POLE-Mutated Molecular Subtype of Endometrioid Carcinoma: An Aggressive Pilomatrix-Like Neoplasm with Diffusely Aberrant ß-Catenin Expression

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ABSTRACT

Endometrioid adenocarcinoma with pilomatrix carcinoma-like morphology represents a recently reported high-grade endometrial carcinoma subtype, frequently harbouring the CTNNB1 gene mutations and demonstrating highly aggressive biological behaviour. However, the present case differs from prior reports by exhibiting a POLE ultra-mutated molecular subtype associated with a favourable prognosis. This study aims to contrast the clinicopathological characteristics of this molecular subtype with conventional cases, elucidate its distinct biological profile, and emphasise the critical correlations between tumour genotype, phenotypic manifestations, and survival outcomes. These findings provide novel insights and evidence to facilitate timely diagnosis and precision therapeutic strategies for this emerging tumour entity.

Key Words: *POLE mutation, β-catenin, Endometrioid adenocarcinoma, Cutaneous pilomatrix carcinoma, CTNNB1 mutation*.

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INTRODUCTION

Over recent years, it has become increasingly evident that endometrioid adenocarcinomas with pilomatrix carcinoma-like morphology and β-catenin aberrations exhibit distinctive morphological and immunophenotypic characteristics. These tumours demonstrate striking histological and immunohistochemical similarities to cutaneous pilomatrix carcinoma. To date, the seven reported cases of this biologically distinct subtype occurred in patients with a mean age of 56 years, demonstrating aggressive clinical behaviour and a propensity for recurrence. Notably, three of the five patients with follow-up data succumbed within 14 months of diagnosis, while three cases presented with metastatic disease at initial evaluation, collectively indicating a dismal prognosis.[1-3]

Herein, the authors summarised the morphological features of β-catenin-aberrant, pilomatrix carcinoma-like endometrioid adenocarcinomas reported in recent literature and described a novel case with divergent molecular and prognostic characteristics (Table I). While the current case shares biological morphology and immunohistochemical profiles with previously described subtypes, it exhibits a distinct molecular subtype (POLE ultra-mutated) and improved prognosis.

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Such endometrioid adenocarcinomas remain under-reported, with the current understanding of their aetiopathogenesis and prognostic determinants being significantly limited.

CASE REPORT

A 50-year perimenopausal woman presented with a six-month history of prolonged irregular menstrual bleeding accompanied by lower abdominal dragging pain and lumbar discomfort. The patient had an unremarkable medical and surgical history. Transvaginal ultrasonography demonstrated endometrial thickening (12 mm) and a 61 × 49 mm isoechoic mass at the cervical os, exhibiting moderate vascularity on colour Doppler flow imaging. Subsequent pelvic MRI and contrast-enhanced CT revealed a suspected cervical malignancy (FIGO Stage IIIB) with superior extension into the uterine corpus and bilateral pelvic sidewall lymphadenopathy (largest node: 22 mm in short-axis diameter).

Following a comprehensive diagnostic evaluation, the patient underwent abdominal radical hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy, para-aortic lymph node dissection, and adhesiolysis under general anaesthesia. Intraoperative findings revealed an anteverted uterus enlarged to approximately 8 weeks' gestational size, with superficial tumour deposits identified on the right ovarian and fallopian tube surfaces, which were excised with clear margins from adjacent non-neoplastic tissue. No evidence of metastatic dissemination or involvement of other intra-abdominal organs was identified.

Table I: Clinical and immunohistochemical characteristics (high-grade component) of cases in the literature.

Cases	1	2	3	4	5	6	7	8
Age	60	65	56	73	38	69	29	50
Clinical outcomes	DOD	LFU	DOD	DOD	AWD	ND	AWD	AWD
Sites of metastasis	Liver Chest wall Brain	Bone Lung Soft tissue	Liver	Liver Lung	Lung Mediastinal LN	Pelvic LN	Lung Sacral bone Brain	–
β-catenin	+	+	+	+	+	+	+	+
CDX2	>50%	>50%	>50%	40%	40%	+	+	+
ER	–	–	–	–	–	–	–	–
PR	ND	ND	ND	ND	ND	–	–	–
PAX8	–	–	–	–	–	–	–	–
MMR	PMS2 MSH6 Intact	PMS2 MSH6 Intact	PMS2 MSH6 Intact	PMS2 MSH6 Intact	PMS2 MSH6 Intact	Loss of MLH1 PMS2	MLH1 PMS2 MSH2 MSH6 Intact	MLH1 PMS2 MSH2 MSH6
P53	Wild-type	Wild-type	Wild-type	Wild-type	Wild-type	Wild-type	Wild-type	Wild-type
P16	Patchy	Patchy	Patchy	Patchy	Patchy	Patchy	Nonblock	Patchy
Synaptophysin	30%	40%	20%	40%	60%	+	10%	+
Chromogranin	5%	10%	2%	5%	10%	+	–	ND
INSM1	–	–	2%	–	–	ND	ND	ND

– Negative; + Positive; AWD, Alive with disease; DOD, Died of disease; ER, Estrogen receptor; LFU, Lost to follow-up; LN, Lymph node; MMR, Mismatch repair; ND, Not described; PAX8, Paired-box gene 8; PR, Progesterone receptor.

Cases 1-5 represent the case series reported by Weisman et al.,[1] case 6 represents the case reported by Arciuolo et al.,[2] case 7 represents the case reported by Keane et al.[3] and case 8 represents this case report.

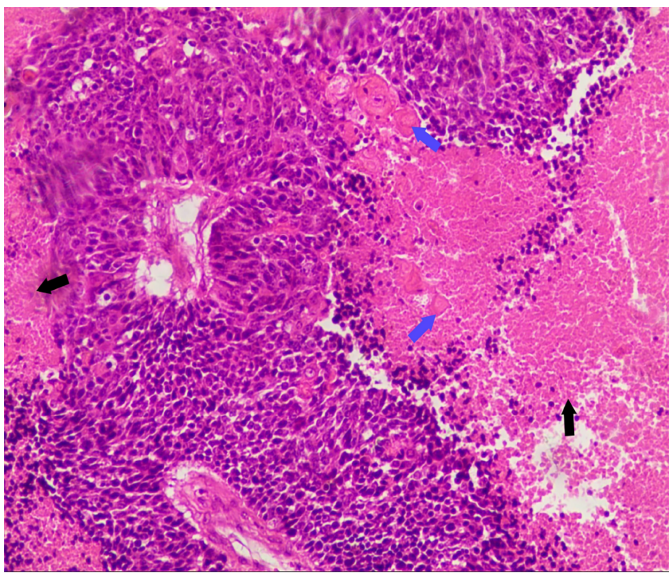

Figure 1: Pathological examination showing poorly differentiated endo-metrioid carcinoma with necrosis. The black arrows point to the necrotic portions, and the blue indicates shadow cell (HE, ×100).

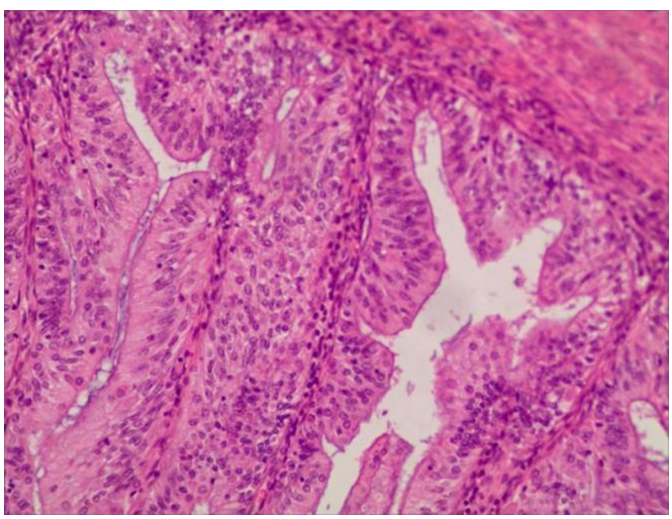

Figure 2: Pathological examination showing well-differentiated endo-metrioid carcinoma.

Histopathological examination confirmed Grade 3 endometrioid adenocarcinoma with β-catenin aberrations and cutaneous pilomatrix carcinoma-like differentiation. Macroscopic assessment demonstrated a 12 × 5 × 3 cm tumour extending from the endocervical canal to the uterine cavity, with a myometrial thickness of 3 cm and a tumour-free margin of 2.4 cm from the deepest invasive front. Microscopic analysis revealed heterogeneous differentiation, predominantly comprising Grade 3 endometrioid adenocarcinoma with geographic necrosis (Figure 1), juxtaposed with focal well-differentiated glandular components (Figure 2). Tumour invasion involved <50% of the myometrial thickness and extended to the outer-third of the cervical fibromuscular wall. Lymphovascular invasion was confirmed, with microscopic tumour involvement of the right ovarian capsule. Parametrial tissues remained uninvolved, and all 49 dissected pelvic lymph nodes were negative for metastatic disease.

The patient was discharged following an uncomplicated two-week postoperative recovery period and subsequently underwent a scheduled chemotherapy with carboplatin (500 mg) and paclitaxel (270 mg) administered at 21-day intervals. Surveillance *via* contrast-enhanced CT imaging of the thorax, abdomen, and pelvis was performed at three-month intervals. At 14 months post-diagnosis, imaging surveillance demonstrated no evidence of locoregional recurrence or distant metastasis, with the patient remaining disease-free by RECIST 1.1 criteria.

DISCUSSION

Endometrioid adenocarcinomas with cutaneous pilomatrix carcinoma-like morphology and concurrent β-catenin aberrations remain exceptionally rare in the published literature, while no studies have reported endometrial adenocarcinomas with POLE ultra-mutated subtypes arising from such tumours. The seven previously documented

cases likely fall within the WHO non-specific molecular profile (NSMP) category, demonstrating CTNNB1 mutations and highly aggressive biological behaviour, with molecular testing confirming the absence of POLE mutations in three of these cases. In alignment with Kurnit *et al*.,[4] whose genomic analysis of 245 endometrioid adenocarcinoma cases demonstrated that CTNNB1 mutations predominantly occur in low-grade tumours across all stages, the present study documents an atypical coexistence of high-grade histological features with CTNNB1 mutations in this distinct carcinoma subtype. Further supporting evidence indicates that aberrant nuclear β-catenin immunohistochemical expression serves as a surrogate method for detecting CTNNB1 exon 3 mutations and that positive nuclear expression of β-catenin immunohistochemistry is a sensitive and specific marker for tumours with CTNNB1 mutations.[5] The present patient tested positive for immunohistochemical β-catenin immunohistochemical nuclear expression, and molecular testing showed CTNNB1 mutation, which is in line with previous studies. Victoor *et al*.[6] demonstrated in their cohort of 120 endometrial carcinomas that aberrant nuclear β-catenin expression predominantly localises to tumours classified as NSMP subtype, with subsequent studies identifying CTNNB1 exon 3 mutations as a novel prognostic biomarker within this molecular category.[7] In contrast to these established associations, the current case exhibits β-catenin nuclear accumulation alongside CTNNB1 mutation within a POLE ultra-mutated molecular context, a combination not previously documented. Notably, molecular stratification studies of CTNNB1-mutant endometrioid adenocarcinomas have historically focused on low-grade tumours, with high-grade variants remaining undercharacterised. The pilomatrix carcinoma-like endometrioid adenocarcinoma described here represents the first investigation of CTNNB1 mutations in high-grade endometrial carcinomas, particularly noteworthy as the first-reported co-occurrence with a pathogenic POLE mutation. This unique molecular profile constitutes a rare tumour subtype with distinct clinico-pathological implications.

The cutaneous pilomatrix carcinoma referenced in this study represents another tumour entity demonstrating a strong clinicopathological correlation with diffuse β-catenin aberrant expression and aggressive clinical behaviour. Beyond β-catenin dysregulation serving as its defining immunophenotypic hallmark,[8] emerging evidence indicate that CDX2 focal expression may be observed in all reported cases.[9] The current FIGO IIIA Grade 3 endometrioid adenocarcinoma with diffuse β-catenin nuclear accumulation exhibits striking morphological overlap with this carcinoma variant, with both entities demonstrating high-grade basaloid tumour cells arranged in solid growth patterns, accompanied by geographic necrosis and shadow cell formation (Figure 1). In this case, the patient underwent surgical intervention followed by adjuvant chemotherapy (carboplatin + paclitaxel), with 14-month imaging surveillance demonstrating no evidence of recurrence or metastatic disease. The prognosis and biological aggressiveness of this endometrioid adenocarcinoma were markedly reduced compared to previously reported β-catenin-aberrant pilomatrix carcinoma-like variants. This divergence likely stems from the distinct molecular phenotype in this case, which falls within the POLE-mutated subtype associated with optimal prognosis in endometrial carcinoma molecular classification, demonstrating <5% recurrence rates even in the high-grade tumours, contrasting with previous cases where CTNNB1 mutations predominantly occurred in the prognostically inferior NSMP.[10] Collectively, endometrial carcinomas exhibiting concurrent POLE mutations and β-catenin dysregulation demonstrate superior clinical outcomes compared to CTNNB1-mutant non-POLE-hypermutated counterparts. Consequently, in clinical practice, immunohistochemical evidence of β-catenin abnormalities necessitates confirmatory molecular profiling to definitively classify the tumour subtype, thereby enabling accurate therapeutic decision-making and prognostic stratification.

In summary, the authors report a case of endometrioid adenocarcinoma with pilomatrix carcinoma-like morphology and β-catenin dysregulation, demonstrating divergent molecular stratification from contemporary classification paradigms while sharing morphological and immunophenotypic similarities with previously described variants. To the authors' knowledge, this represents the first documented POLE ultra-mutated subtype exhibiting histo-morphological mimicry of cutaneous pilomatrix carcinoma. The concurrent presence of CTNNB1 mutation and POLE hypermutated genotype in this tumour correlates with a more favourable prognosis compared to the recently reported β-catenin-aberrant pilomatrix carcinoma-like cases. Prior studies indicated that such tumours predominantly cluster within the NSMP category, demonstrating aggressive clinical behaviour and poor prognostic outcomes. The co-occurrence of POLE mutation and β-catenin dysregulation in this case may indicate improved prognosis, thus in clinical practice, tumours demonstrating β-catenin abnormalities on immunohistochemistry should not be presumptively classified as non-specific molecular profile (NSMP) type, despite most studies associating β-catenin positivity with NSMP classification.[6] Under such circumstances, molecular profiling to confirm the pathological subtype is recommended to guide precise therapeutic strategies and prognostic evaluation. Therefore, while histomorphological and immunohistochemical assessments remain pivotal in endometrial carcinoma management, molecular characterisation proves indispensable for optimising treatment precision and prognostic stratification.

PATIENT'S CONSENT:
Informed consent was taken from the patient.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
DY: Conception of the work, collection of data from the patient,

case report, and drafting of the manuscript.
XQ: Analysis of data and critical revision.
YL: Contribution to the conception of the work, literature search, data collection, drafting of the manuscript, and revising the manuscript critically for important intellectual content.
YQ: Interpretation of data and critical revision.
ZW: Collection of data from the patient and critical revision.
All authors approved the final version of the manuscript to be published.

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