

CASE SERIES

Superficial Spreading Squamous Cell Carcinoma Endometrium and Ichthyosis Uteri with CINIII with p16 Expression: Report of 2 Unusual Cases*Neelam Sood¹, Kumar Sharad Sinha^{1*}**¹Department of Pathology, DeenDayal Upadhyay Hospital, Govt. of NCT, Harinagar, Delhi-110064 (Delhi) India***Abstract:**

We report two interesting and rare case reports, a 60 year old with well differentiated squamous cell carcinoma of cervix with superficial spreading into the endometrium, other female of 70 year old with features of CIN III also involving the endometrium with multifocal epidermidization consistent with ichthyosis uteri, involving cervix and endometrium. p16 was used as a surrogate marker which was positive for neoplastic cells in both the cases, showing HPV aetiology. Superficial spreading squamous cell carcinoma of the cervix is a rare entity, with less than 30 cases reported in the literature. Primary endometrial squamous cell carcinoma usually occurs in postmenopausal women with mean age of presentation being 67 years. It is postulated that tumour may arise from ichthyosis uteri. Demonstration of p16 positivity in tumour cells helps in revealing HPV aetiology was also confirmed thus signifying its usefulness. Hence, we report these rare entities.

Keywords: Endometrium, Squamous Cell Carcinoma, Ichthyosis Uteri

Introduction:

Squamous Cell Carcinoma (SCC) of the upper female genital tract, including the endometrium, fallopian tubes, ovary etc are extremely rare with cases reported singly with less than 30 cases reported in the literature, all these cases are in stage 1B or higher [1]. There is a possibility of following pathogenic mechanisms which include 1) de novo carcinogenesis; 2) extensive squamous metaplasia (ichthyosis uteri) in the mucosa of the upper genital tract with subsequent malignant

transformation; 3) endometrioid adenocarcinoma with predominantly squamous differentiation; and 4) mucosal spread from cervical SCC [2].

SCC is the most common malignant tumour of the cervix that comprise of 70-80% of cervical malignant tumours. 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 tumour tissue is called superficial spreading SCC and is an extremely rare entity which has been reported [3-5].

The presence of squamous epithelial lining in the endometrium, termed ichthyosis uteri, a condition in which the endometrium is replaced by keratinized squamous epithelium, leukoplakia epidermidization, psoriasis uteri, epidermoid heteroplasia, cholesteometra, indirect regenerative squamous metaplasia etc., has been described under many conditions and is benign in most of the cases. Invasive squamous cell carcinoma of the endometrium is rare and is thought to arise by one of the two mechanisms: upward spread of a primary cervical lesion or transformation of reserve or stem cells positioned between the glandular basement membrane and the endometrial columnar epithelium [6].

Human papillomavirus (HPV) infection is associated with the development of both cervical and endometrial SCC, and p16, a surrogate

marker for HPV infection is positive in HPV-associated cervical SCCs and precancerous squamous intraepithelial lesions. However, the utility of p16 expression and HPV DNA status have not been clearly determined in patients with primary SCC of the upper genital tract [7].

Case Report-1:

A 60-year-old multiparous, postmenopausal woman presented with the history of abdominal mass for last 6-7 months, which was progressively increasing in size with pap smear examination showed features of HSIL. The patient was operated upon and a pan hysterectomy specimen was received, uterus with cervix measuring 9x7x 6.5 cm, right ovary measuring 2.5x1.5x1cm, right fallopian tube- 6cm, left ovary -3x1.5x1cm and left fallopian tube -5.5cm. Cervix showed presence of circumferential and infiltrative growth.

Microscopy:

Sections through the uterus with cervix, showed features of Well differentiated Squamous cell carcinoma which was multifocal, circumferentially involving the cervical wall (>3/4th wall thickness) with foci of transformation from CINIII to invasive squamous cell carcinoma. The tumour was extending partially into endocervical canal. The endometrial lining was partially replaced by squamous epithelium in cake icing pattern with marked dysplasia (carcinoma in situ). The underlying atrophic endometrial glands also showed focal transformation to carcinoma *in situ* III(CINIII) (Fig.1A-D). Myometrium and parametrium were uninvolved. No lymphovascular invasion noted.

IHC Study:

The formalin-fixed, paraffin-embedded tissue blocks of the resected specimens were cut into 3- μ m-thick sections, deparaffinized and rehydrated

and were immunohistochemically stained by monoclonal antibodies using p16(Biocare), p53(Biocare) and ki-67(Dako).

The neoplastic epithelium on both cervix and endometrium showed strong p16 (Fig.1E- F) and Ki-67 expression (Fig.1 H), p53 (Fig.1G) was moderately positive.

Case Report-2:

A 70-year-old multiparous, postmenopausal woman presented with the history of mass abdomen for last 4 months, which was progressively increasing in size. Pap smear revealed features of atypical squamous cells and cervical biopsy revealed presence of CINIII features.

Pan hysterectomy specimen was received, specimen of uterus with cervix measuring 10x7.5x4cm (Fig.2A) showing dilated endometrial cavity lined by white shining thick membrane with corrugated surface. Right ovary measuring 2.5x1.5x0.5cm, right fallopian tube-4cm, left ovary measuring 15x10x5cm, with cut section showing-cystic and solid areas with presence of blood clots and left fallopian tube-6.5cm.

Microscopy:

Sections from cervix and endometrium showed marked epidermidization with surface papillations. Extensive multifocal areas of moderate dysplasia to carcinoma in situ were seen (Fig.2B-D). No myometrial or parametrial invasion was noted. Fallopian tubes and ovaries were unremarkable.

IHC Study:

Strong p16(Biocare) expression was noted in the dysplastic and carcinoma in situ cells arising from the endometrium (Fig. 2E-F). p53(Biocare) was also focally positive (Fig.2G), and Ki-67(Dako) index was 60% (Fig.2H).

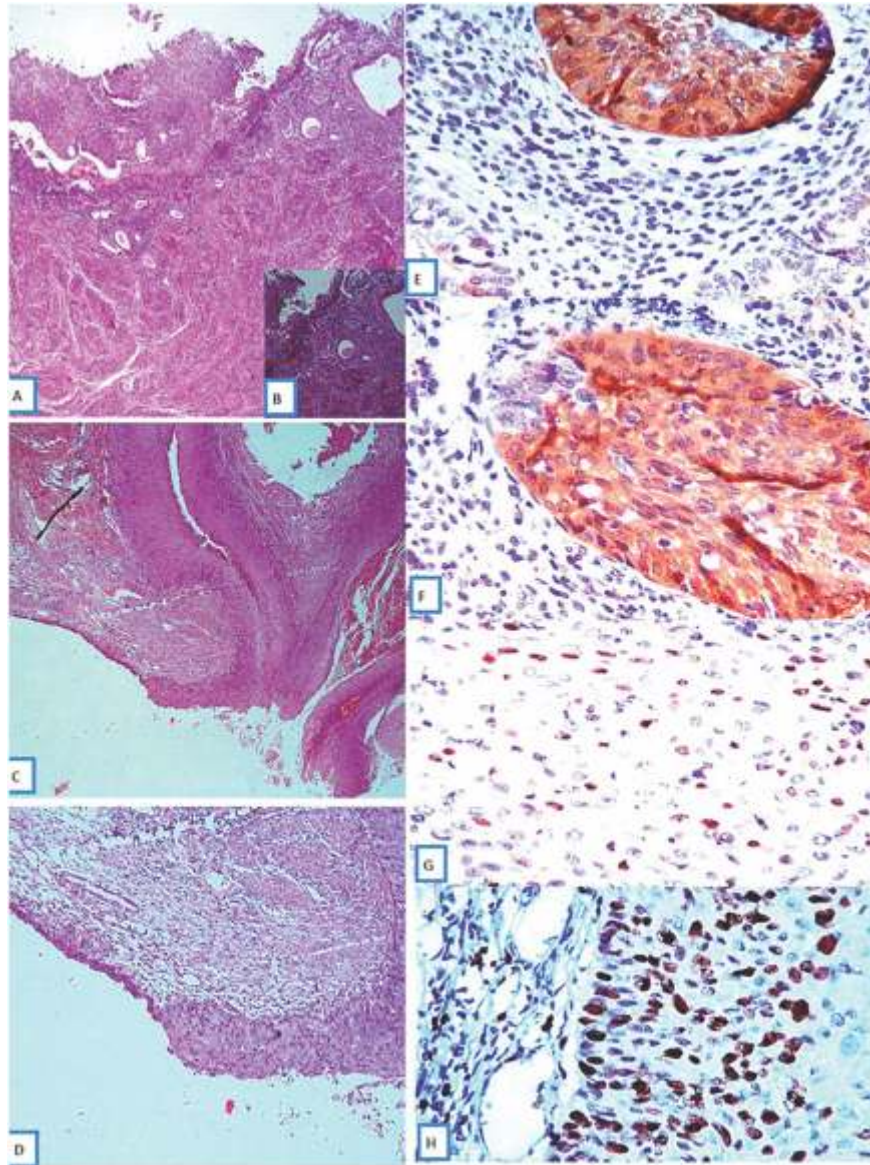


Fig.1(A,B): Features of Invasive Squamous Cell Carcinoma with Endometrial Lining Partially Replaced by Squamous Epithelium in Cake Icing Pattern with Marked Dysplasia (Carcinoma in Situ) (H&E, 40X)

Fig.1(C,D): Tumour Tissue Spreading into the Endocervical Canal (H&E, 40X)

Fig.1(E,F): Neoplastic Epithelium on the Endometrium showed Strong p16 Positivity (100X)

Fig.1 (G): Moderate p53 Positive Cells (100X)

Fig.1 (H): Strong Ki-67 Positive Cells (100X)

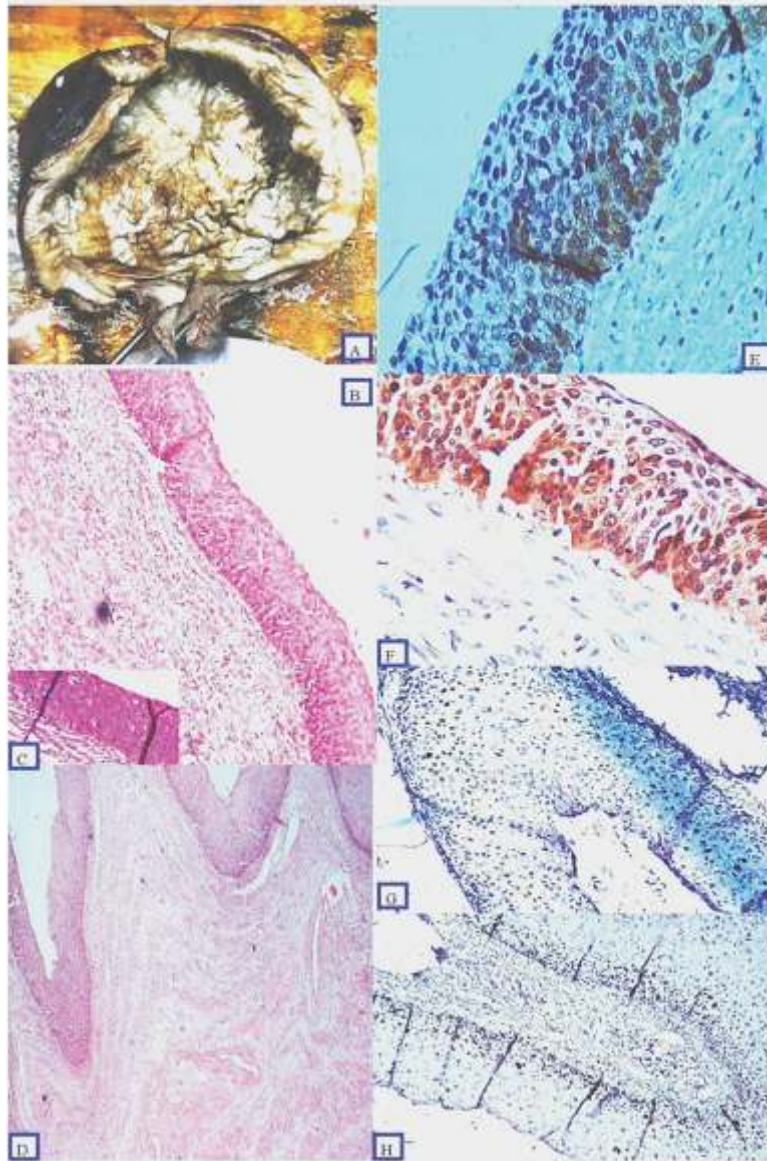


Fig.2 (A): Specimen of Uterus with Cervix showing Dilated Endometrial Cavity Lined by White Shining Thick Membrane with Corrugated Surface.

Fig. 2 (B-D): Cervix and Endometrium Showing Marked Epidermidization with Surface Papillations and Extensive Multifocal Areas of Moderate Dysplasia to Carcinoma in Situ. (H&E, 40X)

Fig.2(E-F): p16 Positivity Noted in the Dysplastic In situ Cells Arising from the Endometrium (100X)

Fig. 2(G): p53 Positive Cells (40X)

Fig. 2(H): Ki-67 Positive Cells (40X)

Discussion:

Endometrial SCC is an extremely rare entity, with only 70 cases being reported in the literature. It is usually seen in postmenopausal women. Goodman *et al.* reported eight cases of squamous cell carcinoma of endometrium in 1996 and reviewed previous 56 reported cases. Various predisposing factors such as early marriage, early first sexual intercourse, and multiparity were seen [8]. Superficial spreading SCC of the uterine cervix involving the endometrium is an extremely rare entity with only 26 cases, which have been reported [9]. Endometrial invasive SCC is thought to arise by one of the two mechanisms: if there is an upward spread of a primary cervical lesion or transformation of reserve or stem cells which are positioned between the glandular basement membrane and the endometrial columnar epithelial layer [6].

Cervical carcinoma generally spreads upward to the parametrium, and through the lymphatic channels invading to the uterine wall. Endometrial SCC can occur by direct extension from carcinoma of the cervix. Uterine corpus involvement by cervical cancer is seen through deep myometrial penetration or via lymphatic dissemination. However, the superficial spread over the contiguous endometrial surface may occur rarely as in case 1 which are evident as whitish patches, on gross, a condition called 'cake icing' or 'Zukerguss' carcinoma, wherein the superficial squamous carcinoma sweeps over or replaces the entire endometrium. The first case showed the endometrium lined with malignant squamous epithelium, with very focal superficial invasion into the underlying myometrium [10]. In our 1st case, p16 positivity in these deep endometrial glands showing transformation supported the theory of transformation of reserve or stem cells positioned between the glandular

basement membrane and the endometrial columnar epithelium. Thus supporting the origin of superficial spreading cervical squamous cell carcinoma is involving the endometrium. Marwah *et al.* [10] have reported 3 cases and Ishida *et al.* have reported 2 cases of cervical superficial spreading squamous cell carcinoma involving the Endometrium [9].

Our 2nd case demonstrated extensive squamous metaplasia with dysplasia with carcinoma *in situ*, providing further support for this proposed sequence. It has been reported that SCC generally does not develop in ichthyosis, however in the 2nd case there was multifocal CIN with remaining areas showing normal stratified squamous epithelium with corroborates the fact that CINIII and SCC can arise in ichthyosis as reported by Murheka *et al.* [11], Bagga *et al.* [12] and Takeuchi *et al.* [13].

P53 protein expression is reported to be seen in primary SCC of the endometrium [14]. In the present study, p53 expression of neoplastic cells was noted in both the cases, suggesting that p53 gene mutation is present in primary SCC of the endometrium. In the present cases, the Ki-67 labeling was very high (70%). These observations demonstrate the malignant nature of the present cases. O' Neill *et al.* also noted HPV infection association with the development of both cervical and endometrial SCC, and p16, a surrogate marker for HPV infection, is consistently positive in HPV-associated cervical SCCs and squamous intraepithelial lesions as seen in our cases [7]. HPV and p16 have been detected in SCCs of the fallopian tube and cervical SCCs *in situ*, suggesting lesion multiplicity and a "field effect" of HPV infection [15], thus it makes our case reports all the more rare and exceptional.

Conclusion:

Superficial spreading squamous cell carcinoma of the cervix is a rare phenomenon, with less than 30 cases reported in the literature, all these cases are in stage 1B or higher. Primary endometrial squamous cell carcinoma usually occurs in postmenopausal women with mean age of

presentation being 67 years. It is believed that tumor may arise from ichthyosis uteri. Demonstration of p16 positivity in tumour cells helps in revealing HPV etiology, as was also confirmed thus signifying its usefulness. Hence, we reported these rare entities.

References

1. Goodrich S, Kebria-Moslemi M, Broshears J, Sutton GP, Rose P. Primary squamous cell carcinoma of the endometrium: two cases and a review of the literature. *Diagn Cytopathol* 2013; 41(9):817-20.
2. Gungor T, Altinkaya SO, Ozat M, Akbay S, Mollamahmutoglu L. Unusual form of superficial spreading squamous cell carcinoma of cervix involving the endometrium, bilateral tubes and ovaries: a case report with literature review. *Arch Gynecol Obstet* 2011; 283(2): 323-27.
3. Tan GC, Isa MR, Ng SP and Jamil MA. Unusual form of superficial spreading microinvasive squamous cell carcinoma of uterine cervix involving the endometrium of uterus. *J Obstet Gynaecol Res* 2004; 30(5): 363-67.
4. Kushima M, Fujii H, Murakami K, Ota H, Matsumoto T, Motoyama T, *et al.* Simultaneous squamous cell carcinomas of the uterine cervix and upper genital tract: loss of heterozygosity analysis demonstrates clonal neoplasms of cervical origin. *Int J Gynecol Pathol* 2001; 20(4): 353-58.
5. Pins MR, Young RH, Crum CP, Leach IH and Scully RE. Cervical squamous cell carcinoma in situ with intraepithelial extension to the upper genital tract and invasion of tubes and ovaries: report of a case with human papilloma virus analysis. *Int J Gynecol Pathol* 1997; 16(3):272-78.
6. Kay S. Squamous cell carcinoma of the endometrium. *Am J Clin Pathol* 1974; 61(2):264-74.
7. O'Neill CJ, McCluggage WG. p16 expression in the female genital tract and its value in diagnosis. *Adv Anat Pathol* 2006; 13(1): 8-15.
8. Goodman A, Zukerberg LR, Rice LW, Fuller AF, Young RH, Scully RE. Squamous cell carcinoma of endometrium: A report of eight cases and a review of the literature. *Gynecol Oncol* 1996;61(1):54-60
9. Ishida M, Okabe H. Superficial spreading squamous cell carcinoma of the uterine cervix involving the endometrium: Report of two cases with emphasis on the likely molecular mechanism. *Oncol Lett* 2013; 5(1): 31-4.
10. Marwah N, Garg M, Singh S, Sethi D, Sen R. Unusual form of squamous cell carcinoma of the cervix extending *in situ* into the endometrium: Three case reports and review of literature. *Int J Appl Basic Med Res* 2012; 2(2): 139-41.
11. Murhekar K, Majhi U, Sridevi V, Rajkumar T. Does "ichthyosis uteri" have malignant potential? A case report of squamous cell carcinoma of endometrium associated with extensive ichthyosis uteri. *Diagn Pathol* 2008; 3:4.
12. Bagga PK, Jaswal TS, Datta U, Mahajan NC. Primary endometrial squamous cell carcinoma with extensive squamous metaplasia and dysplasia. *Indian J Pathol Microbiol* 2008; 51(2): 267-8.
13. Takeuchi K, Tsujino T, Yabuta M, Kitazawa S. A case of primary squamous cell carcinoma of the endometrium associated with extensive "ichthyosis uteri". *Eur J Gynaecol Oncol* 2012; 33(5):552-4.
14. Griordano G, D'Adda T, Merisio C, Gnetti L. Primary squamous cell carcinoma of the endometrium: a case report with immunohistochemical and molecular study. *Gynecol Oncol* 2005; 96(3): 876-79.
15. Wang Z, Dong J, Eyzaguirre EJ, Tang WW, Eltorkey MA, Qiu S. Detection of human papilloma virus subtypes 16 and P16 (ink4a) in invasive squamous cell carcinoma of the fallopian tube and concomitant squamous cell carcinoma *in situ* of the cervix. *J Obstet Gynaecol Res* 2009; 35(2): 385-9.

*Author for Correspondence: Dr. Kumar Sharad Sinha, Department of Pathology, Deen Dayal Upadhyay Hospital, Govt. Of NCT, Delhi-110064 India Email: kumarsharadsinha@yahoo.co.in Cell: 9582397446