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Case report

Squamous morphology in endometrial tumours: two challenging cases including a rare pilomatrix-like variant

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Abstract

Endometrial carcinoma with predominant squamous differentiation is rare and poses diagnostic difficulties. Pilomatrix-like high-grade endometrioid carcinoma (PiMHEC) is a recently described aggressive variant, while primary squamous cell carcinoma (PSCC) of the endometrium is also very uncommon. We present two challenging cases comparing their clinicopathological and immunohistochemical features. Two postmenopausal women presenting with vaginal bleeding underwent endometrial sampling followed by total hysterectomy with bilateral salpingo-oophorectomy and sentinel lymph node evaluation. Histopathology and immunohistochemistry were performed, including ER, PR, p53, p16, p40, beta-catenin, and MMR proteins. Case 1 was diagnosed as a PiMHEC, characterized by basaloid nests, ghost cell keratinization, lower-grade glandular components, diffuse nuclear/cytoplasmic beta-catenin expression and MMR proficiency. Focal lymphovascular invasion was observed and nodes were negative. Case 2 was a PSCC showing nests of keratinizing squamoid cells, strong p40 positivity, membranous beta-catenin, negative ER/p16, and extensive lymphovascular invasion with isolated nodal tumour cells. No glandular or pilomatrix differentiation was present and there was no background cervical intraepithelial neoplasia. PiMHEC and PSCC are rare endometrial malignancies that may appear morphologically similar but demonstrate distinct immunophenotypic profiles. Accurate diagnosis requires careful histological assessment, appropriate immunohistochemistry, and exclusion of cervical or metastatic disease. PiMHEC characteristically shows aberrant nuclear and cytoplasmic β-catenin expression, reflecting frequent *CTNNB1* mutations, a useful feature for guiding optimal management. Tumours with *CTNNB-1* mutation are currently classified in the subset of “no specific molecular profile” category of endometrial carcinomas. Early recognition is essential due to the aggressive clinical behaviour of these tumours.

Keywords: endometrial neoplasms; squamous cell carcinoma; pilomatrix-like high-grade endometrioid carcinoma; beta-catenin

Introduction

Endometrial carcinoma is the most common gynaecologic malignancy and according to the 2023 FIGO staging system, it is broadly categorized into non-aggressive and aggressive subtypes. Non-aggressive subtypes include low-grade (FIGO grades 1 and 2) endometrioid carcinomas, while aggressive subtypes

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comprise high-grade (FIGO grade 3) endometrioid carcinoma, serous carcinoma, clear cell carcinoma, carcinosarcoma and mesonephric-like carcinoma (1). Predominant squamous differentiation in endometrial tumours is uncommon, occurring either as squamous differentiation in endometrioid carcinoma or rarely as primary squamous cell carcinoma (PSCC) of the endometrium (2,3). Pilomatrix-like high-grade endometrioid carcinoma (PiMHEC) is a recently described aggressive variant, characterized by basaloid nests, shadow (ghost) cells, geographic necrosis, and frequent association with low-grade endometrioid components (2–5). PiMHEC can mimic other high-grade endometrial malignancies, including FIGO grade 3 endometrioid carcinoma, dedifferentiated carcinoma, carcinosarcoma, and squamous cell carcinoma (2). PSCC is also exceedingly rare, with prevalence under 0.5% of all uterine carcinomas (2,6,7). The diagnosis relies on Fluhmann and WHO criteria, which require the absence of a coexisting endometrioid carcinoma, no continuity with the cervical squamous epithelium, exclusion of a primary cervical squamous cell carcinoma, presence of intercellular bridges and keratinization. These criteria are essential to distinguish true primary endometrial squamous neoplasms from secondary involvement by cervical tumours or from endometrioid carcinomas with squamous differentiation, ensuring accurate classification (2).

Case History

Case 1

A 63-year-old woman presented with postmenopausal bleeding. Ultrasound revealed a thickened endometrium, and curettage was performed, which showed particulate white fragments. On microscopy, there were sheets and nests of squamoid cells. Some nests showed ghost-cell keratinization. Occasional crowded endometrioid glands were present (Figure 1). Immunohistochemistry revealed diffuse nuclear and cytoplasmic beta-catenin expression (Figure 2) and proficient MMR (MLH1, PMS2, MSH2, MSH6). ER was negative in the basaloid component but preserved in the low-grade component. CDX2 was focally positive in the basaloid component. The findings suggested pilomatrix-like high-grade endometrioid carcinoma, likely associated with *CTNNB1* mutation.

Subsequent hysterectomy, including bilateral adnexa and pelvic sentinel lymph nodes, revealed a friable tan endometrial mass measuring 35 × 25 × 30 mm, replacing most of the endometrium with distortion of the myometrium. Microscopically, the tumour predominantly comprised nests and sheets of squamous material with ghost cells. There were also basaloid nests, solid areas of a high-

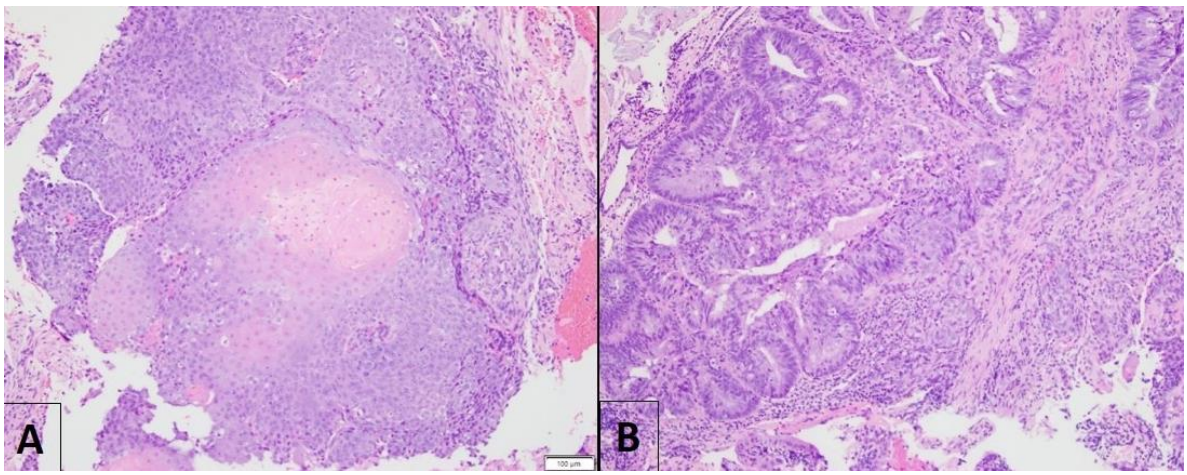

Figure 1: 1 (Case 1): A – Basaloid nests with ghost cell formation in endometrial curettings (H&E, ×100), B – Admixed lower-grade glandular component in curettings (H&E, ×100).

grade endometrioid carcinoma and a lower grade component with gland forming tumour groups adjacent to this. The tumour involved the outer half of the myometrium (12/17 mm) and there was focal lymphovascular invasion. Pelvic sentinel lymph nodes were negative. Immunohistochemistry confirmed prior findings, with additional findings of wild-type p53. The peritoneal washings were negative. The final diagnosis was pilomatrix-like high-grade endometrioid carcinoma, FIGO grade 3.

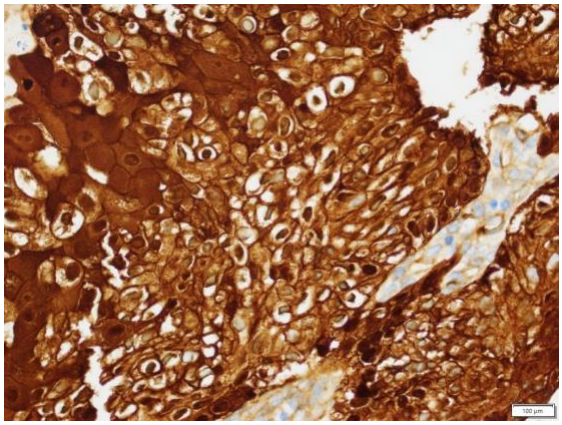

Figure 2: (Case 1): β-catenin immunohistochemistry showing nuclear and cytoplasmic positivity (×400).

Case 2

A 65-year-old woman presented with postmenopausal bleeding and a slightly thickened endometrium (6mm). Initial endometrial sampling by pipelle showed fragments of tissue containing squamous morules, several with nuclear atypia, and some atypical appearing glandular elements. The squamous and glandular components both showed positive nuclear immunolabelling for oestrogen receptor (ER). p16 immunostaining was mosaic. The glandular epithelium displayed a wild-type pattern of p53 expression, whereas the squamous epithelium showed strong basal nuclear labelling. Findings were concerning for a carcinoma with squamous differentiation, prompting further surgical evaluation.

Hysterectomy with bilateral adnexa and pelvic sentinel lymph nodes revealed a tan soft lesion measuring 50 × 40 × 35 mm, occupying the full thickness of the myometrium and abutting the serosa. Microscopically, the tumour consisted of nests and islands of squamoid cells with keratin pearl formation and central necrosis, consistent with poorly differentiated squamous cell carcinoma, grade 3. No atypical glandular component, sarcomatous differentiation or pilomatrix differentiation was observed after extensive sampling. Immunohistochemistry demonstrated strong p40 positivity, membranous beta-catenin expression, negative ER and p16, and wild-type p53. Extensive lymphovascular invasion was present, with isolated tumour cells in one of the sentinel lymph nodes. There was focal anterior cervical stromal invasion without epithelial involvement or intraepithelial neoplasia. The right fallopian tube showed surface tumour involvement, while other

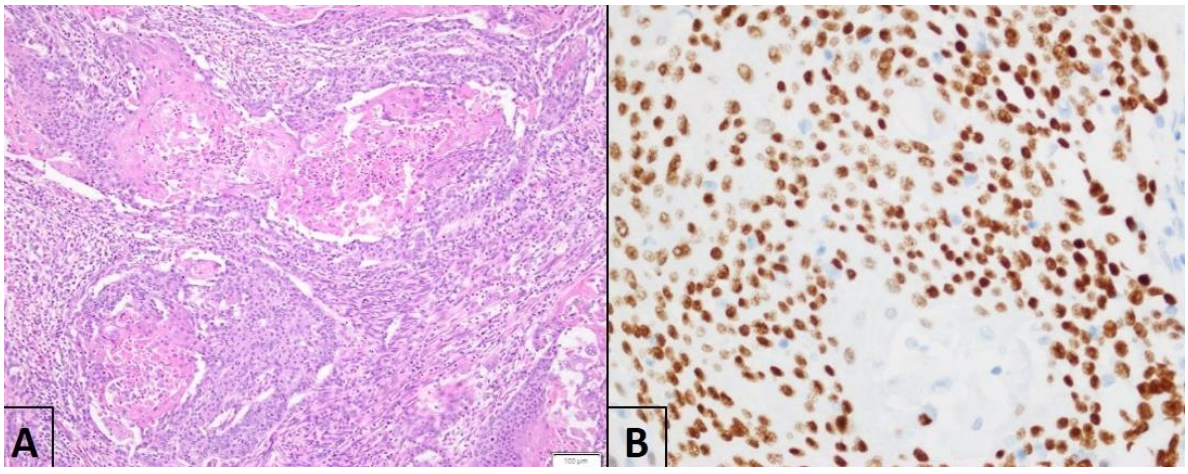

Figure 3 (Case 2): A –Squamous differentiation with keratin pearl formation and nuclear pleomorphism (H&E, ×100). B – p40 immunohistochemistry showing diffuse nuclear positivity (×400).

adnexal structures were negative for malignancy. The peritoneal washings were negative. This case was diagnosed as a squamous cell carcinoma of the endometrium.

The features of the two cases are summarised in table 1.

Discussion

These cases highlight the diagnostic spectrum of endometrial carcinoma with squamous morphology including the challenges in distinguishing between PiMHEC and PSCC. Recent research, particularly through The Cancer Genome Atlas (TCGA), has highlighted the molecular diversity of endometrial adenocarcinomas, which correlates with varying clinical outcomes (1,3,8).

PiMHEC shows high-grade differentiation resembling cutaneous pilomatrix carcinoma, typically a rare aggressive skin tumour. While pilomatrix carcinoma primarily arises in the skin, similar tumours can rarely occur in visceral organs including the uterus, ovary, breast, bladder, colon, gallbladder, and lung (1,4). PiMHEC is an aggressive variant of endometrial carcinoma characterized by basaloid morphology with peripheral palisading and abrupt keratinization forming ghost (shadow) cells, resembling pilomatrixoma of the skin. These tumours typically show aberrant nuclear and cytoplasmic β-catenin expression as in this case, reflecting frequent *CTNNB1* mutations (1,4). These tumours may explain the high-risk group of "No Specific Molecular Profile" category of endometrial cancers, which have similar outcomes to *TP53*-mutant tumours (1,3,4). They are usually MMR proficient and often demonstrate oestrogen receptor (ER) negativity in the high-grade basaloid component which were identified in this case as well (1,4). Some PiMHEC cases are MMR-deficient, which might suggest a better prognosis, although evidence is limited. A characteristic feature is the presence of an associated low-grade endometrioid glandular component, which may show conventional morphology and retain ER expression, highlighting the biphasic nature of the tumour (1). This dual morphology, together with the distinctive immunophenotype and molecular profile, helps distinguish PiMHEC from other high-grade endometrial carcinomas with squamous differentiation(2–5). Shadow cells are a defining morphologic feature of PiMHEC and may be identifiable even in small biopsy specimens (3,4). The high-grade component of PiMHEC can mimic other high-grade endometrial malignancies, including poorly differentiated squamous carcinoma, FIGO grade 3 endometrioid carcinoma, and dedifferentiated carcinoma, making accurate diagnosis challenging. Also shadow cells can be seen in isolation in otherwise typical endometrioid carcinomas (2–5,8).

A review of 37 cases of PSCC (1997–2022) showed that patients' ages ranged from 28 to

Feature	Case 1: Pilomatrix-like Endometrioid CA	Case 2: Squamous Cell CA
Age	63	65
Presentation	Postmenopausal bleeding	Postmenopausal bleeding
Histology	Basaloid nests, ghost cells, lower-grade glands	Nests/islands of squamoid cells, keratin pearls
Immunoprofile	Beta-catenin nuclear/cytoplasmic, MMR proficient, ER +/-	p40+, Beta-catenin membranous, ER-, p16-
Myometrial invasion	12/17 mm	21/24 mm
Lymphovascular invasion	Focal	Extensive
Adnexal involvement	None	Right fallopian tube
Sentinel nodes	Negative	Isolated tumour cells in one node
Grade	3	3

Table 1: Summary of clinical and histological findings of the cases

90 years (average 62 years), with common initial symptoms including postmenopausal bleeding in most women (45%) (2). Malignancy may be present even when endometrial thickening is minimal as in this case; in fact, her ultrasound would likely have appeared normal if the thickness had been <4mm. In this case, a good endometrial sample was obtained with a pipelle, although hysteroscopy remains the gold-standard diagnostic method. There are distinct diagnostic criteria including the absence of coexisting glandular carcinoma, no connection with cervical squamous epithelium, and no primary cervical squamous lesion as seen in case number 2 (1,2,6,7). Its pathogenesis is not fully understood but may involve chronic inflammation, pyometra and cervical stenosis. Hypotheses include bidirectional differentiation of endometrial precursor cells, heterotopic cervical tissue, stem cell reserve, and squamous metaplasia. Association with human papillomavirus infection is not well documented (2). Histologically, PSCC is characterized by nests of squamoid cells with keratin pearl formation, central necrosis, extensive lymphovascular invasion, and strong p40 immunoreactivity. Prognosis is generally poorer than that of conventional endometrioid carcinoma and is closely related to tumour stage [6,7,9].

Differentiating PiMHEC from PSCC and other high-grade endometrial tumours can be challenging due to overlapping histological features. PiMHEC can be distinguished from grade 3 endometrioid carcinoma, dedifferentiated carcinoma, and carcinosarcoma by the presence of ghost cells, diffuse nuclear β-catenin, and ER negativity in basaloid areas, whereas PSCC shows keratin pearl formation, p40 positivity, and membranous β-catenin expression (2,8,9). Thorough sampling, deeper levels and immunohistochemistry are therefore essential to avoid diagnostic pitfalls, particularly in limited biopsy specimens. Management for both PiMHEC and PSCC generally involves total hysterectomy with bilateral adnexectomy and sentinel lymph node evaluation (1,2). Adjuvant therapy, including chemotherapy or radiotherapy, is considered based on tumour grade, stage, and lymphovascular invasion. Further research is necessary to develop other effective treatment strategies (1,20). Early and accurate recognition of these rare entities is crucial because of their aggressive clinical behaviour and potential for recurrence (2–7). Awareness of their distinguishing morphologic, immunophenotypic, and, in the case of PiMHEC, molecular features facilitates timely diagnosis and guides optimal patient management.

Conclusion

Endometrial carcinoma with predominant squamous morphology is uncommon and includes pilomatrix-like high-grade endometrioid carcinoma and primary squamous cell carcinoma. PiMHEC is a recently described entity characterized by basaloid nests, ghost cells, low-grade glandular component, nuclear/cytoplasmic beta catenin positivity, frequent *CTNNB1* mutations, and aggressive behaviour even when detected at an early stage. PSCC is rare, often associated with chronic endometrial inflammation, shows keratin pearl formation and p40 positivity, and carries a poor prognosis. Accurate morphologic assessment, supported by immunohistochemistry and molecular characterization, is essential for diagnosis, prognostication, and guiding appropriate management.

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