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Integrated Study Master Thesis

Giant Cell Carcinoma of the Endometrium: A Case Report of a Rare Entity and Review of the Literature

Endometro gigantinių ląstelių karcinoma: atvejo aprašymas ir literatūros apžvalga

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LIST OF ABBREVIATIONS

AE1/AE3 – Cytokeratin clones AE1 and AE3 (pan-cytokeratin antibody)

AKT – Protein kinase B (AKT serine/threonine kinase)

ARID1A – AT-rich interactive domain-containing protein 1A (SWI/SNF subunit)

ARID1B – AT-rich interactive domain-containing protein 1B (SWI/SNF subunit)

BSO – Bilateral salpingo-oophorectomy

CAM5.2 – Cytokeratin clone CAM5.2 (low molecular weight cytokeratin marker)

CD68 – Cluster of differentiation 68 (histiocytic/macrophage marker)

CHEC – Corded and hyalinized endometrial carcinoma

CK5 – Cytokeratin 5

CK7 – Cytokeratin 7

CKs – Cytokeratins (general)

DNA – Deoxyribonucleic acid

ECIS – European Cancer Information System

EGCC – Endometrial giant cell carcinoma

EMA – Epithelial membrane antigen

EMT – Epithelial-to-mesenchymal transition

EpCAM – Epithelial cell adhesion molecule

ER – Estrogen receptor

ERBB2 – Erb-B2 receptor tyrosine kinase 2 (gene encoding HER2)

ESGO – European Society of Gynaecological Oncology

ESP – European Society of Pathology

ESTRO – European Society for Radiotherapy and Oncology

FIGO – Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics)

GCC – Giant Cell Component

GLOBOCAN – Global Cancer Observatory (IARC cancer incidence and mortality database)

HER2 – Human epidermal growth factor receptor 2

HMB45 – Human melanoma black 45 (melanocytic marker)

IARC – International Agency for Research on Cancer

ICI – Immune checkpoint inhibitor

IHC – Immunohistochemistry / immunohistochemical

KRAS – Kirsten rat sarcoma viral proto-oncogene

L1CAM – L1 cell adhesion molecule

MLH1 – MutL homolog 1 (mismatch repair protein)

MMR – Mismatch repair

MMRd – Mismatch repair-deficient

MSH2 – MutS homolog 2 (mismatch repair protein)

MSH6 – MutS homolog 6 (mismatch repair protein)

MSI – Microsatellite instability

MSI-H – Microsatellite instability-high

MSS – Microsatellite stability

mTOR – Mechanistic target of rapamycin

mut/Mb – Mutations per megabase

NGS – Next-generation sequencing

NSMP – No specific molecular profile (TCGA subgroup)

p16 – p16INK4a (cyclin-dependent kinase inhibitor; surrogate marker for HPV/serous carcinoma)

p53 – Tumour protein p53 (protein product of TP53 gene)

PAX8 – Paired box gene 8 (Müllerian epithelial lineage marker)

PCR – Polymerase chain reaction

PD-1 – Programmed cell death protein 1

PD-L1 – Programmed cell death ligand 1

PI3K – Phosphatidylinositol 3-kinase

PIK3CA – Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene encoding PI3K p110α)

PMS2 – PMS1 homolog 2 (mismatch repair protein)

pMMR – Mismatch repair-proficient

POLE – DNA polymerase epsilon (exonuclease domain mutations define ultramutated subgroup)

PR – Progesterone receptor

ProMisE – Proactive Molecular Risk Classifier for Endometrial Cancer

PTEN – Phosphatase and tensin homolog (tumour suppressor gene)

S100 – S100 calcium-binding protein (melanocytic/neural marker)

SCNA – Somatic copy-number alteration

SMA – Smooth muscle actin

SMARCA4 – SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4 (BRG1)

SOX10 – SRY-box transcription factor 10 (neural crest/melanocytic marker)

SWI/SNF – SWItch/Sucrose Non-Fermentable (chromatin remodeling complex)

TAH – Total abdominal hysterectomy

TCGA – The Cancer Genome Atlas

TIL – Tumour-infiltrating lymphocyte

TMB – Tumour mutational burden

TP53 – Tumour protein p53 gene

USC – Uterine serous carcinoma

WHO – World Health Organization

SUMMARY

Endometrial giant cell carcinoma (EGCC) is an exceptionally rare and poorly characterised variant of endometrial carcinoma. This thesis details a case of EGCC and reviews the current literature. A review of published case reports and series in the English-language literature was conducted to summarise the clinicopathological characteristics of this rare carcinoma. The key findings are presented in a structured format to facilitate comparison.

We describe the case of a 68-year-old woman who initially presented with postmenopausal vaginal bleeding. She underwent surgical management, followed by multiple lines of systemic chemotherapy. The disease progressed rapidly, and she died 12 months after diagnosis.

The literature review shows heterogeneity in clinical presentation, therapeutic approaches, and patient outcomes. Notably, the aggressive course observed in this carcinoma does not appear to correlate directly with FIGO (Fédération internationale de Gynécologie et d'Obstétriques) stage, and the proportion of giant cells does not consistently increase with advancing disease stage, suggesting that it may represent a separate marker of adverse tumour biology rather than reflecting tumour burden.

These findings highlight the importance of recognising this carcinoma as a distinct pathological entity. Improved delineation of tumours with similar morphology may facilitate more consistent histopathological reporting and more accurate prognostication and clinical management. Further investigation into this carcinoma's biological and molecular characteristics is essential to improve diagnostic accuracy and inform future therapeutic strategies, given its aggressive behaviour and poor outcomes.

Keywords: Endometrial Giant Cell Carcinoma, Endometrial Cancer, Giant Cells, Cellular Cannibalism

SANTRAUKA

Endometro gigantinių ląstelių karcinoma (EGLK) yra itin retas ir mažai žinomas endometro karcinomos variantas. Šiame darbe aprašomas EGLK atvejis ir apžvelgiama susijusi literatūra. Siekiant apibendrinti šios retos karcinomos klinikines ir patologines charakteristikas, atlikta anglų kalba paskelbtų atvejų aprašymų ir atvejų serijų apžvalga. Pagrindinės išvados pateikiamos struktūrizuota forma, siekiant palengvinti jų palyginimą.

Darbe aprašomas 68 metų moters atvejis, kuriai iš pradžių pasireiškė pomenopauzinis kraujavimas iš makšties. Jai buvo atliktas chirurginis naviko pašalinimas, po kurio taikyta daugiaeilė sisteminė chemoterapija. Liga sparčiai progresavo, ir pacientė mirė praėjus 12 mėnesių nuo pirminės diagnozės nustatymo.

Literatūros apžvalga atskleidžia klinikinio pasireiškimo, taikomų gydymo metodų ir išeičių nevienodumą. Pažymėtina, kad šiai karcinomai būdingas agresyvus biologinis elgesys tiesiogiai nekoreliuoja su FIGO stadija, o gigantinių ląstelių komponento dalis nedidėja progresuojant ligai. Tai leidžia manyti, kad šis požymis gali pats savaime atspindėti nepalankų naviko biologinį elgesį, neatsižvelgiant į kitus parametrus.

Šie rezultatai pagrindžia poreikį EGLK išskirti kaip nepriklausomą histopatologinį endometro karcinomos variantą. Tikslesnis EGLK atskyrimas nuo morfologiškai panašių navikų leistų užtikrinti nuoseklesnę histopatologinę diagnostiką, tikslesnę prognozę ir geresnį klinikinį valdymą. Atsižvelgiant į agresyvų šios karcinomos pobūdį ir prastą pacienčių prognozę, tolimesni biologinių ir molekulinių charakteristikų tyrimai yra būtini siekiant pagerinti diagnostinį tikslumą ir identifikuoti veiksmingiausias gydymo strategijas.

Raktažodžiai: endometro gigantinių ląstelių karcinoma, endometro vėžys, gigantinės ląstelės, ląstelių kanibalizmas.

INTRODUCTION

Endometrial cancer, arising from the uterine corpus, is one of the most common gynaecological malignancies in the World Health Organisation (WHO) European Region. According to recent estimates from GLOBOCAN 2022 (1) and data aligned with the WHO, approximately 140,000–150,000 new cases are diagnosed annually in Europe, making it the fourth most common cancer in women after breast, colorectal, and lung cancers. The age-standardised incidence rate in Europe is among the highest worldwide, at approximately 14.9 per 100,000 women, compared with a global average of 8.4 per 100,000. Mortality remains a significant concern, with an estimated rate of 2.8 per 100,000 women, reflecting persistent disparities in early detection and access to optimal treatment.

Notwithstanding advances in diagnostic and therapeutic approaches, both the incidence and mortality of endometrial cancer continue to increase in many European countries. This trend is predominantly ascribed to the rising prevalence of risk factors, including obesity, metabolic syndrome, and increased life expectancy. Furthermore, there is notable geographical variation within Europe, with higher incidence and mortality rates observed in Central and Eastern regions compared with Northern and Western Europe. This is likely to reflect differences in healthcare systems, screening practices, and population risk profiles. Projections indicate that, in the absence of effective preventive strategies, the burden of uterine cancer will continue to rise in the coming decades.

Endometrial giant cell carcinoma (EGCC) is an exceptionally rare variant of endometrial carcinoma, first described in 1991 (2). To date, the number of reported cases in the literature is limited, although the true incidence is likely underestimated due to under-recognition and diagnostic challenges. The rarity of this entity has resulted in limited evidence base, which in turn restricts the ability to define its biological behaviour, prognostic factors, and optimal management strategies.

The histological characterisation of EGCC is marked by the presence of atypical mononuclear and multinucleated giant tumour cells within an endometrial carcinoma (3). The cells are characteristically arranged in sheets or poorly cohesive nests, exhibiting marked nuclear pleomorphism and atypical mitotic activity. In many cases, the giant cell component is admixed with conventional endometrial carcinoma subtypes, most commonly endometrioid, serous, or clear cell patterns. The unusual morphology of EGCC may pose a challenge in distinguishing it from other high-grade or giant cell-rich malignancies (4).

At present, EGCC is not recognised as a distinct entity in the WHO classification of female genital tumours, largely due to the limited number of reported cases and the lack of comprehensive molecular characterisation. The absence of formal classification systems leads to diagnostic uncertainty and variability in reporting. Improved recognition and more consistent histopathological characterisation are, therefore, essential to advance understanding of this entity.

AIM AND OBJECTIVES OF THE THESIS

The overarching aim of this thesis is to characterise endometrial giant cell carcinoma (EGCC) through a dual approach: a detailed original case report followed by a structured comparative analysis of all previously published cases. Together, these components are intended to advance understanding of EGCC's clinical Behaviour, histopathological identity, and diagnostic significance.

The specific objectives are as follows. First, to present the original case in full detail, including clinical history, histopathological and immunohistochemical findings, molecular profiling, treatment course, and outcome. Second, to systematically identify and analyse all previously reported EGCC cases, summarising clinicopathological patterns in a structured format to enable meaningful cross-case comparison. Third, to evaluate the relationship between the giant cell component and tumour stage, aggressiveness, and patient prognosis, with particular attention to whether this component constitutes an independent biological marker rather than merely a reflection of disease burden. Fourth, to assess the diagnostic challenges posed by EGCC, including its distinction from morphologically similar neoplasms. Fifth, to review current therapeutic strategies and their relevance, given the aggressive clinical course consistently reported across cases.

MATERIALS AND METHODS

The present thesis comprises two constituent elements. Firstly, a single-patient case report is presented. Secondly, a structured literature review is conducted focusing on endometrial giant cell carcinoma (EGCC). The case report component aimed to describe the clinical course, histopathological findings, molecular characteristics, treatment, and outcome of a patient diagnosed with EGCC. The literature review sought to contextualise the present case within the currently available scientific evidence. Given the rarity of this tumour entity, the most appropriate methodological approach was a combination of individual case analysis and published data, to provide both detailed clinicopathological insight and broader comparative interpretation.

Written informed consent was obtained from the patient before this case report was prepared. The data for the case report were obtained retrospectively from the patient's medical records, including demographic information, clinical presentation, diagnostic imaging, operative records, adjuvant treatment, follow-up data, and clinical outcome. A comprehensive array of histopathological data was meticulously retrieved from the original pathology reports, encompassing gross examination and microscopic findings, immunoprofile and molecular testing results, including next-generation sequencing where applicable. Before analysis, all patient data were anonymised in accordance with institutional confidentiality standards and ethical principles governing retrospective clinical research.

A comprehensive literature review was conducted utilising established biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. This approach was used to identify all available publications on EGCC and endometrial carcinomas with giant cell components. A comprehensive search strategy was employed, encompassing various combinations of search terms such as "endometrial giant cell carcinoma," "giant cell carcinoma of the endometrium," "endometrial carcinoma with giant cells," and related synonyms. Eligible studies included case reports, case series, and pertinent clinicopathological reviews, provided that all publications were in English. A further step in the research process involved screening the reference lists of retrieved articles to identify additional relevant publications. The extracted variables encompassed patient age at diagnosis, presenting symptoms, tumour stage, histological subtype, proportion of giant cell component, immunohistochemical profile, molecular findings, treatment modality, recurrence, metastasis, and survival outcome.

The collected data were then analysed descriptively to identify recurring clinicopathological patterns and current knowledge gaps regarding this rare malignancy. Continuous variables (patient age) were summarised as median and range. Categorical variables (FIGO stage, histological type, management, outcome) were summarised as absolute counts and percentages. Where follow-up data were unavailable or recorded as "no

information," the case was classified as having an unknown outcome and excluded from outcome frequency calculations but retained in all other analyses.

Outcomes were categorised as: 1. Remission/no evidence of disease (NED); 2. Deceased; 3. Alive with disease or documented recurrence/metastasis; and 4. Unknown. A comparative outcome analysis between early-stage (FIGO I–II) and advanced-stage (FIGO III–IV) cases was performed by calculating outcome frequencies in each group. Given the small sample size (n=28), formal statistical inference tests (e.g., chi-square) were not applied, as they would lack sufficient power. All analyses were performed manually.

CASE PRESENTATION

1. Clinical History and Initial Diagnosis

A 68-year-old primiparous woman presented with a four-month history of postmenopausal vaginal bleeding and lower abdominal pain. Her medical history was notable for hypothyroidism and primary arterial hypertension, and she had been menopausal for 16 years. The patient's surgical history included a vaginoplasty with synthetic implant placement and cervical amputation for stage III pelvic organ prolapse, performed one year before the onset of bleeding.

Four months before the current presentation, the patient underwent hysteroscopy, which identified an atrophic endometrium and a 1.5 cm endometrial polyp in the left uterine horn. A subsequent histopathological evaluation after polypectomy suggested a hyperplastic endometrial polyp without atypia. In view of persisting symptoms, a second hysteroscopy was performed. This revealed friable, white masses within the uterine cavity. Histopathological analysis of the endometrial curettage specimens identified an undifferentiated carcinoma (Figure 1), with a minor component of poorly differentiated (FIGO grade 3, G3) serous papillary carcinoma infiltrating the myometrium.

Immunohistochemical (IHC) staining showed that both components were positive for PAX8 and CK7, supporting the hypothesis of Müllerian epithelial differentiation. The serous (papillary) component showed focal positivity for oestrogen receptor (ER), CK5, and p16, together with diffuse, strong (aberrant) p53 expression, consistent with a *TP53*-mutant immunophenotype (Figure 2).

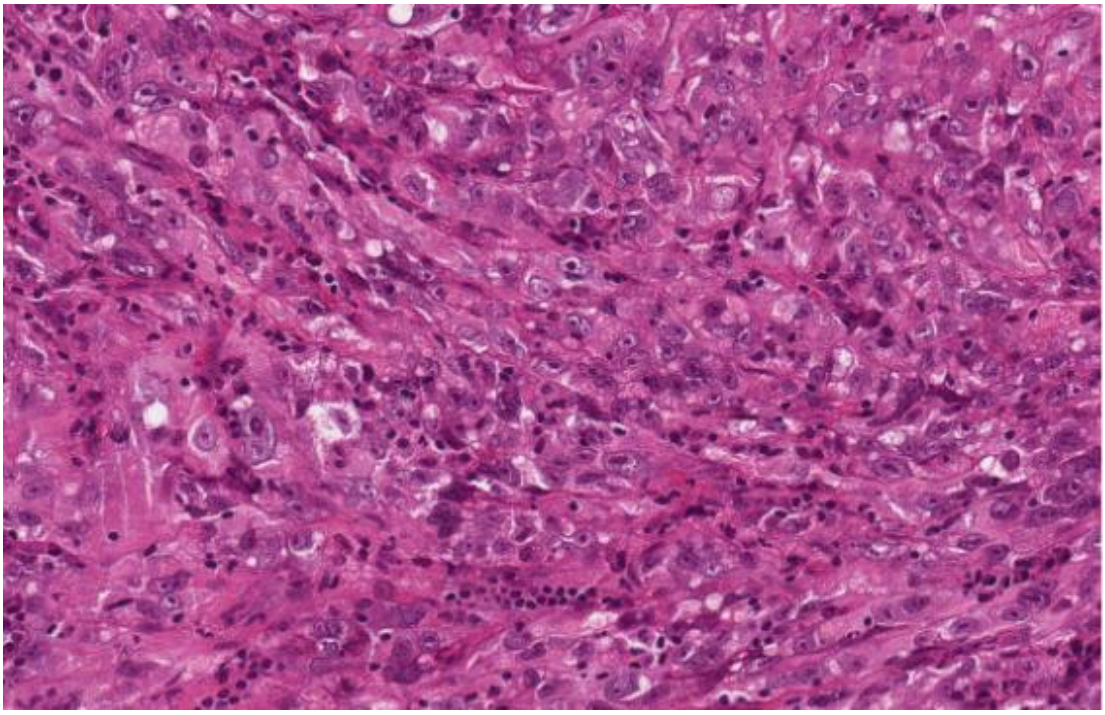

Figure 1. Histological image from the hysteroscopic material, haematoxylin and eosin (H&E), magnification x200. The slide shows solid sheets of giant, highly pleomorphic tumour cells.

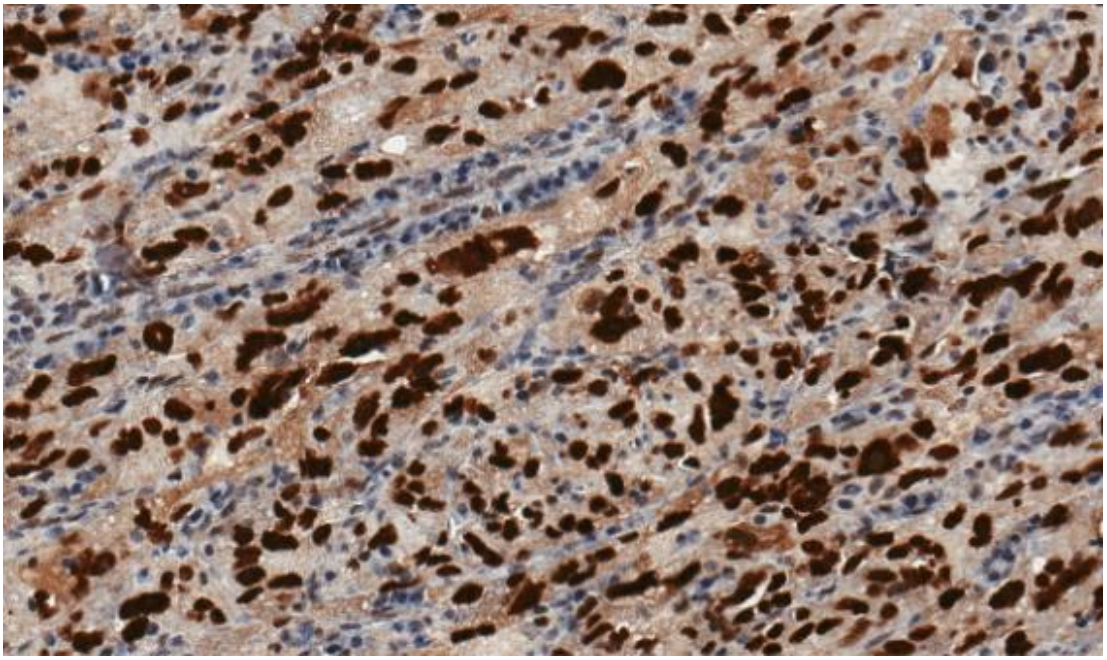

Figure 2. Histological image from the hysteroscopic material, immunohistochemical staining for p53, magnification x200. The tumour cells show a strong diffuse nuclear reaction for p53.

2. Surgical Staging and Resection

Two months after the initial diagnosis, the patient underwent primary cytoreductive surgery via exploratory laparotomy. The procedure comprised total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), infracolic omentectomy, and systematic pelvic and para-aortic lymphadenectomy. Peritoneal biopsies were performed to complement surgical staging and in line with FIGO recommendations.

3. Histopathological Analysis after Resection

Postoperative histological examination revealed that the tumour had extended into the cervical stroma. The specimen was characterised by solid sheets of dyscohesive, highly pleomorphic tumour cells, with a predominant giant-cell morphology, including multinucleated tumour giant cells, and evidence of cellular cannibalism (Figure 3).

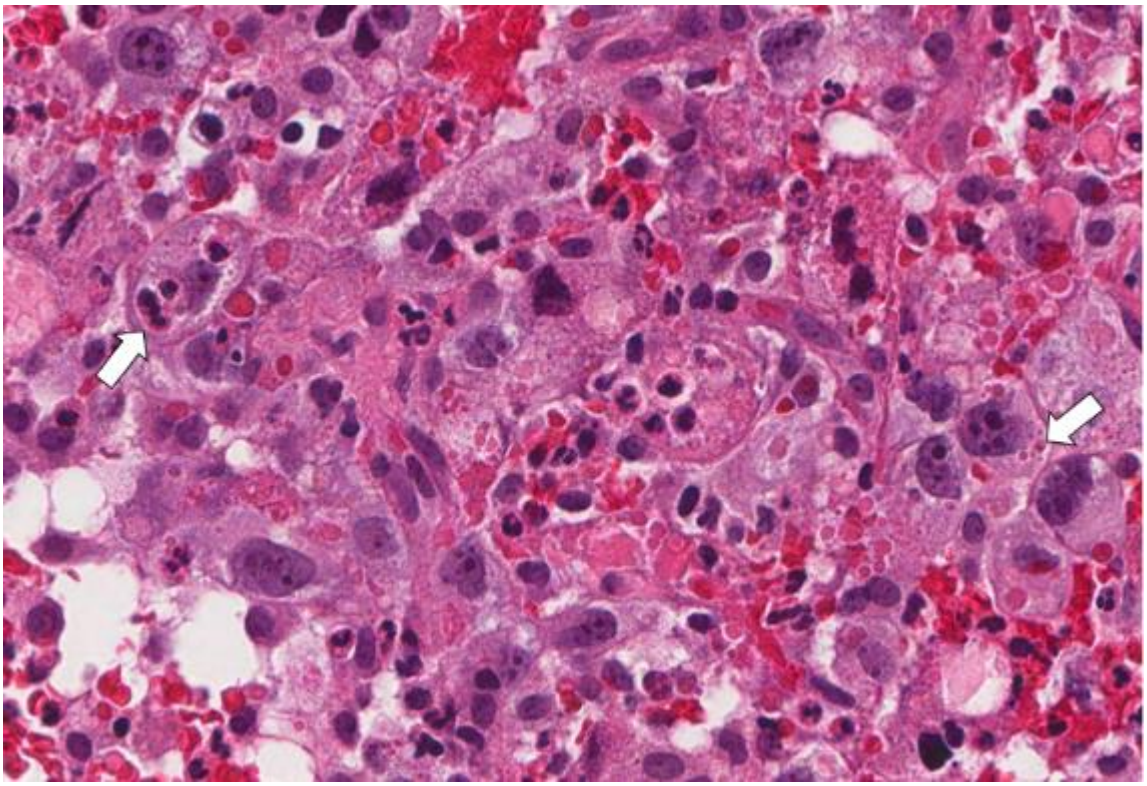

Figure 3. Histological image from the resected material, hematoxylin and eosin (H&E), magnification x400. The slide shows giant, highly pleomorphic tumour cells with signs of cellular cannibalism (arrows).

The immunohistochemical profile of the surgical specimen refined the diagnostic interpretation: the tumour cells, including most of the giant cells, showed a profile consistent with a high-grade undifferentiated

carcinoma. These cells retained Pan-Cytokeratin (Figure 4) and PAX8 positivity while being negative for CK5, p16, and ER. Furthermore, p53 expression was heterogeneous (wild-type pattern) in approximately 60% of the nuclei, indicating immunophenotypic heterogeneity.

Mismatch repair (MMR) proteins (PMS2, MSH6, MSH2, and MLH1) showed retained nuclear expression, indicating a mismatch repair–proficient (pMMR) phenotype and microsatellite stability (MSS). CD68 staining revealed scattered foreign-body-type giant cells, likely attributable to the preceding surgical intervention rather than constituting a component of the malignant epithelial tumour.

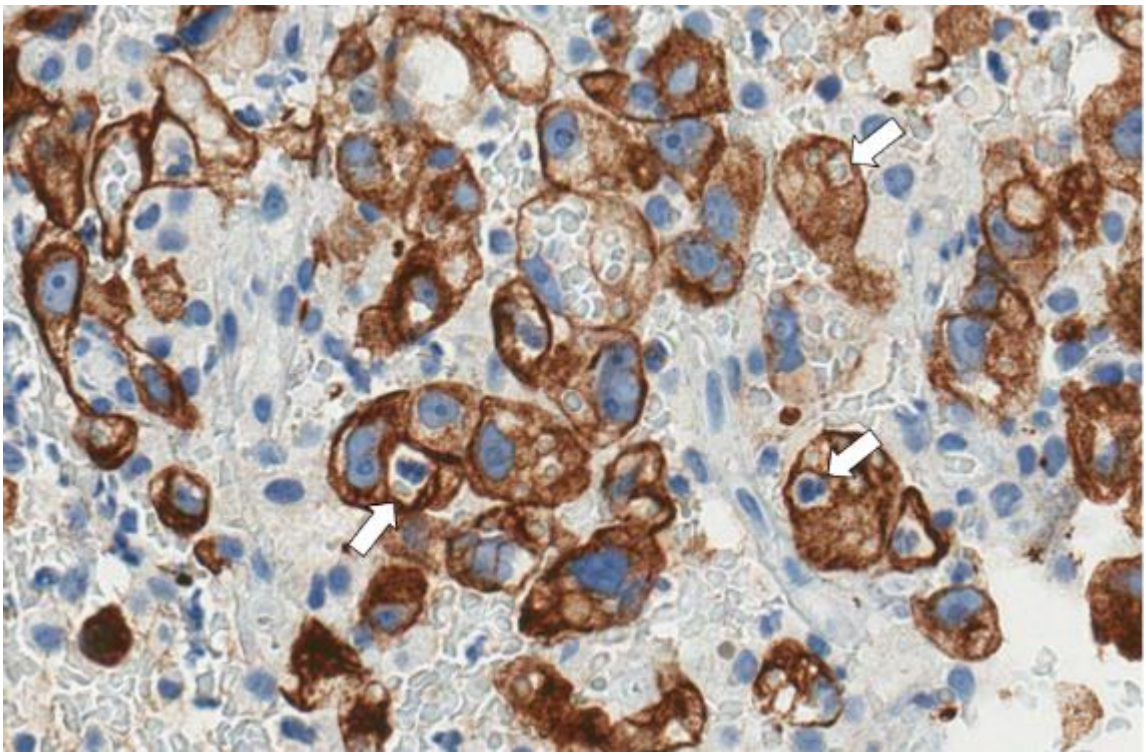

Figure 4. Histological image from the resected material, immunohistochemical staining for Pan-Cytokeratin's (PanCK), magnification x400. The tumour cells show a strong diffuse reaction in the cell membrane and a focal cytoplasmic reaction for PanCK. Arrows mark signs of cellular cannibalism.

4. Final Diagnosis and Molecular Profiling

The final pathological diagnosis was endometrial undifferentiated carcinoma (FIGO grade 4, G4), with prominent giant cell morphology (giant cell–rich variant; also referred to in the literature as endometrial giant cell carcinoma, EGCC). A minor (approximately 5%) component of poorly differentiated (FIGO grade 3, G3) serous papillary carcinoma was identified only in the initial biopsy. The disease was staged as pT2, N1, M0

(FIGO stage IIIC1). Subsequent next-generation sequencing (NGS) of the giant cell component identified mutations in *PIK3CA* (c.3140A>G) and *TP53* (c.770T>C), consistent with a high-grade molecular profile and involvement of the PI3K/AKT/mTOR signalling pathway.

5. Treatment, Follow-up & Outcome

The first treatment step was surgical debulking of tumour masses. Subsequently, the patient was advised to consult an oncologist to determine further treatment options. She received 2 cycles of initial polychemotherapy with Cisplatin and Doxorubicin. At the one-month follow-up after the surgical procedure, a vaginal metastasis was identified on gynaecological examination. A subsequent biopsy was performed. Histological examination revealed an undifferentiated giant cell carcinoma in the subepithelial stroma of the vagina. Four months after the surgical procedure, the patient had developed multiple metastases to the lungs and pelvic bones. Thereafter, palliative chemotherapy was initiated. The regimen consisted of Carboplatin and Paclitaxel, and later, Ifosfamide. Despite aggressive treatment, the patient passed away one year after the initial diagnosis due to disease progression.

RESULTS OF COMPARATIVE ANALYSIS OF PUBLISHED AND PRESENT EGCC CASES

1. General Characteristics and Historical Context

A total of 14 articles, encompassing 27 patients, met the inclusion criteria for this review (Table 1). Most of these reports originated in the United States and the United Kingdom and were published in international journals specialising in gynaecology, pathology, and molecular oncology.

The first description of giant cells in endometrioid carcinomas was reported by Jones et al. in 1991, who described a series of 6 patients (2). Following this initial discovery, a significant temporal gap occurred until Skubitz and Manivel revisited the subject in 2007 (5). In subsequent years, the presence of giant cell components (GCC) has been documented more consistently; however, the total number of reported cases remains low. This scarcity is likely attributable to the absence of standardised diagnostic criteria for defining and reporting the giant cell entity in endometrial malignancies. Notably, molecular analysis was not performed in any of the reviewed cases, leaving the molecular profile of this entity largely uncharacterised and reliant solely on morphological findings.

Table 1. Clinicopathological Data of the Present Case and 27 Previously Reported Cases of Endometrial Giant Cell Carcinoma

Case	Author, Year	Age	Symptoms	GCC %	Conventional Type	FIGO	Management	Follow-up
1	Jones et al., 1991	43	Vaginal bleeding	15%	Endometrioid G2/3	Ia	None	Remission
2	Jones et al., 1991	66	Vaginal bleeding	Pred.	Endometrioid G2/3	Ia	TAH/BSO + RT	Remission
3	Jones et al., 1991	64	Vaginal bleeding	Pred.	Endometrioid G2/3 + spindle	Ia	TAH/BSO + RT + CT	Deceased
4	Jones et al., 1991	85	Vaginal bleeding	Pred.	Endometrioid	IIa	TAH/BSO	Deceased
5	Jones et al., 1991	63	Vaginal bleeding	15%	Endometrioid G2/3	IVb	TAH/BSO + oment. + RT	Deceased
6	Jones et al., 1991	71	Vaginal bleeding	Pred.	Endometrioid G2/3	IVb	TAH/BSO + oment. + RT	Unknown
7	Skubitz & Manivel, 2007	55	VB + weight loss + cough	70%	NS	IVc	Neo/adj CT + TAH/BSO	Unknown
8	Mardi & Sharma, 2008	70	PM bleeding	Pred.	High-grade adenoca.	IIIa	TAH/BSO	Unknown
9	Mulligan et al., 2010	53	Vaginal bleeding	<50%	High-grade endometrioid + CC	Ia	TAH/BSO/LND/oment.	NED 32 mo
10	Mulligan et al., 2010	58	Vaginal bleeding	<50%	Endometrioid + spindle	Ia	TAH/BSO + RT	NED 168 mo
11	Mulligan et al., 2010	60	Anaemia	100%	None	Ib	TAH/BSO + RT (pelv + abd)	Lung mts 48 mo
12	Mulligan et al., 2010	67	Vaginal bleeding	90%	Serous	Ia	TAH/BSO/LND + CT + RT	NED 16 mo
13	Mulligan et al., 2010	83	Pelvic mass	30%	Endometrioid	IIIc2	TAH/BSO + CT + RT	NED 15 mo
14	Bhattacharyya et al., 2012	70	PM bleeding	80%	Endometrioid	Ib	TAH/BSO + RT	Recurrence 4 yr
15	Bennett et al., 2015	47	Pelvic pain	70%	Endometrioid	IVc	TAH/BSO + CT + RT	AWD 13 mo
16	Bennett et al., 2015	57	Vaginal bleeding	30%	Endometrioid	Ic	Lap hyst + BSO	Remission 5.5 yr

Case	Author, Year	Age	Symptoms	GCC %	Conventional Type	FIGO	Management	Follow-up
17	Bennett et al., 2015	59	Abdom. distension + pain	50%	Endometrioid	IVc	TAH/BSO/LND + CT	Deceased 2 mo
18	Sharma et al., 2016	60	PM bleeding	60%	Endometrioid	Ib	TAH/BSO	Unknown
19	Mardi, 2018	71	Vaginal bleeding	95%	Endometrioid + undiff.	IIIa	TAH/BSO + RT	Unknown
20	Ayık Aydın et al., 2019	75	Vaginal bleeding	NS	Endometrioid G2/3	IIIc1	TAH/BSO + LND + CT	Unknown
21	Arafah et al., 2021	71	Vaginal bleeding	>95%	None	Ia	Robotic hyst + BSO + LND	Unknown
22	Arciuolo et al., 2022	55	NS	NS	Low-grade endometrioid	Ib	TAH/BSO	Remission
23	Arciuolo et al., 2022	76	NS	NS	Serous	Ib	TAH/BSO	Remission
24	Arciuolo et al., 2022	66	NS	NS	Low-grade endometrioid	Ia	TAH/BSO	Remission
25	Tang et al., 2022	55	PM bleeding	Pred.	Serous (10%)	Ia	TAH/BSO + LND	Remission 1 yr
26	Xie et al., 2022	39	Vaginal bleeding	85%	Endometrioid adenoca.	Ia	TAH + neo/adj CT	Remission 37 mo
27	Martins Gama et al., 2025	70	PM bleeding	15%	NS	IIIa	TAH/BSO + oment. + CT	Remission 38 mo
28	**Present case**	**68**	**VB + abd. pain**	**95%**	**Serous papillary (5%)**	**IIIc**	**TAH + CT**	**Deceased 1 yr**

Continuation Table 1. Clinicopathological Data of the Present Case and 27 Previously Reported Cases of Endometrial Giant Cell Carcinoma

Notes: Case 28 is the present case, marked with darker shading.

I. Giant Cell Component (GCC), % – proportion of giant cell component within the tumour mass.
II. Conventional component – coexisting carcinoma histomorphological type.
III. FIGO staging follows the edition applicable at the time of original publication.

Abbreviations: Abd – abdominal; Ajd – adjuvant; AWD – alive with disease; BSO – bilateral salpingo-oophorectomy; CT – chemotherapy; GCC – giant cell component; Lap hyst – laparoscopic hysterectomy; LND – lymph node dissection; Mo – months; Mts – metastasis; NED – no evidence of disease; Neo – neoadjuvant; ND – not described; Neo – neoadjuvant; NS – not specified; Oment – omentectomy; Pelv – pelvic; PM –

postmenopausal; Pred. – predominant; RT – radiation therapy; TAH – total abdominal hysterectomy; VB – vaginal bleeding; Yr – year.

2. Clinical Presentation

The clinical profile of the reviewed cases predominantly features postmenopausal women, with ages ranging from 39 to 85 years (median 66 years). The age distribution was broadly unimodal, with a peak frequency in the 60–79-year range (Table 2). Only three patients (10.7%) were below age 50, confirming that EGCC predominantly affects postmenopausal women. Two patients (7.1%) were aged ≥80 years.

Table 2. Age Distribution of EGCC Patients

Age Group	Number of Patients	Percentage
<50 years	3	10.7%
50–59 years	7	25.0%
60–69 years	8	28.6%
70–79 years	8	28.6%
≥80 years	2	7.1%
Total	**28**	**100.0%**

Common presenting symptoms included vaginal bleeding, abdominal pain, or distension. Vaginal or postmenopausal bleeding was the main presenting symptom, reported in the substantial majority of cases with documented symptoms (~85% of those with recorded presentations). Five cases were specifically recorded as postmenopausal bleeding. Atypical presentations included isolated anaemia (case 11), pelvic mass without bleeding (case 13), severe pelvic pain (case 15), and abdominal distension with pain (case 17). Three cases from the 2022 Arciuolo series (cases 22, 23, and 24) did not specify presenting symptoms.

3. FIGO Staging

The complete FIGO stage distribution is presented in Table 3. Stage Ia was the most commonly recorded stage, accounting for 10 of 28 cases (35.7%). When early (I–II) and advanced (III–IV) stages are considered collectively, early-stage disease accounted for 60.7% of cases (17/28), and advanced-stage disease for 39.3% (11/28). All four Stage IV cases (IVb and IVc) had documented lung, supraclavicular, or other distant metastases at presentation.

Table 3. FIGO Stage Distribution

FIGO Stage	Number of Patients	Percentage
Ia	10	35.7%
Ib	5	17.9%
Ic	1	3.6%
IIa	1	3.6%
IIIa	3	10.7%
IIIc	3	10.7%
IVb	2	7.1%
IVc	3	10.7%
Total	**28**	**100.0%**

4. Histopathological Features

The GCC % was quantified to some degree in 24 of the 28 cases. The giant cell component comprised a variable proportion of the tumour, ranging from 15% to 100% across reported cases. The proportion was described as "predominant" (without precise quantification) in 6 cases and was not specified or not determinable in 4 cases (14.3% of total; cases 20, 22-24). Pure giant cell carcinoma, with no identifiable conventional component, was documented in 2 cases (11 and 21).

For the 24 cases with reported GCC data, cases have been assigned to three groups based on the documented or estimated proportion:

I. **Low GCC <50%):** 7 cases (25.0% of total series; 29.2% of cases with reported GCC). Includes cases 1, 5 and 27 (GCC = 15%), cases 13 and 16 (GCC = 30%), cases 9 and 10 (GCC <50%).

II. **Medium GCC (50–74%):** 4 cases (14.3% of total; 16.7% of reported). Includes case 17 (GCC = 50%), case 18 (GCC = 60%), and cases 7 and 15 (GCC = 70%).

III. **High GCC (≥75%):** 13 cases (46.4% of total; 54.2% of reported). Includes cases 2, 3, 4, 6, 8, and 25 (all described as predominant, estimated GCC ≥ 75%); case 14 (GCC = 80%), case 26 (GCC = 85%), case 12 (GCC = 90%), cases 19 and 28 (GCC = 95%), cases 11 and 21 (pure GCC cases).

The distribution of the conventional carcinoma component is summarised in Table 4. Endometrioid adenocarcinoma, spanning various grades, was by far the most frequent coexisting histomorphological type, identified in approximately 68% of cases. Serous carcinoma was the next most common, present in approximately 14% of cases, either as a primary component or as a minor element.

Table 4. Conventional Carcinoma Component by Histomorphological Type

Histomorphological type	Number of Patients	Percentage
Endometrioid (any grade)	19	67.9%
Serous carcinoma	4	14.3%
Mixed/other (undifferentiated, clear cell, spindle)	3	10.7%

5. Management Strategies

The management modalities employed across the 28 cases are summarised in Table 5. Surgical resection in the form of total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) or a minimally invasive equivalent was performed in 27 of 28 cases (96.4%), confirming that surgery is the near-universal cornerstone of EGCC management. One case (case 1, Jones et al., 1991) was recorded as receiving no treatment, though this likely reflects incomplete documentation from an early report.

Adjuvant radiation therapy was administered in 11 cases (39.3%), while chemotherapy was employed in 10 cases (35.7%), either as adjuvant, neoadjuvant, or combination therapy. Lymph node dissection was performed in 6 cases (21.4%) and omentectomy in 5 cases (17.9%). Surgery as the sole treatment modality with no adjuvant therapy was recorded in 10 cases (35.7%), predominantly in Stage Ia disease.

Table 5. Employed Treatment Methods

Treatment	Number of Patients	Percentage
Hysterectomy (any type)	27	96.4%
Adjuvant radiation therapy	11	39.3%
Chemotherapy (any timing)	10	35.7%
Lymph node dissection	6	21.4%
Omentectomy	5	17.9%
Surgery alone (no adjuvant)	10	35.7%

6. Clinical Outcomes

Clinical outcome data were available for 21 of 28 cases (75.0%). Seven cases (25.0%) were classified as having unknown or unrecorded outcomes. Among the 21 cases with known outcomes, 13 (61.9%) achieved remission, or NED, 5 (23.8%) died of disease, and 3 (14.3%) were alive with disease or documented recurrence/metastasis (Table 6).

Table 6. Clinical Outcomes among Cases with Known Follow-up

Outcome	Number of Patients	Percentage
Remission / NED	13	61.9%
Deceased	5	23.8%
Alive with disease/recurrence	3	14.3%
Total (known outcomes)	**21**	**100.0%**

The five deceased patients spanned multiple stages: two Stage I cases (cases 3 and 4), one Stage IVb case (case 5), one Stage IVc case (case 17), and the present case (Stage IIIc). The earliest recorded death occurred 2 months after diagnosis (case 17, Stage IVc), whereas the longest survival among deceased patients was approximately 1 year (present case). Among patients in remission or NED, one patient (case 10) remained disease-free at 168 months (14 years), representing the longest documented follow-up in the series.

Table 7 presents outcomes stratified by FIGO stage group. Among early-stage patients (FIGO I–II, n=17) with recorded outcomes, 73.3% achieved remission or NED (11/15 with known outcomes), 13.3% died (2/15), and 13.3% had disease persistence or recurrence. Among advanced-stage patients (FIGO III–IV, n=11) with recorded outcomes, only 33.3% achieved remission (2/6 with known outcomes), while 50.0% died and 16.7% had persistent disease. The proportion of unknown outcomes was substantially higher in the advanced-stage group (5/11, 45.5%) than in the early-stage group (2/17, 11.8%).

Table 7. Outcomes Stratified by FIGO Stage Group

Outcome	Early stage (I–II)	%	Advanced stage (III–IV)	%	Total Patient Number
Remission / NED	11	73.3%*	2	33.3%*	13
Deceased	2	13.3%*	3	50.0%*	5
Disease/recurrence	2	13.3%*	1	16.7%*	3
Unknown / no info	2	11.8%**	5	45.5%**	7
Total (all cases)	**17**	**-**	**11**	**-**	**28**

* Percentages for remission, deceased, and disease/recurrence are calculated from known-outcome cases only.

** Percentages for unknown are calculated from total cases in each group.

7. The Relationship between Giant Cell Component and FIGO Stage

A primary finding of this review is the lack of a direct correlation between the proportion of giant cells and the clinical stage of the carcinoma. Evidence suggests that a high percentage of giant cells does not necessarily indicate advanced disease (Stage III or IV). For instance, cases with a predominant giant cell component have been frequently identified in FIGO Stages I or II (6).

Specific examples highlight this discrepancy:

I. In four cases (Cases 2,3,4,6) where giant cells predominated, the clinical stages ranged widely from I to IV (2).

II. Other cases (cases 9–13) demonstrated even larger GCC, case 11 presented only with a complete giant cell pattern (GCC = 100%) at Stage I, while case 13 had a significantly lower count (GCC = 30%) despite being Stage IIIa (7).

These observations suggest that the giant cell component may serve as an independent histological criterion rather than a marker of higher stage or of natural disease progression to a dedifferentiated tumour. The detailed GCC distribution across FIGO stages is presented in Table 8.

Table 8. Cross-tabulation: GCC Level × FIGO Stage Group

GCC Level	Stage I	Stage II	Stage III	Stage IV	Total
Low (<50%)	4 (57%)	—	2 (29%)	1 (14%)	**7**
Medium (50–74%)	1 (25%)	—	—	3 (75%)	**4**
High (≥75%)	8 (62%)	1 (8%)	3 (23%)	1 (8%)	**13**
Not reported	3 (75%)	—	1 (25%)	—	**4**
Total	**16**	**1**	**6**	**5**	**28**

Note: cell values = n (row %); row percentages are of the GCC group total.

Notably, the High GCC Level is predominantly Stage I, but this may reflect the biological behaviour of EGCC, a tumour that frequently causes early symptomatic bleeding (enabling early diagnosis), rather than any protective effect of a high giant cell fraction.

8. Prognostic Significance and Clinical Outcomes

While the Giant Cell Component (GCC) does not strictly correlate with the FIGO stage (Table 9), a higher GCC level may be an additional indicator of tumour aggressiveness or adverse prognosis in some cases. Emerging evidence on survival and recovery patterns suggests that GCC distribution may be associated with a more aggressive clinical trajectory.

Despite undergoing radical surgical intervention supplemented by chemotherapy and radiotherapy, some patients with EGCC experienced rapid deterioration in health. This is evidenced by early metastasis and disease-related mortality shortly after diagnosis. Notably, Cases 3 and 11 illustrate that even in Stage I disease, a substantial giant cell component may be associated with relapse and accelerated disease progression.

9. Limitations and Future Directions

The synthesis of current literature emphasises the need for a formal histopathological classification system specific to giant cell components. Current reporting remains inconsistent, hindering clinicians' ability to draw robust conclusions about survival and management. Establishing standardised histological descriptions would allow for:

I. Uniform diagnosis: Distinguishing giant cell carcinomas from other high-grade pathological entities.
II. Predictive Accuracy: Better assessment of tumour aggressiveness regardless of the initial stage.

III. Refined Management: Developing targeted treatment protocols for this specific, aggressive subtype of endometrial cancer.

Table 9. All 28 EGCC Cases: GCC Level x FIGO Stage x Outcome

GCC Level	FIGO Stage	n	Remission / NED	Deceased	Disease / Recurrence	Unknown	Case No.
Low (<50%), n=7 (known=7)	**Stage I**	**4**	4/4 (100%)	0	0	0	1, 9, 10, 16
	Stage III	**2**	2/2 (100%)	0	0	0	13, 27
	Stage IV	**1**	0	1/1 (100%)	0	0	5
Low (<50%), subtotal		**7**	**6/7 (86%)**	**1/7 (14%)**	**0**	**0**	
Medium (50–74%), n=4 (known=2)	**Stage I**	**1**	—	—	—	1/1 (100%)	18
	Stage IV	**3**	0	1/2 (50%)	1/2 (50%)	1/3 (33%)	7, 15, 17
Medium (50–74%), subtotal		**4**	**0**	**1/2 (50%)**	**1/2 (50%)**	**2/4 (50%)**	
High (≥75%), n=13 (known=9)	**Stage I**	**8**	4/7 (57%)	1/7 (14%)	2/7 (29%)	1/8 (13%)	2, 3, 11, 12, 14, 21, 25, 26
	Stage II	**1**	0	1/1 (100%)	0	0	4
	Stage III	**3**	0	1/1 (100%)	0	2/3 (67%)	8, 19, 28*
	Stage IV	**1**	—	—	—	1/1 (100%)	6
High (≥75%), subtotal		**13**	**4/9 (44%)**	**3/9 (33%)**	**2/9 (22%)**	**4/13 (31%)**	
Not Reported, n=4 (known=3)	**Stage I**	**3**	3/3 (100%)	0	0	0	22, 23, 24
	Stage III	**1**	—	—	—	1/1 (100%)	20
Not Reported, subtotal		**4**	**3/3 (100%)**	**0**	**0**	**1/4 (25%)**	
TOTAL		**28**	**13/21 (62%)**	**5/21 (24%)**	**3/21 (14%)**	**7/28 (25%)**	

Note: Remission/NED, Deceased, and Disease/Recurrence expressed as n/known-outcome cases in cell (%); Unknown as n/cell total (%). Subtotal rows summarise each GCC group across all stages. The total row summarises the entire series.

Abbreviations: AWD – alive with disease; GCC – giant cell component; NED – no evidence of disease; * present case (no. 28).

LITERATURE REVIEW

1. Normal Endometrial Anatomy and General Overview of Endometrial Cancer

1.1. Normal Endometrial Anatomy

The endometrium is the hormonally responsive mucosal lining of the uterine corpus that undergoes dynamic, cyclical changes throughout the menstrual cycle. It comprises three principal components: the surface epithelium, endometrial glands, and stroma. The surface epithelium is continuous with the glandular epithelium, while the glands are tubular structures embedded within a highly vascularised stromal matrix containing immune and stromal cells.

Anatomically, the endometrium has two layers: the basal (*stratum basale*), adjacent to the myometrium and stable, and the functional (*stratum funcionale*), which proliferates and differentiates during the cycle. Ultrastructurally, the endometrium is hormone-responsive, with junctions, microvilli, and organelles. Its function is regulated by the hypothalamic–pituitary–ovarian axis; oestrogen stimulates proliferation during the proliferative phase, while progesterone prepares the functional layer for the secretory phase. If fertilisation does not occur, declining hormone levels reduce blood flow in the spiral arteries, resulting in ischaemia and tissue necrosis. This process, known as functional layer shedding, occurs during menstruation and prepares the uterus for the next cycle. Disruption of this process may cause endometrial disorders, including hyperplasia and carcinoma (8).

1.2. General Classification of Endometrial Cancer

Endometrial carcinoma is the most common malignancy of the uterine corpus and comprises a heterogeneous group of tumours with diverse histopathological and molecular characteristics. According to the World Health Organisation Classification of Female Genital Tumours, classification has traditionally been based on histomorphological features, but it increasingly incorporates molecular characteristics to improve diagnostic precision and prognostic stratification (9,10). While endometrioid carcinoma remains the most common subtype, other recognised epithelial variants include serous, clear cell, and mucinous carcinomas, as well as rare patterns such as villoglandular, corded, and hyalinized carcinomas. Notably, rare entities such as Endometrial Giant Cell Carcinoma are not currently recognised as distinct diagnostic categories in the WHO

classification; instead, they are described as rare morphological variants within the spectrum of high-grade carcinomas (4,11).

Endometrial carcinoma is the most common malignancy of the uterine corpus. Traditionally, it is classified into two broad pathogenetic types based on histological features and clinical behaviour.

Type I carcinomas, primarily endometrioid adenocarcinomas, account for most cases and are typically oestrogen-dependent. These tumours frequently arise from endometrial hyperplasia, most commonly in perimenopausal women. Histologically, they are characterised by well-formed glandular structures lined by columnar to cuboidal cells with pseudostratified nuclei and low- to intermediate-grade cytological atypia. At the molecular level, Type I tumours frequently harbour mutations in *PTEN, PIK3CA*, and *KRAS* and may exhibit microsatellite instability (MSI). Clinically, these tumours are usually low-grade and carry a relatively favourable prognosis. In contrast, Type II carcinomas are oestrogen-independent and typically arise within the atrophic endometrium of postmenopausal women. This group encompasses high-grade histological subtypes, including serous, clear cell, mixed, undifferentiated, and dedifferentiated carcinomas.

I. Serous carcinoma is distinguished by marked nuclear atypia, prominent nucleoli, and high mitotic activity, often exhibiting papillary growth.
II. Clear cell carcinoma presents with distinct cell borders, clear cytoplasm, and diverse architectural patterns such as papillary, tubulocystic, or solid growth.
III. Undifferentiated and dedifferentiated carcinomas lack conventional glandular differentiation and are characterised by highly aggressive clinical behaviour.
IV. Mixed carcinomas contain at least two histological components (each comprising >10% of the tumour), with the prognosis generally dictated by the most aggressive element.

Type II tumours are strongly associated with *TP53* mutations and extensive genomic instability, correlating with their virulent clinical course. Undifferentiated and dedifferentiated carcinomas are particularly important within this group, as they are rare, highly aggressive, and frequently underrecognized. Dedifferentiated carcinoma is characterised by the coexistence of a low-grade endometrioid component and an undifferentiated component, reflecting tumour progression and biological heterogeneity (12).

1.3. Modern Molecular Classification

Recent advances in molecular pathology have significantly refined the classification of endometrial carcinoma (13). The landmark study conducted by the Cancer Genome Atlas Research Network identified four molecular subgroups distinguished by their prognostic implications:

I. POLE-ultramutated; associated with an excellent prognosis despite exhibiting high-grade morphology;
II. Mismatch repair-deficient (MMRd); characterised by MSI-hypermutation and intermediate clinical outcomes
III. Copy-number low (NSMP); generally representing low-grade tumours with a "no specific molecular profile" and a favourable prognosis
IV. Copy-number high (Serous-like); distinguished by *TP53* mutations and adverse clinical outcomes (14,15)

Table 10. Overview of the four molecular subtypes of endometrial carcinoma, their frequency, key molecular alterations, prognosis, and therapeutic relevance.

Subtype	Frequency	Key alteration	Prognosis	Therapy relevance
POLE-ultra mutated	~5–10%	*POLE* exonuclease mutation; TMB >100 mut/Mb	Excellent	An ICI candidate despite a high grade
MMR-deficient (MMRd)	~25–30%	*MLH1* methylation or Lynch germline; MSI-H	Intermediate	Pembrolizumab (PD-1 inhibitor)
Copy-number low (NSMP)	~40–50%	No defining alteration; ER/PR positive	Favourable	Hormonal therapy; risk stratification ongoing
Copy-number high (Serous-like)	~15–20%	*TP53* mutation + widespread SCNAs; *ERBB2 (HER2)* amplification (~25–30%)	Poor	Anti-HER2 therapy (trastuzumab) in the HER2+ subset

Abbreviations: TMB – tumour mutational burden; MSI-H – microsatellite instability-high; NSMP – no specific molecular profile; SCNA – somatic copy-number alteration; ICI – immune checkpoint inhibitor; ER – oestrogen receptor; PR – progesterone receptor.

These molecular classifications have been incorporated into contemporary clinical frameworks, including the FIGO and international management guidelines, reflecting their clinical relevance for risk stratification and

therapeutic decision-making. (6,18,17). Additional molecular alterations, including deficiencies in the SWI/SNF complex and aberrant p53 expression, have been linked to aggressive tumour behaviour and dedifferentiation (18,19). Comprehensive features of each type are summarised in Table 10.

1.3.1. *POLE*-Ultra mutated

This subtype is defined by pathogenic mutations in the exonuclease domain of the *POLE* gene, which encodes the proofreading subunit of DNA polymerase epsilon. These mutations impair the enzyme's ability to correct replication errors, resulting in an extraordinarily high tumour mutational burden (TMB) — often exceeding 100 mutations per megabase (mut/Mb).

Despite frequently exhibiting high-grade histological features (including grade 3 endometrioid or serous-like morphology), *POLE*-ultramutated tumours have a paradoxically excellent prognosis, with very low rates of recurrence and disease-specific mortality. The favourable outcome is thought to be driven by robust anti-tumour immune responses: the extreme neoantigen load generated by hypermutation attracts tumour-infiltrating lymphocytes (TILs), effectively suppressing disease progression.

This subtype accounts for approximately 5–10% of endometrial carcinomas and is identified by targeted sequencing or hotspot mutation testing of the *POLE* exonuclease domain (most commonly codons 286 and 411). It is also considered a candidate for immune checkpoint inhibitor (ICI) therapy due to its high immunogenic burden. (15,17).

1.3.2. Mismatch Repair-Deficient (MMRd)

This subtype arises from defects in the DNA mismatch repair (MMR) system, most commonly from somatic hypermethylation of the *MLH1* promoter (sporadic cases) or from germline mutations in *MLH1, MSH2, MSH6,* or *PMS2* (Lynch syndrome-associated cases). This results in microsatellite instability-high (MSI-H) status and a high, though not extreme, tumour mutational burden.

MMRd tumours account for roughly 25–30% of endometrial carcinomas and span a wide histological spectrum, from low-grade endometrioid to dedifferentiated carcinomas. Clinical outcomes are intermediate — better than those of the copy-number high group but less favourable than those of POLE-ultramutated tumours. Importantly, MMRd status is a predictive biomarker for response to immune checkpoint inhibitors, particularly PD-1/PD-L1 inhibitors. Pembrolizumab is approved for MMR-deficient tumours in the recurrent and

metastatic setting. Testing is performed by immunohistochemistry (IHC) for MLH1, PMS2, MSH2, and MSH6 protein expression, or by PCR/NGS-based MSI analysis. (15,17,22,23).

1.3.3. Copy-Number Low / No Specific Molecular Profile (NSMP)

This is the most heterogeneous subtype, defined by exclusion: tumours that lack POLE mutations, have intact MMR function, and do not harbour *TP53* mutations or widespread somatic copy-number alterations (SCNAs). Accordingly, the "no specific molecular profile" designation reflects molecular negativity rather than a distinct oncogenic pathway.

The majority are low-grade (FIGO grade 1–2, G1-2) endometrioid carcinomas with oestrogen receptor (ER) and progesterone receptor (PR) positivity, reflecting the hormonal pathogenesis typical of type I endometrial carcinomas. Prognosis is generally favourable, with most patients diagnosed at an early stage and achieving excellent long-term survival.

However, this category remains a research priority because it is large (~40–50% of cases) and clinically heterogeneous. A subset of NSMP tumours with high L1CAM expression, aberrant p53 on IHC without a confirmed mutation, or other high-risk features can have worse-than-expected outcomes. Ongoing efforts aim to refine risk stratification within this group. (17,24,25).

1.3.4. Copy-Number High / Serous-Like (*TP53*-Mutated)

This subtype is characterised by near-universal somatic *TP53* mutations along with widespread somatic copy-number alterations, reflecting chromosomal instability reminiscent of high-grade serous ovarian carcinoma — hence the "serous-like" designation. It encompasses uterine serous carcinoma (USC), grade 3 endometrioid carcinoma with a high copy-number profile, and clear cell carcinomas with *TP53* mutations.

These tumours display aggressive biology: they are frequently diagnosed at an advanced stage, show early lymphovascular invasion and extra-uterine spread, and carry a poor prognosis with high rates of recurrence despite adjuvant therapy.

HER2 (ERBB2) amplification occurs in approximately 25–30% of uterine serous carcinomas, and trastuzumab-based regimens have shown clinical benefit in this *HER2*-positive subset. *TP53* mutation status is assessed by IHC (aberrant p53 expression — either diffuse strong or complete null) with confirmatory sequencing in equivocal cases (17,25,26).

2. Uncommon Histological Subtypes and EGCC Overview

2.1. Rare Morphological Variant

Rare morphological variants of endometrial carcinoma have increasingly been recognised to improve diagnostic accuracy and tumour subclassification. Altered differentiation patterns, specifically squamous, mucinous, and morular differentiation, are most frequently observed in endometrioid-type adenocarcinomas and are typically absent in serous, clear cell, or other high-grade histotypes. These include patterns such as squamous, mucinous, ciliated, papillary, microglandular, and spindled differentiation, as well as corded and hyalinised endometrial carcinoma (CHEC) (15). Mixed endometrial carcinomas, defined by the presence of at least two distinct histological components, are of particular clinical importance, as the most aggressive component typically determines prognosis. Despite these advances, certain rare variants, including endometrial giant cell carcinoma (EGCC), remain unrecognised as distinct entities in current classification systems (4).

Squamous or morular differentiation can range from benign appearances to overt cytological malignancy; occasionally, glycogen-rich squamous areas may produce a clear cytoplasmic appearance, necessitating careful differentiation. The designation of mucinous differentiation is strictly reserved for tumours demonstrating true intracytoplasmic mucin production, as intraluminal mucin alone is insufficient for this classification. Furthermore, secretory differentiation is histologically identified by characteristic subnuclear and supranuclear vacuolization.

Additional rare variants include:

I. Ciliated (tubal type) differentiation: Resembles fallopian tube epithelium and is characterised by scattered ciliated cells with apical terminal bars.
II. Papillary variants: Characterised by villoglandular architecture, as well as non-villous papillary and micropapillary structures.
III. Microglandular or microcystic patterns: These mimic microglandular hyperplasia and are defined by small glands frequently containing intraluminal neutrophils.
IV. Spindled differentiation: Features bland, spindle-shaped tumour cells that coalesce with conventional epithelial components, reflecting a partial epithelial–mesenchymal transition (EMT)-like morphology.

Corded and Hyalinised Endometrial Carcinoma (CHEC), characterised by tumour cells arranged in cords and trabeculae within a prominent, dense, hypohyaline stroma, is a highly distinctive pattern. Finally, mixed endometrial carcinoma is diagnosed when at least two distinct histological subtypes coexist within the same tumour. The most common combination involves endometrioid and serous components, with the minor

component comprising at least 5% of the total tumour volume. This classification is clinically significant, as the patient's prognosis is generally driven by the most aggressive histological component, such as serous, clear cell, or neuroendocrine differentiation.

2.2. Endometrial Giant Cell Carcinoma (EGCC)

EGCC is an exceptionally rare variant of high-grade endometrial carcinoma, characterised by a predominance of atypical mono- and multinucleated giant tumour cells. Due to its rarity, EGCC is not recognised as a distinct entity in the 5th edition (2020) WHO Classification and is instead considered within the spectrum of undifferentiated and dedifferentiated carcinomas. Undifferentiated carcinomas account for less than 2% of all endometrial cancers.

Histologically, EGCC is defined by the presence of highly pleomorphic mono- and multinucleated giant tumour cells, often arranged in poorly cohesive sheets or nests. These tumours frequently coexist with components of conventional endometrial carcinoma, supporting a dedifferentiation-related pathogenesis. Additional aggressive morphological features include atypical mitotic activity, emperipolesis, and cellular cannibalism (25,26).

Immunohistochemically, EGCC typically shows focal expression of epithelial markers, including keratins AE1/AE3 and CAM5.2, as well as epithelial membrane antigen (EMA). Additionally, hormone receptors (ER/PR) are generally negative or focally positive. Loss of E-cadherin expression is frequently observed, reflecting reduced cellular cohesion and features of epithelial–mesenchymal transition. It is imperative to exclude sarcomas, trophoblastic neoplasms, and melanoma, which require negative staining for lineage-specific markers such as desmin, S100, and HMB45. (3).

From a molecular perspective, reported cases of EGCC frequently overlap with undifferentiated or dedifferentiated endometrial carcinoma and often show TP53 abnormalities and relative mismatch repair (MMR) proficiency. This molecular profile supports classification within the "copy-number high/p53-abnormal" category of the Cancer Genome Atlas (TCGA) molecular framework. (13,23).

Considering these three aspects, including EGCC in the WHO classification as a separate entity, becomes more likely. It could enable better surveillance of cases, more accurate diagnoses, and support for patients in deciding on treatment strategies.

2.2.1. Cellular Cannibalism

Cellular cannibalism is a tumour-associated phenomenon in which malignant cells internalise viable or dying cells. This process has been linked to tumour aggressiveness, metabolic adaptation, and immune evasion, and is considered a marker of high-grade malignancy and poor prognosis (24). Unlike phagocytosis by immune cells, this process is carried out by malignant epithelial cells themselves. Consequently, it is regarded as an aberrant tumour-associated behaviour rather than a physiological clearance mechanism. Morphologically, it is characterised by a large "host" tumour cell containing an intact or partially degraded second cell within its cytoplasm. This phenomenon differs from the simple engulfment of debris in that the internalised cell frequently retains identifiable nuclear and cytoplasmic structures. The phenomenon under discussion is closely related to other cell-in-cell processes, such as entosis, a form of non-apoptotic cell death in which a living, typically cancerous or detached, epithelial cell actively invades and is engulfed by a neighbouring cell, creating a characteristic “cell-in-cell” structure. However, in the context of cancer, it is generally interpreted within a broader spectrum of tumour cell cannibalism. Cellular cannibalism is widely regarded as an indication of high-grade malignancy and tumour plasticity from a functional perspective. It is most frequently observed in poorly differentiated carcinomas and aggressive neoplasms. Proposed biological explanations for this phenomenon include loss of cell adhesion, cytoskeletal reorganisation, and activation of actin-dependent engulfment mechanisms. These mechanisms enable tumour cells to internalise neighbouring cells. This may provide a survival advantage under conditions of nutrient deprivation, hypoxia, or metabolic stress, as internalised cells can potentially serve as a temporary nutrient source. Furthermore, cellular cannibalism has been linked to immune evasion, whereby tumour cells may internalise immune effector cells, such as lymphocytes, thereby diminishing anti-tumour immune activity within the microenvironment. Despite a lack of a comprehensive understanding of the precise molecular mechanisms underlying this phenomenon, a consistent correlation has been observed between the presence of this alteration and adverse clinical outcomes, including poor differentiation, increased tumour aggressiveness, and a worse prognosis across various cancer types. (1,2,25–27).

2.2.2. Giant Cell Morphology in Tumours and Main Differential Diagnostics

Giant cells are markedly enlarged, typically measuring 50–100 μm in diameter. They are characterised by abundant cytoplasm and may contain either a single large pleomorphic nucleus or multiple nuclei (multinucleation). These cells arise through several mechanisms, including nuclear division without cytokinesis, cell fusion, or endoreduplication. In neoplastic settings, tumour giant cells typically display

hyperchromatic nuclei, prominent nucleoli, and atypical mitotic figures. Distinguishing these malignant cells from reactive, non-neoplastic multinucleated cells (such as osteoclast-like giant cells) is crucial, as the latter lack significant nuclear atypia (28,29).

Although uncommon in gynaecological cancers, giant cell morphology is well documented across various cancer types. In endometrial carcinoma, these cells are primarily associated with undifferentiated or dedifferentiated subtypes, indicating high-grade transformation and aggressive biological behaviour (29). Giant cell features also occur in serous carcinomas of the endometrium and ovary, as well as in clear cell carcinoma, though typically as a focal rather than a dominant pattern. In cervical cancer, multinucleated tumour giant cells are occasionally seen in poorly differentiated squamous cell carcinoma.

Reactive histiocytic elements, such as CD68-positive osteoclast-like giant cells, may also be present in rare cases of endometrial and ovarian disease. Overall, the presence of malignant giant cells is a hallmark of advanced disease, increased proliferative activity, and a poorer patient prognosis. (30).

The differential diagnosis of these tumours is extensive and requires careful integration of histomorphology and immunohistochemistry.

Key considerations include:

I. undifferentiated/dedifferentiated endometrial carcinoma;
II. leiomyosarcoma with pleomorphic giant cells;
III. carcinosarcoma (malignant mixed Müllerian tumour);
IV. high-grade serous carcinoma with anaplastic features.

Non-epithelial malignancies, such as malignant melanoma or high-grade sarcomas, must be excluded using lineage-specific markers, including S-100, SOX-10, or desmin (1,9). Additionally, metastatic tumours, such as renal cell carcinoma, should be considered when appropriate.

A critical diagnostic distinction lies between malignant giant cells and benign osteoclast-like giant cells. The latter are uniform and express histiocytic markers (CD68), whereas malignant giant cells show marked pleomorphism, high mitotic activity, and at least focal expression of epithelial markers (e.g., CKs, EMA) (12). Supporting evidence for high-grade malignancy includes the loss of E-cadherin or aberrant p53 expression (29). Precise classification is vital, as the presence of giant cells directly correlates with tumour grade, histogenesis, and clinical outcome.

3. Prognosis and Clinical Outcomes

EGCC is associated with an aggressive clinical course. Reported median survival is frequently less than 1–2 years (29,31). Patients often present at advanced FIGO stages (III–IV) with deep myometrial invasion and early lymphatic or haematogenous dissemination. Standard treatment comprises total hysterectomy and bilateral salpingo-oophorectomy, supplemented by platinum-based chemotherapy and radiotherapy. Despite these multimodal strategies, patients continue to show high rates of disease progression and relapses (2,5,28,31,27). Notably, available evidence suggests that the proportion of the giant cell component does not correlate directly with tumour stage, indicating that giant cell morphology may be an independent adverse prognostic factor.

4. Molecular Pathological Features and Therapeutic Targets

4.1. Molecular Profiling in EGCC

EGCC molecularly overlaps with undifferentiated carcinomas, most frequently showing *TP53* abnormalities consistent with a copy-number-high (serous-like) TCGA subgroup (1). Another hallmark is the frequent loss of SWI/SNF complex components (e.g., ARID1A and SMARCA4), which is associated with dedifferentiation and chemotherapy resistance. (9,12,29).

4.2. The Role of *PIK3CA* and Targeted Therapy

Mutations in the *PIK3CA* gene and activation of the *PI3K/AKT/mTOR* pathway are frequent in endometrial carcinoma (15) and may contribute to tumour progression and therapeutic resistance. In high-grade tumours, *PIK3CA* mutations often co-occur with *TP53* alterations, suggesting synergistic effects that enhance metastatic potential and therapeutic resistance. (16,17,18,29,30). This pathway represents a potential therapeutic target, as *PI3K/AKT/mTOR* inhibitors (e.g., alpelisib, everolimus) are increasingly being investigated in clinical trials for refractory endometrial cancers (1).

5. Synthesis of Literature Findings

The current literature highlights the rarity and clinical significance of EGCC, as well as substantial gaps in knowledge regarding its diagnosis, molecular characteristics, and optimal management. The emphasis is on the finding that the proportion of giant cells does not necessarily correlate with FIGO stage. High percentages

of giant cell components have been observed in Stages I or II, yet the prognosis remains poor. This underscores the need for a formal histopathological classification system specific to giant cell components to facilitate more precise conclusions regarding aggressiveness and survival rates. Notably, since molecular profiling was not conducted in any of the identified historical cases. Future research should focus on integrating histopathological and molecular findings through collaborative efforts to establish evidence-based diagnostic and therapeutic frameworks.

DISCUSSION

Endometrial giant cell carcinoma (EGCC) represents an exceptionally rare and poorly characterised variant of endometrial carcinoma. Based on the presented case and a comprehensive literature review comprising only 14 published articles reporting 28 cases, the evidence remains scarce, underscoring the limitations in defining its biological behaviour, diagnostic criteria, and optimal management strategies (1,9,12,29,31). Most published reports originate from specialist centres in North America and the United Kingdom, reflecting both the rarity of the disease and the likelihood of underrecognition in routine practice.

Clinically, EGCC predominantly affects postmenopausal women, although cases have been described across a broad age range (39–85 years). The most common presenting symptoms include abnormal vaginal bleeding, abdominal pain, and abdominal distension, which are nonspecific and overlap with those of conventional endometrial carcinoma (9,12,29,31). This overlap presents a diagnostic challenge in routine clinical settings.

A key finding of this review is that the extent of the giant cell component does not appear to correlate directly with FIGO stage. Several reported cases demonstrated a predominant giant cell component despite the disease being confined to stage I, whereas more advanced tumours occasionally showed lower proportions of giant cells (1,9,29). This observation suggests that the giant cell component should not be interpreted merely as a reflection of tumour burden or stage progression. Instead, it may represent an independent histopathological marker of aggressive tumour biology, with potential prognostic relevance beyond conventional anatomical staging.

In this context, the predominance of early-stage EGCC at diagnosis requires careful interpretation. Across the reviewed series, Stage I disease accounted for most cases (16/28, 57.1%), which could superficially suggest a less aggressive tumour. However, this distribution is more likely to be explained by the tumour's clinical presentation than by its biology. Because EGCC arises within the endometrial cavity, it commonly causes postmenopausal vaginal bleeding at an early anatomical stage, prompting timely investigation before

substantial extrauterine spread occurs. This pattern mirrors that of conventional endometrioid carcinoma and reflects anatomical accessibility rather than biological indolence.

Importantly, available outcome data do not support a favourable prognosis, even in Stage I disease. Among Stage I cases with reported follow-up, both recurrence and disease-related death were documented despite early diagnosis and surgical treatment. Early bleeding should therefore be regarded as a consequence of tumour location rather than as evidence of low aggressiveness. The rapid progression, early metastatic spread, and treatment resistance observed in the present case and in several historical reports appear to reflect intrinsic tumour biology rather than stage at presentation. Indeed, early symptomatic presentation in EGCC may paradoxically indicate aggressive behaviour, as rapidly proliferating, poorly cohesive tumours within the endometrial cavity are more likely to produce early bleeding while harbouring molecular alterations that facilitate systemic dissemination once local barriers are breached.

A major limitation in the current literature is the absence of standardised histopathological criteria for EGCC. Reporting remains inconsistent, with some studies quantifying the proportion of giant cells and others describing it only qualitatively. Establishing a dedicated classification framework—incorporating morphology, proportion, immunophenotype, and associated conventional tumour components—would improve diagnostic reproducibility, facilitate cross-study comparison, and enhance clinicopathological correlation. Such a system would also help clarify whether EGCC represents a distinct biological entity or a morphological pattern shared across multiple high-grade endometrial carcinomas. (27,29).

This thesis further emphasises the growing importance of molecular pathology. Modern classification systems, including the FIGO 2023 staging update, incorporate molecular subgroups derived from The Cancer Genome Atlas (TCGA) and recognise the prognostic significance of alterations such as *TP53* mutations, mismatch repair deficiency, POLE mutations, and NSMP status (2,5). Molecular profiling is therefore relevant not only for prognostic stratification but also for identifying potential therapeutic targets.

The present case can be classified using both conventional histomorphology and modern molecular profiling, and both approaches support the same conclusion: this tumour represents a highly aggressive form of endometrial carcinoma. Histologically, the dominant component met criteria for undifferentiated carcinoma, composed of solid, dyscohesive sheets of highly pleomorphic cells lacking glandular differentiation, with prominent giant-cell morphology consistent with endometrial giant cell carcinoma (EGCC). A minor serous papillary component (approximately 5%), identified only in the initial hysteroscopic biopsy, formally classified the tumour as a mixed carcinoma under WHO criteria, in which the most aggressive component determines prognosis. Within the traditional Type I/Type II framework, the tumour was clearly Type II, arising in a

postmenopausal woman with atrophic endometrium and demonstrating oestrogen-independent, high-grade morphology with aggressive clinical behaviour. Pathological staging was pT2 N1 M0 (FIGO Stage IIIC1).

Next-generation sequencing identified concurrent somatic *TP53* (c.770T>C) and *PIK3CA* (c.3140A>G) mutations. Immunohistochemistry showed retained expression of all mismatch repair proteins, confirming a mismatch repair-proficient (pMMR), microsatellite-stable (MSS) phenotype. Together, these findings place the tumour within the TCGA copy-number high/p53-abnormal ("serous-like") subgroup, which carries the poorest prognosis among the four molecular categories. The *TP53* mutation was associated with diffuse aberrant p53 overexpression in the initial biopsy. Interestingly, the resection specimen showed a heterogeneous, predominantly wild-type p53 staining pattern despite the confirmed mutation, most likely reflecting intratumoural heterogeneity or clonal evolution between biopsy and surgery. This phenomenon is increasingly recognised in *TP53*-mutant high-grade carcinomas and has important implications for diagnostic sampling.

The concurrent *PIK3CA* mutation results in the well-characterised H1047R substitution, leading to constitutive activation of the *PI3K/AKT/mTOR* signalling pathway. Although *PIK3CA* alterations are not specific to the copy-number-high subgroup, their coexistence with *TP53* mutations has been associated with enhanced metastatic potential and resistance to platinum-based chemotherapy, both of which were evident in this case. From a therapeutic perspective, the *pMMR/MSS* phenotype limits eligibility for immune checkpoint inhibitors under current indications. However, the activated *PI3K/AKT/mTOR* pathway may represent a potential therapeutic target, and agents such as everolimus and alpelisib are currently under investigation in refractory endometrial carcinomas with *PIK3CA* mutations.

Current literature on the molecular basis of endometrial giant cell carcinoma (EGCC) remains extremely limited. Nevertheless, the observed concordance between undifferentiated/giant-cell morphology and the high-copy-number molecular subgroup is biologically plausible. *TP53*-driven chromosomal instability promotes loss of differentiation, while additional molecular alterations may further facilitate dedifferentiation towards a giant cell phenotype. This molecular context may also explain the stage-independent aggressiveness reported in EGCC, suggesting that the capacity for rapid progression and metastatic dissemination is established early in tumour evolution at the genomic level rather than acquired progressively during disease progression. Reported clinical courses, including rapid metastatic spread and poor survival despite multimodal treatment, are consistent with the known behaviour of copy-number high endometrial carcinomas and underscore the urgent need for more effective targeted therapeutic strategies for this rare but highly aggressive tumour subtype. From a clinical perspective, awareness of EGCC is essential among pathologists, gynaecologic oncologists, and multidisciplinary tumour boards. Because the tumour is not yet formally recognised as a separate entity in

current WHO classifications, it may be overlooked or misclassified. Improved recognition would enhance reporting quality, support referral to specialised centres, and encourage molecular testing in diagnostically challenging or clinically aggressive cases (27,29).

Future research should focus on developing international multicentre registries and collaborative databases for rare endometrial tumours. Systematic collection of clinicopathological, molecular, treatment, and survival data is necessary to establish evidence-based diagnostic criteria and therapeutic recommendations. Particular emphasis should be placed on clarifying the prognostic impact of the giant cell component, identifying recurrent genomic alterations, and evaluating targeted therapies for actionable pathways, such as *PI3K/AKT/mTOR* or *p53*-associated mechanisms. (5,28,32).

CONCLUSION

Endometrial giant cell carcinoma (EGCC) is a rare, poorly understood variant of endometrial carcinoma, with few reported cases. Limited data hinder the understanding of its behaviour, diagnosis, and treatment. It mainly affects postmenopausal women and presents symptoms similar to conventional endometrial carcinoma. A key finding is that the proportion of giant cells does not correlate with FIGO (Fédération internationale de Gynécologie et d'Obstétriques) stage, suggesting it may be an independent marker of aggressive tumour biology. This highlights the need for a standard histopathological classification, as inconsistent current reporting impedes comparisons across studies.

The work also emphasises the importance of molecular pathology. Incorporating molecular classification systems, including TCGA (The Cancer Genome Atlas) subgroups, is crucial for improved prognostic stratification and the development of future targeted therapies. Increased clinical awareness is necessary, as EGCC is not yet recognised in WHO classifications, which risks underdiagnosis or misclassification. Future research should focus on international collaborations and multicenter registries to systematically gather clinicopathological and molecular data. These efforts are vital to establishing diagnostic and treatment strategies and understanding the prognostic role of giant cells.

In summary, EGCC is a rare but aggressive cancer with often poor outcomes. This thesis supports the idea that giant cell morphology may be an independent adverse prognostic factor. Progress in standardising diagnosis, molecular characterisation, and research collaboration is essential to improve understanding, management, and prognosis of this challenging disease.

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