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CASE REPORT

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Endometrial giant cell carcinoma: a case report and review of the literature

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Abstract

Background: Endometrial giant cell carcinoma (EGCC) is a rare form of endometrial carcinoma (EC) with limited documentation in medical literature, consisting of only two small series and a few case reports. Till now, the World Health Organization (WHO) classification of endometrial neoplasms does not recognize EGCC as a distinct entity. Due to its rarity, there is a lack of comprehensive data on the biological characteristics, clinical management and prognosis of EGCC. **Cases**: In this report, we present a rare case of EGCC in a 55-year-old postmenopausal woman, describe its clinicopathologic features and review the relevant literature. The patient underwent a comprehensive surgical procedure, including a total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Postoperative radiochemotherapy was not administered, and no evidence of disease recurrence was observed during the one-year follow-up period. **Conclusions**: Although there is insufficient evidence to definitively classify EGCC as a distinct uterine malignancy, our review of the relevant literature suggests that it may exhibit aggressive behavior based on its clinicopathological and molecular characteristics, and the presence and/or percentage of giant cell components should be clearly mentioned in pathological reports to highlight uncertainty regarding its biological characteristics. Further accumulation of experiences is necessary to improve the diagnosis and treatment of this uncommon tumor.

Keywords

Giant cell carcinoma; Endometrial carcinoma; Carcinosarcoma; p53; Case report

1. Introduction

Endometrial carcinoma (EC) is a significant health concern, ranking as the sixth most frequently diagnosed cancer in women and the second most common carcinoma affecting the female genital tract [1]. Based on its histological morphology, it can be divided into different subtypes, of which the endometrioid type is the most prevalent. Endometrial giant cell carcinoma (EGCC) is a recently defined variant subtype of EC, and it has not yet been listed as a distinct entity in the current WHO classification of endometrial neoplasms. Only two small series and a few case reports have been described in the literature [2–9]. Due to its rarity, there is a scarcity of data regarding the biological characteristics, clinical management and prognosis of EGCC. Herein, we report the case of a 55-year-old postmenopausal woman diagnosed with EGCC, describe its clinicopathological features, and review available literature, which might help pathologists and gynecologists recognize this rare new uterine malignancy.

2. Case presentation

A 55-year-old postmenopausal Chinese woman (gravidity 2 and parity 2) with a Body Mass Index (BMI) of 30 presented with vaginal bleeding that gradually increased in amount and frequency for approximately 2 months. She had been postmenopausal for 2 years and had a medical history of hypertension. Transvaginal ultrasound examination showed an echogenic polypoid mass measuring 1.8 cm × 1.2 cm × 1.6 cm in the uterine cavity. Preoperative tumor markers (including carbohydrate antigen 125 (CA125, 14.61 U/mL), carbohydrate antigen199 (CA19-9, 25.37 U/mL), alpha-Fetoprotein (AFP, 2.46 ng/mL) and carcinoembryonic antigen (CEA, 2.49 ng/mL) were within the normal range. Subsequently, a hysteroscopic procedure was performed to resect the lesion, and all excised tissues were submitted for pathological examination.

Microscopic examination revealed an intriguing composition of the tumor. Notably, within a background of multifocal necrosis, the tumor exhibited a large number of multinucleated and mononucleated giant cells arranged in a solid growth pattern (Fig. 1). The multinucleated giant cells displayed abundant eosinophilic cytoplasm and multiple pleomorphic vesicular nuclei with prominent nucleoli (Fig. 2A). On the other hand, the mononucleated giant cells resembled the multinucleated cells in morphology, with each mononucleated giant cell containing a single round nucleus characterized by prominent nucleoli but without pleomorphism (Fig. 2B). Numerous atypical

mitosis events were observed within the tumor. Additionally, a small portion (approximately 10%) was found to consist of conventional EC components, which appeared mostly as serous carcinoma and focally as endometrioid differentiation, mixed with giant cell components. There was no clear demarcation between these components, and no sarcomatous component was identified. Immunohistochemical staining revealed that the tumor cells (both the giant tumor cell component and the serous carcinoma component) were strongly positive for epithelial membrane antigen (EMA) (Fig. 3A), aberrant nuclear expression of p53 (Fig. 3B), Vimentin (Fig. 3C) and Paired Box Gene 8 (PAX-8). Focal positivity was also observed for estrogen receptor (ER), progestogen receptor (PR), insulin-like growth factor II mRNA-binding protein 3 (IMP3) and Wilm's Tumor Protein (WT-1), while negativity was noted for NapsinA, Hepatocyte nuclear factor 1-beta (HNF-1β), p16, β-human chorionic gonadotrophin (β-hCG), cluster of differentiation 68 (CD68) and Desmin. Additionally, retention of SMARCA4 (BRG1), SMARCB1 (INI1) and mismatch repair (MMR) proteins, including MLH1, PMS2, MSH2 and MSH6, was observed in all tumor cells (Fig. 3D–F). Subsequently, the Proactive Molecular Risk Classifier for EC (ProMisE) was used, which showed that the tumor was of the p53-mutant subtype. The final pathological diagnosis confirmed the presence of EGCC accompanied by serous carcinoma. Preoperative imaging examinations, including Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), revealed no positive findings. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Following the surgery, all excised endometrial tissues were submitted for pathological examination, and no residual tumor was identified. Based on the absence of uterine myometrial invasion, the surgical stage of the tumor was determined as Federation International of Gynecology and Obstetrics (FIGO) IA (2018). The patient did not receive chemoradiotherapy postoperatively, and a follow-up CT scan conducted after one year demonstrated no evidence of disease.

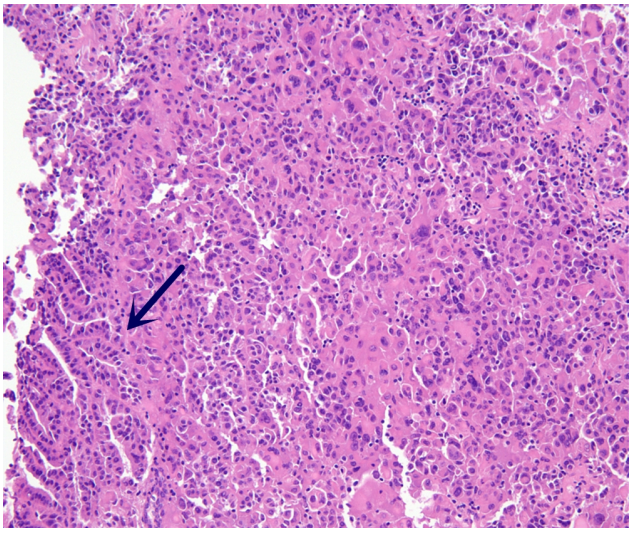

FIGURE 1. Tumor histopathology. The endometrial tumor was remarkably composed of a large number of giant cells in sheet-like growth pattern, a small portion was found to consist conventional EC components (black arrow).

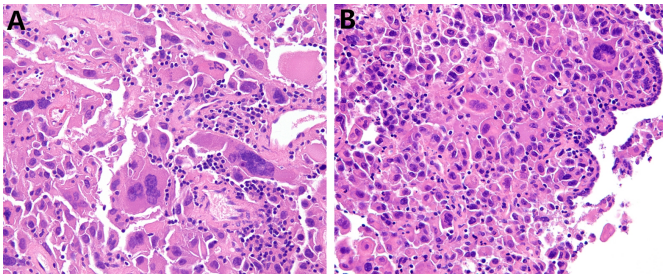

FIGURE 2. Tumor histopathology. The giant tumor cells contained abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli, which presented as multinucleated giant cells (A) and mononucleated giant cells (B).

3. Discussion

EGCC, a rare variant of endometrial cancer, was initially described by Jones *et al.* [2] in 1991. Since then, only 20 cases, including the present case, have been reported in scientific literature (**Supplementary Table 1**). Currently, this specific entity has not been acknowledged as a distinct variant of EC in the most recent WHO classification of female genital tumors. The age range of EGCC patients is between 43 and 83 years, with a median age of 66 years. Nearly all patients presented with vaginal bleeding as the primary symptom, while two exhibited anemia or pelvic mass.

Jones *et al.* [2] originally defined the characteristic microscopic features of EGCC as the presence of bizarre multinucleated and giant tumor cells, which constituted a significant portion of the tumor, while the remaining portion of the tumor typically consisted of either mononuclear undifferentiated carcinoma or a more conventional type of EC, such as endometrioid carcinoma, serous carcinoma or clear cell carcinoma. Interestingly, 18 of the 20 EGCC cases described thus far were accompanied by a conventional carcinomatous component, with endometrioid carcinoma being the most prevalent (14 out of 18 cases). This observation led us to hypothesize that the giant cells might arise from a dedifferentiation process within a conventional carcinoma. However, the precise percentage of giant cell content required for a definitive diagnosis of EGCC remains undefined. The reported literature indicates a wide range of giant cell percentages, varying from 15% to 100% [2–9]. In cases where the giant cell component comprises at least 10% of the entire tumor, it is recommended to diagnose it as a mixed carcinoma, with an estimated percentage assigned to each component [4]. In the absence of additional evidence, it is worth noting a specific case within the series reported by Jones *et al.* [2], where the giant cell component constituted only 15% of the tumor. Despite this relatively low percentage, the patient exhibited ovarian and omental metastases. It is important to highlight that when the giant cell component accounts for less than 10% of the tumor, the term "mixed carcinoma" is not recommended. Instead, it is advised to document the presence of this component while indicating that the biological characteristics are uncertain [4].

Table 1 (Ref. [2, 4, 6–9]) provides an overview of the immunohistochemical features observed in previous cases, including this present case. In most cases, positive immunohis-

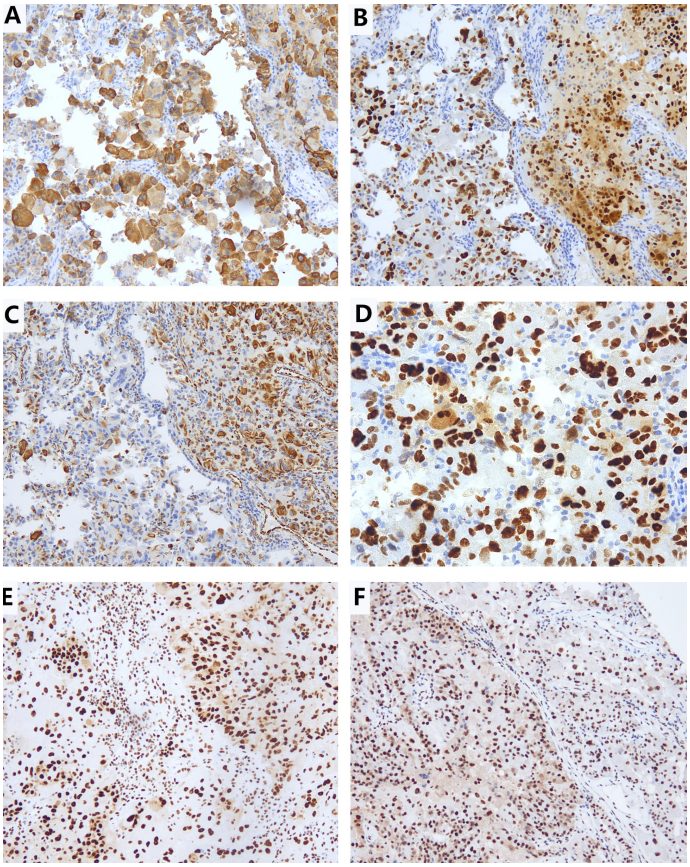

FIGURE 3. Tumor immunophenotype. Immunohistochemistry demonstrated positive staining for EMA (A), p53 (B) and Vimentin (C) in all tumor cells, mismatch repair proteins (the marker shown in D was MSH6), SMARCA4 (E) and SMARCB1 (F) were retained.

TABLE 1. The significant immunohistochemical phenotype of the reported cases of endometrial giant cell carcinoma (only the markers evaluated in at least 4 cases are shown).

Markers	Number of cases	Pattern
Epithelial markers (epithelial membrane antigen (EMA) [2, 4, 6, 7, 9]; AE1/AE3 [2, 4, 6, 9]; Cytokeratin 7 (CK7) [8]; CAM5.2 [2, 4, 8]; e-cadherin [9])	14	Focally/multifocally/strongly positive in giant cells; positive in conventional carcinoma components
Vimentin [2, 4, 6–9]	14	Positive in 8/14 cases
β-human chorionic gonadotrophin (β-hCG) [2, 4, 6–9]	14	Negative in all cases
Muscle markers (desmin [2, 6–9]; smooth muscle-actin (SMA) [2, 6, 9]; h-caldesmon [7]; myogenic differentiation 1 (MYOD1) [7]; myogenin [8]; muscle-specificactin (MSA) [9]; calponin [9])	10	Negative in all cases
Mismatch repair (MMR) [4, 8, 9]	10	Retained in all cases
Histiocytic markers (cluster of differentiation 68 (CD68) [6, 8, 9]; lysozyme [2])	9	Negative in all cases
Estrogen receptor (ER) and progestogen receptor (PR) [6–9]	7	Focally/multifocally positive in 6/7 cases, negative in 1/7 cases
p53 [7–9]	6	Wild-type in 4/6 cases, mutant-type in 2/6 cases
p16 [7–9]	6	Diffusely positive in 4/6 cases, negative in 2/6 cases
SMARCA4 (BRG1) and SMARCB1 (INI1) [9]	4	Retained in all cases
α-fetoprotein [6, 9]	4	Negative in all cases

MMR: mismatch repair.

tochemical staining for epithelial markers (EMA, AE1/AE3 and CAM5.2) was observed in both the giant cell and conventional carcinoma components, confirming their epithelial origin. However, three cases from the series reported by Arciuolo*et al.* [9] showed partial loss of epithelial markers (e-cadherin), which has not been reported in other cases. Vimentin, ER, PR and p16 demonstrated variable positivity in EGCC. The expression pattern of p53 varied, with both wild-type and mutant-type observed. Conversely, the tumor cells were tested negative for β-hCG, histiocytic markers (CD68 and lysozyme), p63 and muscle markers (Desmin, Smooth Muscle Actin (SMA), h-Caldesmon, Myogenic Differentiation 1 (MYOD1), Myogenin, Muscle Specific Actin (MSA) and Calponin). The expression of mismatch repair proteins was retained in all cases. In this present case report, we observed that both the giant tumor cell component and the serous carcinoma component exhibited uniform positivity for p53 (mutant-type) and IMP3, suggesting that the giant cells may represent a dedifferentiated manifestation of serous carcinoma and that the giant cell changes might be likely a form of differentiation that can manifest in various types of uterine carcinomas.

The differential diagnosis of EGCC includes other endometrial tumors that may also exhibit similar giant cell components. Uterine choriocarcinoma or EC with choriocarcinomatous differentiation can present with trophoblastic-type giant cells. However, patients with these tumors typically have elevated serum β-hCG levels, and positive immunohistochemical staining for β-hCG, p63, MelCAM and human placental lactogen (HPL) in trophoblastic cells can be diagnostically helpful. Approximately 40% of EGCC cases (7 out of 18) may contain areas with mesenchymal and undifferentiated components [2, 4, 9], making it challenging for pathologists to differentiate EGCC from endometrial carcinosarcoma (ECS), undifferentiated endometrial carcinoma (UDEC), and dedifferentiated endometrial carcinoma (DDEC). According to the findings reported by Arciuolo *et al.* [9], EGCC may share some similarities with UDEC, DDEC and ECS. However, it is important to note that EGCC differs from these malignancies in terms of morphology, immunophenotype and The Cancer Genome Atlas (TCGA) molecular signatures. In EGCC, a strong EMA staining, the absence of spindle or chondroid morphology, and negativity for muscle markers suggest that the giant cells are likely of epithelial origin. Conversely, specific mesenchymal differentiation can be identified in ECS through immunohistochemistry. Compared to UDEC/DDEC, EGCC exhibits significant pleomorphism, contrasting with the histopathological diagnostic criteria of the former two tumors. In this case report, UDEC could be ruled out due to the presence of a differentiated component (serous carcinoma). Genetic analysis or immunohistochemistry can be utilized to detect inactivated molecular mutations or negative protein expression of SMARCA4 (BRG1), SMARCB1 (INI1), or both ARID1A and ARID1B in UDEC/DDEC [10], none of which have been found in EGCC. Furthermore, the focal and perinuclear dot-like immunohistochemical staining pattern for EMA and cytokeratin typically seen in UDEC/DDEC is distinct from that observed in EGCC, and the positive PAX-8 staining in our case strongly argues against a diagnosis of DDEC as well.

Regarding the molecular classification of endometrial cancer (EC), EGCC also demonstrates differences from ECS and UDEC/DDEC. Most cases of ECS exhibit abnormal p53 expression, while UDEC and DDEC are frequently deficient in MMR and show a high frequency of POLE mutations [11, 12]. In a molecular study of four EGCC cases using available data, none exhibited POLE mutations or MMR protein deficiency. As a result, two cases were classified as "no specific molecular profile", while the other two were categorized as "p53-abnormal", including the case presented in this report. In regard to EGCC, most reported cases were found to be MMR-proficient (10 out of 10) and p53-wild-type (4 out of 6). Thus, Arciuolo *et al.* [9] hypothesized that EGCC is predominantly derived from "no specific molecular profile" carcinomas, although it is not exclusively limited to this subtype. However, the case described in this report represents an additional instance of a p53-mutant malignancy within the EGCC category. To better understand and confirm the molecular classification of EGCC, more cases should be examined, which might also lead to the development of guidelines for its clinical management.

All EGCC patients in the reported cases in literature underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic and paraaortic lymphadenectomy. Some patients received adjuvant chemotherapy and radiation therapy. Of all reported cases, 6/20 were in advanced stages at the time of diagnosis. Among the 15 cases with available follow-up data, 5 had a poor prognosis, with 3 patients succumbing to the disease and 2 experiencing extrauterine metastases. The remaining 10 patients survived without evidence of disease, with follow-up periods ranging from 3 to 168 months. Most of these patients (9 out of 10) were classified as FIGO stage IA. Thus, the prognosis of EGCC remains unclear and appears to be strongly influenced by the stage of the disease, despite the aggressive biological characteristics observed in previously reported cases. In the case presented here, no residual tumor was found in the hysterectomy specimen, and the clinical stage was early. However, due to the high-grade histopathological features and molecular classification, adjuvant treatment was recommended to the patient. Nonetheless, she declined to receive any chemoradiotherapy and has remained disease-free during the 1-year follow-up period. More follow-up data are necessary to assess the biological characteristics and prognosis of EGCC accurately.

4. Conclusion

In conclusion, EGCC represents a rare morphological feature observed in malignant uterine tumors, often coexisting with other conventional types of EC. As EGCC is not currently recognized as a distinct entity in the WHO classification of endometrial neoplasms, the term "endometrial carcinoma with giant cell changes" could also be appropriate. We believe it is crucial to emphasize the presence and/or percentage of giant cell components in the pathology report, indicating the uncertain biological characteristics of the tumor. Although there is insufficient evidence to definitively establish EGCC as a distinct type of uterine malignancy, the description of

its clinicopathological and molecular features in the relevant literature suggests that it may exhibit aggressive behavior. Our current study also has potential limitation. Due to the small amount of tumor tissue, we did not perform additional molecular analyses, such as whole exome sequencing, to reveal whether there were some other underlying molecular alterations in the tumor. However, further experience is necessary to accurately diagnose and treat this rare tumor.

ABBREVIATIONS

EGCC, Endometrial giant cell carcinoma; EC, Endometrial carcinoma; ECS, Endometrial carcinosarcoma; UDEC, Undifferentiated endometrial carcinoma; DDEC, Dedifferentiated endometrial carcinoma; WHO, World Health Organization; BMI, Body Mass Index; CA, carbohydrate antigen 125; CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; PAX-8, Paired Box Gene 8; ER, estrogen receptor; PR, progestogen receptor; IMP3, II mRNA-binding protein 3; WT, Wilm's Tumor Protein; HNF-1β, Hepatocyte nuclear factor 1-beta; β-hCG, β-human chorionic gonadotrophin; CD, cluster of differentiation; MMR, mismatch repair; ProMisE, Proactive Molecular Risk Classifier for EC; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; FIGO, Federation International of Gynecology and Obstetrics; SMA, Smooth Muscle Actin; MYOD1, h-Caldesmon, Myogenic Differentiation 1; MSA, Muscle Specific Actin.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this case are included within the article.

AUTHOR CONTRIBUTIONS

XT—drafted the manuscript and assisted with the clinical data collection and interpretation. LL—contributed to pathological examination and IHC and molecular test. WJ—made the pathology diagnosis, revised the manuscript and approved the final version to be published. All the authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was not applicable for this study. Written informed consent for publication of the clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1900472212837548032/attachment/Supplementary%20material.docx.

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