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CASE REPORT

Superficial spreading cervical squamous cell carcinoma in situ with extensive endomyometrial infiltration masquerading as a primary endometrial cancer

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The presence of squamous cell carcinoma (SCC) on endometrial histology raises the possibility of a primary endometrial carcinoma, as well as secondary endometrial involvement by SCC from another site, especially the cervix. This distinction relies on numerous cardinal clinical and pathologic findings and may occasionally be problematic. We document an unusual tumour in a postmenopausal woman who presented with clinical and radiologic features of a primary endometrial cancer, confirmed on endometrial histology as a keratinising SCC. Subsequent pathologic evaluation of the hysterectomy specimen, however, demonstrated an exclusively in situ cervical SCC, with extensive endometrial intramucosal spread and widespread infiltration of the myometrium, macroscopically mimicking a primary endometrial neoplasm. We review the pathologic distinction between primary endometrial SCC and secondary corpus involvement of cervical SCC, as well as the broader differential diagnosis when SCC is identified on endometrial histology.

Keywords: superficial spreading, cervical squamous cell carcinoma, secondary endomyometrial infiltration, primary endometrial squamous cell carcinoma, human papillomavirus

Introduction

Primary squamous cell carcinoma (SCC) of the endometrium is exceedingly rare and constitutes less than 0.5% of all endometrial cancers.[1-3] Diagnosis always requires careful exclusion of secondary uterine corpus involvement by SCC from another site, most frequently the cervix. While the tumour's primary site is usually apparent on clinical and radiologic grounds, this distinction may sometimes be problematic.

We report a case of a postmenopausal woman with clinical and radiologic features of a primary endometrial tumour, confirmed by a preoperative endometrial biopsy as keratinising SCC. After the comprehensive hysterectomy specimen pathologic examination and subsequent molecular testing, the tumour was found to represent a primary cervical SCC in situ with extensive replacement of the endometrium and widespread myometrial infiltration.

Case report

A 65-year-old gravida 3, para 3 Caucasian female presented with one week of postmenopausal haemorrhage, followed by a periodic offensive vaginal discharge. Medical history included previous large loop excision of the transformation zone (LLETZ) 33 years ago and longstanding systemic hypertension. The histological findings of the LLETZ biopsy and subsequent screening history were unknown. There is no history of prior irradiation. Gynaecological examination revealed an unremarkable cervix and slightly bulky uterus. Transvaginal ultrasound (TVU) demonstrated a normal cervix but a large uterine fundus-centred tumour extensively infiltrating the myometrium (Figure 1). A pelvic computed tomography (CT) scan confirmed these findings, with no other regional tumour involvement.

A preoperative endometrial biopsy confirmed an infiltrating, moderately differentiated keratinising SCC, while simultaneous

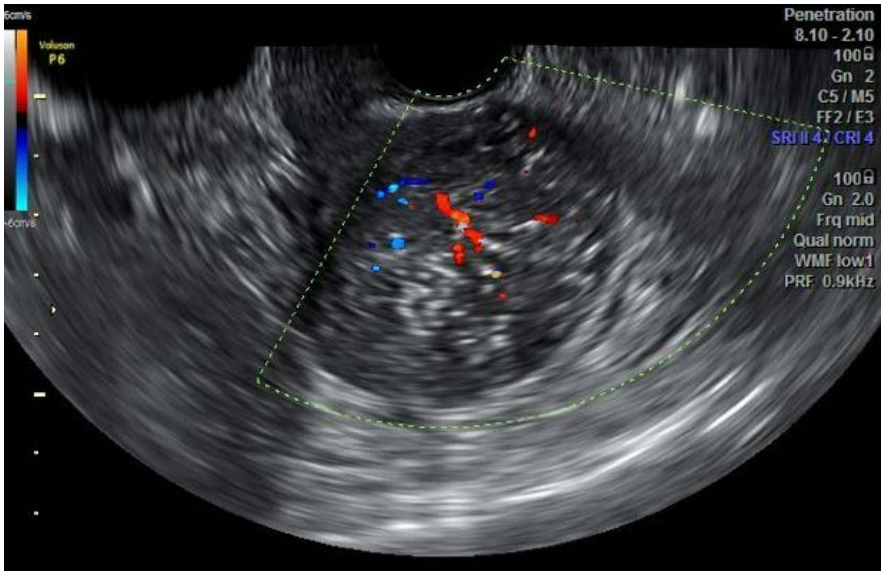

Figure 1: Endovaginal ultrasound image demonstrating a large uterine corpus tumour with extensive myometrial infiltration

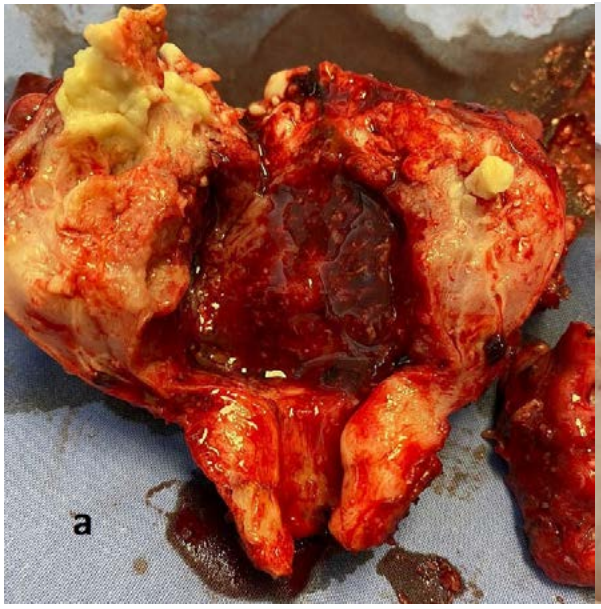

Figure 2a: Hysterectomy specimen showing diffuse corpus and fundus wall invasion by tumour with associated paste-like keratin.
Note the haemorrhagic uterine content and only slightly irregular cervix demonstrating some contamination by the myometrial keratinous material.

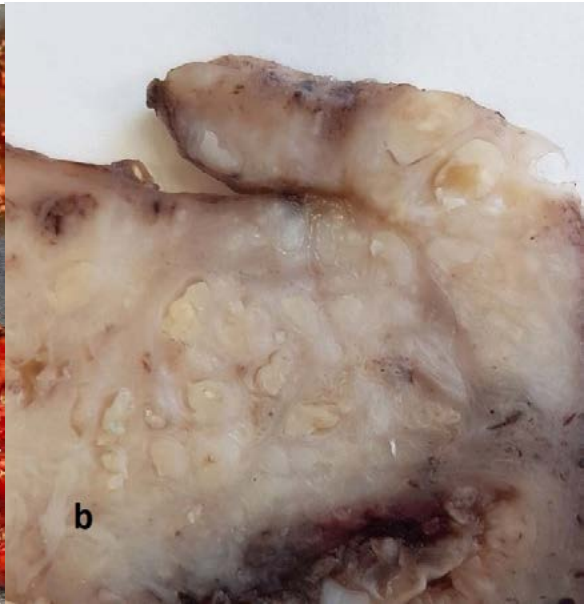

Figure 2b: Formalin-fixed laboratory slice of the uterine fundus revealing an attenuated endometrium (top) and thickened myometrium with transmural tumour infiltration and striking keratin plug formation.

ThinPrep® cervical cytology showed a high-grade squamous intraepithelial lesion (HSIL). Owing to the combination of the patient's clinical presentation and cervical cytology findings, it was decided to perform a total abdominal hysterectomy with bilateral adnexectomy and pelvic sentinel lymph node mapping (without additional colposcopic biopsy).

Macroscopy of the hysterectomy specimen revealed almost entire replacement of the uterine corpus by a granular, friable tan to grey, endophytic tumour with abundant mural yellow paste-like material (Figure 2a). The cervix appeared slightly irregular, but no clear masses or polyps were identified on serial sectioning.

Widespread myometrial invasion and focal serosal tumour extension were noted (Figure 2b).

Uterine corpus histology showed diffuse endometrial replacement by SCC in situ, with widespread myometrial invasion by moderately differentiated keratinising SCC (Figure 3a). The tumour comprised infiltrating nests and solid sheets of polygonal cells with well-developed intercellular bridges, moderate nuclear pleomorphism, brisk mitotic activity, focal dyskeratosis and areas of clear cell change. The sheets demonstrated prominent central keratinisation, corresponding to the paste-like areas visible macroscopically. Despite extensive sampling, no associated endometrioid, other adenocarcinomatous or sarcomatous component was identified. Histology of the cervix, which was submitted in its entirety, revealed an extensive HSIL, ranging from grade II cervical intraepithelial neoplasia (CIN II) to SCC in situ, contiguous with the endometrial in situ SCC (Figure 3b). There was patchy circumferential scarring (compatible with the previous LLETZ procedure), but no microinfiltration or invasive carcinoma

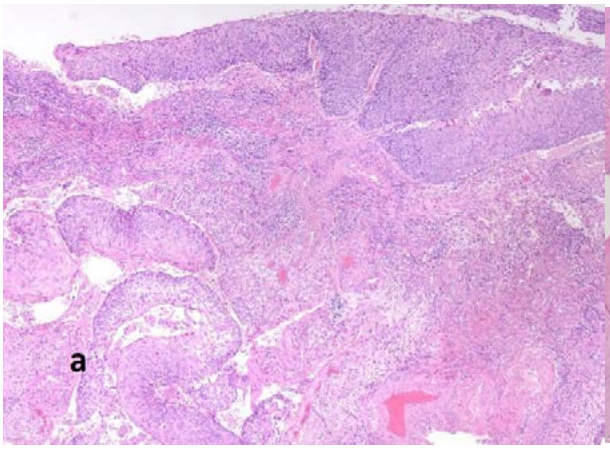

Figure 3a: Corpus tumour histology showing endometrial replacement by SCC in situ (top) and underlying myometrial infiltration by keratinising squamous cell carcinoma (haematoxylin and eosin stain, original magnification x100)

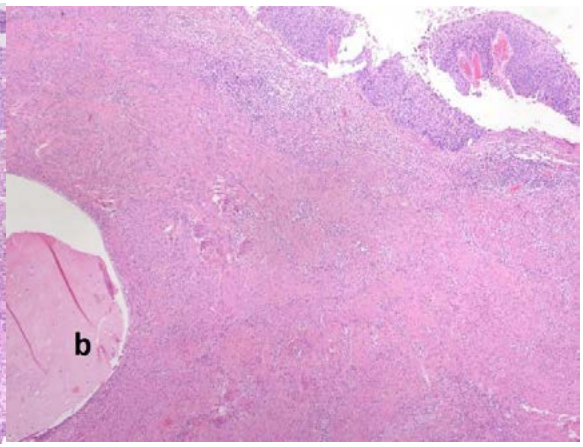

Figure 3b: Uterine cervix microphotograph with superficial SCC in situ (top right), dilated endocervical gland (bottom left) and no evidence of tumour stromal invasion. The in situ SCC was contiguous with the endometrial pathology (haematoxylin and eosin stain, original magnification x100)

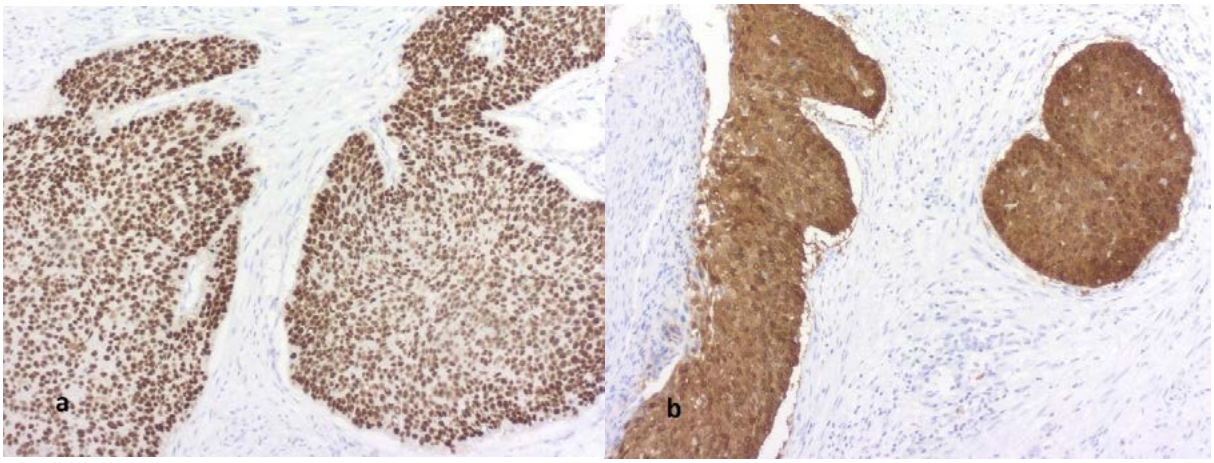

Figure 4a: Diffuse p63 protein nuclear staining supporting the squamous tumour morphology (original magnification x200)

Figure 4b: P16 protein immunoperoxidase stain showing diffuse positivity in the corpus tumour (original magnification x200)

was identified. Ultra-staging examination (haematoxylin and eosin, as well as pan-cytokeratin immunohistochemical staining of more than 10 levels) of three pelvic sentinel lymph nodes was negative for metastatic tumour.

Immunohistochemistry (IHC) performed on the corpus tumour revealed strong diffuse positivity for p63 protein and CK5/6, supporting a squamous phenotype (Figure 4a). P16 protein showed strong diffuse nuclear and cytoplasmic staining in both in situ and infiltrating components (Figure 4b). CA125, CK7, vimentin, p53 protein, GATA binding protein 3, TTF1 (thyroid transcription factor 1), CDX2 (caudal-related homeobox gene 2), oestrogen receptor (ER) and progesterone receptor (PR) stains were negative.

Polymerase chain reaction (PCR) testing was undertaken on formalin-fixed paraffin-embedded (FFPE) corpus tumour tissue and confirmed the presence of high-risk human papillomavirus (HR-HPV) DNA, genotype 16.

The postoperative course was uneventful. The patient received adjuvant chemoradiation therapy (due to focal uterine serosal involvement by tumour) and she is currently recurrence-free, eight months after surgery.

Discussion

A patient presenting with clinical and radiologic features of a uterine corpus tumour and SCC on endometrial histology raises numerous diagnostic considerations. These include primary endometrial malignancy and secondary uterine corpus involvement by direct infiltration or metastatic deposits of SCC from another site.

Primary SCC of the endometrium has been introduced as a distinct entity in the 2020 World Health Organization (WHO) classification of female genital tract tumours.[1] Morphologically, it is identical to SCC seen elsewhere in the female genital tract. The tumour typically affects postmenopausal women, presents with vaginal bleeding and is associated with chronic uterine inflammation, including longstanding pyometra, cervical stenosis and ichthyosis uteri.[3,4] The presence of a precursor lesion and associated conventional endometrioid adenocarcinoma on histology supports a primary endometrial origin. The latter component may only be detected after comprehensive sampling, however, and is infrequently represented on limited endometrial biopsy or curettage material. The diagnosis of a primary uterine carcinosarcoma (malignant mixed Müllerian tumour [MMMT]) with an overriding SCC component also warrants consideration, but requires histologic confirmation of an associated malignant mesenchymal component.[5]

Secondary corpus infiltration by SCC of other genital tract, and less often, extragenital sites is an important diagnostic consideration. Direct infiltration by cervical SCC is most frequent, although direct spread from a locally advanced urinary tract, anocolorectal or vaginal primary may be seen. The primary tumour site is usually clinically and radiologically apparent and the presence of precursor lesions at these sites further supports the diagnosis.

Distinction between primary endometrial SCC and secondary corpus infiltration by a cervical SCC poses a particular problem due to the contiguity of these two sites. Careful clinical and radiologic evaluation usually confirms the epicentre of the neoplasm on the uterine cervix in patients with secondary uterine corpus infiltration. Unusual cases, however, may demonstrate a bulky corpus tumour mass with lesser involvement of the cervix.

A rare dilemma arises with superficial spreading cervical SCC in situ, which may show contiguous upward intramucosal extension with involvement of the endometrium and even fallopian tube lining.[6] In such cases, infiltration may occur in the female genital tract outside the cervix, mimicking a primary neoplasm of that site. Endometrial involvement by cervical HSIL or SCC in situ is a distinctly rare phenomenon, with only 15 cases reported in the English literature between 1971 and 2019.[7] Furthermore, only two of these cases were associated with myometrial invasion, one microinvasive and the other superficially infiltrating.[8] To our knowledge, the present case is the first to report extensive myometrial infiltration by SCC associated with cervical SCC in situ (devoid of any detectable cervical stromal invasion).

Diagnostic criteria for the distinction between primary and secondary endometrial squamous neoplasia (including in

situ lesions) were originally proposed in 1928 by Fluhmann.[9] According to these criteria, diagnosis of primary endometrial SCC requires the absence of (i) contiguity between the endometrial neoplasm and cervical squamous epithelium, and (ii) primary squamous neoplasia of the cervix (either in situ or invasive). Subsequent commercially available IHC markers, including p16 protein, have contributed little to this distinction. P16 positivity (indicating protein overexpression) is a surrogate marker for oncogenic HPV infection, but has been documented in endometrial SCC and is negative in some cervical SCC.[10,11]

Detection of HR-HPV DNA in tumour tissue by in situ hybridisation (ISH) or molecular testing is a more direct indicator of oncogenic HPV infection and militates against the diagnosis of primary endometrial SCC. Although isolated cases of purported primary endometrial SCC have demonstrated HR-HPV DNA,[12,13] this finding is not supported by most series.[10,14] Such cases may well represent upward extension of SCC arising from metaplastic squamous epithelium in the endocervical canal, given the exquisitely site- and tissue-specific oncogenic role of HR-HPV.[14]

Secondary uterine corpus involvement by metastatic SCC is extremely rare. Such deposits arise due to angiolymphatic tumour spread and may occur with SCC of other genital tract sites, such as the cervix, vagina, vulva and ovary (most often associated with an ovarian dermoid cyst or endometriosis).[6] The most common extragenital primary sites include the breast (metaplastic carcinoma), lung, pancreas and urinary tract, although such metastatic spread is usually associated with advanced disease and frequently only detected at autopsy.[15] Metastases to the uterine corpus preferentially involve the myometrium, with endometrial involvement typically showing interglandular spread. Relatively site-specific IHC stains, such as GATA3 (breast and urinary tract), CDX2 (lower gut) and TTF1 (lung) may occasionally be helpful in this setting.

Primary endometrial SCC is rare and has a dismal prognosis. Treatment options include total abdominal hysterectomy with nodal sampling/dissection and chemoradiation, although there may be relative radioresistance.[16] Literature on the treatment and outcome of a clinical presentation as documented in this patient is extremely limited. In the largest case review series of 31 patients, no follow-up data were available in 15 of the cases.[7] Currently, the European Society for Medical Oncology (ESMO) advocate an algorithmic approach, based on FIGO (International Federation of Gynecology and Obstetrics) grade and staging.[17]

Conclusion

The finding of SCC on endometrial histology raises numerous diagnostic considerations, each with different management and outcome implications. Careful macro- and microscopic specimen evaluation, comprehensive sampling and ancillary HR-HPV DNA testing will facilitate a correct diagnosis, even where clinical and imaging findings are misleading. Additionally, the presence of cervical HSIL in a patient with SCC on endometrial histology should always raise suspicion for a surreptitious underlying cervical neoplastic process, despite the absence of detectable infiltrating cervical malignancy.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This case report was approved by the Research Ethics Committee, University of Pretoria (number 535/2021).

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