo-myometrial distinction appears preserved (blue arrow). The pink friable mass continues into the cervix almost reaching upto the external os (black arrow)

in 21.21% and vaginal discharge in 12.12% of the women. Routine Papanicolaou (pap) smear was an aid in diagnosis with 21.21% of the women identified during screening. Pelvic examination findings were reported in 26 cases (54.16%), and 6 of these (23.08%) women had a normal-looking cervix^[5-10] where the diagnosis was made on a pap smear. Another 4 (15.38%) had cervical stenosis (one case had stenosis post conization performed 16 years ago).^[11-14,9,10] The cervix was firm flushed with vagina in 3 (11.54%) cases,^[13,15,16] and a visible cervical mass was reported in 11 (42.31%) women.^[4,12,13,17-21]

Histological subtype and extent

Of the 39 cases for whom a histological subtype was available, the commonest was squamous cell carcinoma reported in 41 (91.11%) cases, adenocarcinoma with an intestinal and mucinous component in one,^[7] squamous cell carcinoma with adenoid variant 12 in one, one adenosquamous variety 22, and one case of verrucous carcinoma 23 [Table 1]. Our case was a squamous cell carcinoma.

An interesting finding was that maximum women had carcinoma *in situ* (50%: 22 of 44) and one had a high-grade squamous intraepithelial lesion (2.27%) that had spread superficially. Total 70.45% of the women had disease of stage 1B or less. Thus, despite a lower stage in the cervix, the tumor extended cephalad, indicating an inherent propensity for cephalad extension rather than infiltration as is the usual case. Our case was stage 1B, reported in 18.18% of the cases.

Vagina was involved in 11 (22.91%: 11 of 48) cases,^[2,12,13,17,19,22,23] one woman (2.08%: 1 of 48) had involvement of vagina and vulva,^[24] and one had an endometrial sarcoma in addition to vaginal and vulval involvement (2.08%).^[25] Nakao *et al.*^[22] reported a rare case of adenosquamous cervical cancer with paradoxical extension. The squamous component extensively

invaded the superficial endometrium and replaced the glandular tissue, whereas the glandular component extended to the vagina replacing the squamous tissue. Out of the 30 cases with available information, the malignancy had reached one or both of the fallopian tubes in 11 cases (36.66%) and one or both ovaries in 7 cases (23.33%).

Adler *et al.*^[20] also reported unusual MRI findings in one patient. Dynamic gadolinium-enhanced MRI revealed a focally thickened endometrium as the major finding, whereas the cervical mass was best seen as an early enhancing lesion visible only on dynamic imaging and was more likely to be missed if dynamic imaging was not used. The full extent of the tumor was not radiologically evident and deep invasion of the cervix and myometrium was not appreciated on imaging precluding accurate diagnosis. A similar finding in our case where the endometrial lesion was the dominant finding creating an illusion of endometrial malignancy.

Choice of surgery

Wertheim's hysterectomy was performed in 56.76% of the women [Table 1]. A radical vaginal hysterectomy was done in one woman with stage 1B carcinoma, and the patient was alive and well at 3 years.^[12] One woman needed a subtotal emergency hysterectomy as she had pyometra and later went into septic shock.^[21] A Wertheim's hysterectomy type III was done in our case.

Mechanism of spread and origin

Cervical stenosis was proposed to be a reason for endometrial rather than the lateral extension.^[13,21] However, our analysis indicates that of the 25 cases with information about the cervical lesion, only 5 (20%) women had stenosis, hence this may not be the only reason for the superficial spread of the tumor.^[11-14]

The mechanism of spread is proposed to be contiguous or trans tubal.^[18] Two authors reported that the superficial spreading cells were strongly positive for CD138.^[16,17] CD 138 or Syndecan 1 is a key cell surface adhesion molecule.^[26] It is a cell surface heparin sulfate proteoglycan that is responsible for cell-cell and cell-extracellular matrix interaction. Expression of CD138 inversely correlates with tumor differentiation and prognosis. CD138 was found to decrease the invasiveness in oral malignancies by modulating the extracellular signal-regulated kinase (ERK) cascade. It has been proposed that this may be one possible reason for the superficial spread of this tumor rather than infiltration due to retained CD138 expression in these cells.^[17]

Another proposed mechanism is the transformation of endometrial cells to squamous rather than actual spread. P16 overexpression and HPV linkage have been proposed to be responsible for transforming the reserve cells in the endometrium misconceived as the superficial spread.^[27] But in another study, Kushima *et al.*^[24] studied the loss of heterozygosity markers in the endometrial cells in five women. The markers helped localize

the cell of origin. The loci for 6p, 6q, 11p, and 11q were found to be positive in endometrial and cervical samples indicating a monoclonal origin of both the tumors supporting spread from cervix rather than endometrial cell transformation.

Survival: [Table 2]

Survival data were available for 18 cases [Table 2]. One had a tumor extending to both the tubes and died of septicemia secondary to pyometra.^[21] One had a tumor extending to the right tubes, and she also had positive pelvic nodes. She died after 4 ½ months due to the disease.^[12] In another woman with fallopian tube involvement, the diagnosis was made on routine pap, and she was alive 4 years after surgery.^[7] Another patient with cervical stenosis and hematometra had a bilateral tube and ovary involvement and was alive at 40 months after radical surgery.^[14] In one woman, the adnexa was not removed as she was operated on for an *in situ* cancer.^[6] In the remaining 8 cases, the tumor did not spread to the tubes or ovaries, and the survival reported varied from 6 months to 11 years. The longest survival reported for CIS is 15 years after surgery and even then, the patient died of bronchopneumonia and cerebral arteriosclerosis with no evidence of clinical recurrence. However, this death was reported in the year 1968 and so considering the limited availability of diagnostic modalities and absence of necropsy, data on recurrence or metastasis is dubious. All women with stage 2A or lesser disease (n = 8) except for the one who died of septic shock, were alive at least 3 months after surgery. Deel *et al.*^[7] postulate that in women with the localized cervical disease, the superficial spread to the endometrium and adnexa may not be associated with an inferior prognosis. Our patient was alive and well at 6 months after surgery. With an increasing number of cases being reported from countries like India, it is recommended that treating physicians remain more vigilant and exercise extra caution while managing these cases.

Wertheim's hysterectomy and survival

Both women with CIS in whom radical hysterectomy was done survived for at least 40 months and 15 years each. For stage 1B (three cases), the longest survival available after radical hysterectomy is alive at 4 years. One woman (1 of 3, 33.33%) with stage 2B disease died after 4.5 years. Radical hysterectomy does appear to prolong life. However, the choice of optimal surgery and if the surgery provides greater benefit to women diagnosed with the superficial spread at the first point of contact remains to be ascertained.

Conclusion

Superficial spread of cervical cancer towards the endometrium is a rare but cognizable phenomenon. This spread may occur irrespective of the stage of the disease in the cervix. Gross examination of the cervix may mislead us towards the extent of the lesion. Caution needs to be exercised when treating *in situ* cases with procedures like loop electrosurgical excision procedure (LEEP) or conization as the lesion may have spread to the endometrium and thus alter the stage and choice of surgery. It is wise to evaluate the endometrium thoroughly

Table 2: Survival in relation to age, history, clinical findings, stage, and cervical stromal invasion, extension to tubes and ovaries, and surgery

Study	Age (yrs)	History	Examination and investigations	Stage	Stromal invasion	Tubes and ovaries	Surgery	Survival
Tan ^[15]	70	Post-menopausal bleed Foul discharge	Firm flushed with vagina Pyometra present	1B2	Yes Micro	Not Involved	TAH BSO*	Alive at 6 months
Fadare ^[4]	38	Pain, discharge	Massively enlarged with ulcerations, HPV, HIV, Hep B, HCV positive	1B2	Yes	Not Involved	Wertheim's	Alive at 9 months
Komanapalli ^[6]	55	Post-menopausal bleed and pain	Normal atrophic	CIS	No	Adnexa Not Removed As Diagnosis CIS†	Total Abdominal Hysterectomy	Alive at 9 months
Kanbour ^[12] 5 Cases	66	Referred	Tumor in cervix, pyometra	2B	Yes	Right Tube	Wertheim's, Lymph Nodes Positive	Died after 4 months
	58	Post-menopausal bleed, pain, lump in abdomen	Cervical stenosis, hematometra	2A	Yes	Not Involved	Wertheim's	Alive at 11 years
	53	Post-menopausal bleed	Tumor in cervix	2B	Yes	Not Involved	Wertheim's	Died after 4½ years
	61	Routine pap	Cervical stenosis	1B	Yes	Not Involved	Wertheim's	Alive at 3 years
Ishida ^[17] 2 Cases	54	Post-menopausal bleed	Tumor in cervix	2B	Yes	Not Involved	Wertheim's	Alive at 2 years
	64	Post-menopausal bleed	Tumor in cervix, vagina involved	2A1	Yes	Not Involved	Wertheim's	Alive at 10 months
	59	Post-menopausal bleed	Tumor in cervix	2B	Yes	Not Involved	Wertheim's	Alive at 6 months
Chao ^[21]	60	Distension of abdomen	Distended cervix and uterus, pyometra	CIS	Yes	Both Tubes Involved	ESHFSS‡	Died after 2 days
Deel ^[7]	50	Routine pap	Normal	1B	Yes	Focal Right Tube	Leep Then Wertheim's	Alive at 4 years
Ferenzycy ^[10]	53	Routine pap	Normal	CIS	No	Not available	Conization than TAH	Alive at 7 years
Gulati ^[19]	57	White discharge, pain in abdomen	Visible growth	2A	Yes	Not available	Wertheim's	Alive at 6 months
Karapoulau ^[9]	69	Routine pap	Normal	CIS	No	Not available	Conization than TAH BSO	Alive at 7 months
Nakajima ^[14]	67	Pain in abdomen	Stenosed	CIS	No	Yes, both tubes and ovaries	Conization than radical hysterectomy, omentectomy and transverse colon resection after 16 years.	Alive at 40 months
	70	Routine pap	Not available	CIS	Yes	Not available	Wertheim's	Died 15 years after surgery due to other causes.
Salm ^[2] 2 cases	44	Routine pap	Normal	CIS	No	Not available	TAH	Alive at 3 months

*TAH BSO=Total abdominal hysterectomy, bilateral salpingo oophorectomy, †CIS=Carcinoma in situ, ‡ESHFSS=Emergency Subtotal Hysterectomy For Septic Shock

in every case of cancer cervix to offer the best management modalities to the patient.

Key points

- Vigilance is the key in managing cancer cervix.
- Superficial involvement of the endometrium and tubes is possible.
- If untreated, this superficial spread may lead to the recurrence of the tumor.
- Need to sample the cervix before surgery in lesions that are found to be endometrial on imaging studies.
- A careful evaluation and therapeutic strategy must be adopted for optimal disease-free outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for

her images and other clinical information to be reported in the journal. The patient understands that her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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