Endometrial clear cell carcinoma with non-gestational choriocarcinoma differentiation: use of rapamycin maintenance

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CASE PRESENTATION

A 60-year-old G2P1 post-menopausal woman whose last documented pregnancy was an induced abortion 33 years prior to presentation in October 1984 complained of a 3-week history of vaginal bleeding. The patient's past medical history was uneventful and she had no surgical history. She denied hormonal replacement therapy. On physical examination, the patient's uterus was mobile and minimally enlarged without pain. Neither a mass nor nodule was present in the bilateral adnexa and the mucosa of the rectum was smooth. A transvaginal ultrasound showed a 4.4×3.6 cm hyperechoic mass inside the uterine cavity.

In August 2017, a curettage was performed and the diagnosis was an endometrial clear cell carcinoma with choriocarcinoma component. The serum β-human chorionic gonadotropin (βhCG) level was elevated to 192 193 mIU/mL (normal <5 mIU/mL), and CA125, CA199, carcinoembryonic antigen, and α-fetoprotein were within normal limits. The patient complained of hemoptysis 4 weeks after the curettage and was referred to our hospital. A computed tomographic (CT) scan of the chest showed multiple metastases, with the largest lesion measuring approximately 24 mm in diameter (Figure 1A1,A2). A magnetic resonance imaging (MRI) scan of the brain was negative for disease, and CT with contrast of the abdomen and pelvic cavity showed an enlarged uterus measuring 6.7×4.2×5.5 cm.

Dr Feng: Did you perform any additional pre-operative work-up in this patient?

To further distinguish the origin of the choriocarcinoma component, short tandem repeat genotyping was performed using the endometrial curettage specimen. As shown in Figure 2, all specimens had alleles of similar sizes, implying that the choriocarcinoma component was not gestational.

In most cases, choriocarcinoma is gestational. However, it can also be non-gestational in origin, which is a rare condition. It is important to distinguish between these two entities since the prognosis and primary treatment are completely different.1 Non-gestational choriocarcinoma carries a worse prognosis and is less sensitive to chemotherapy.1,2 Occasionally, non-gestational choriocarcinoma may be distinguished by history or histopathological examination. However, the correct diagnosis is difficult to make by trophoblastic morphology alone.3 This is particularly so in women with a history of pregnancy, where intra-uterine gestational choriocarcinoma is most common. Molecular genetic analysis may help confirm the origin and has been shown to benefit clinical practice.4 There are reports of pure non-gestational uterine choriocarcinoma confirmed by short tandem repeat analysis. However, regarding mixed endometrial tumors, the only previously reported case was diagnosed with a non-gestational...
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Dr Feng: What would be your proposed treatment plan for this patient?

In mixed endometrial carcinoma, most of the histopathological sub-type admixed with the choriocarcinoma component is endometrioid adenocarcinoma. To the extent of our knowledge, only three cases with the sub-type of clear cell endometrial cancer have been reported (Table 1). The present case is the only one with pre-operative extensive pulmonary metastasis.

Considering the significantly elevated β-hCG level, the biopsy pathology and the diffused lesions in both lungs, it was believed that the pre-operative pulmonary metastases mainly consisted of choriocarcinoma component and the patient was not suitable for primary surgery. According to the National Comprehensive Cancer Network (NCCN) guideline on trophoblastic component mixed with endometrial cancer due to the fact that the patient was nulligravida. Some authors believe that the choriocarcinomatous component concurrent with another endometrial tumor should belong to non-gestational choriocarcinoma and represents the aberrant differentiation of the conventional carcinoma component. In fact, a uterine gestational choriocarcinoma co-existing with an endometrial carcinoma may also exist. As the pathogenesis of the non-gestational choriocarcinoma component concurrent with another tumor is not well understood, it is critical to clarify the origin of the trophoblastic component combined with endometrial carcinoma. If possible, an early introduction of genetic genotyping in treating refractory choriocarcinoma or trophoblastic tumor component mixed with another cancer should be made in order to avoid extensive chemotherapy and initiate the multidisciplinary treatment as soon as possible.

Figure 1  Pulmonary lesions by chest CT at different stages of treatment. (A1, A2) Pre-operative chest CT scan showing multiple pulmonary metastases with the largest lesion measuring about 24 mm in diameter. (B1, B2) Chest CT scan indicating that the original pulmonary lesions disappeared after primary treatment. (C1, C2) First time relapse: multiple newly seen nodules measuring 0.5–1.2 cm of both lungs were found on PET-CT scan. (D) During treatment of the first-time relapse, after 11 cycles of EMA/CO, the pulmonary lesion enlarged inside the right lung shown on the chest CT scan. (E) The chest CT scan indicated residual lesions in the right lung after IMRT of the pulmonary lesion, which indicated thoracoscopic surgery afterwards. CT, computed tomography; EMA/CO, etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine chemotherapy; IMRT, intensity modulated radiotherapy; PET-CT, positron emission tomography-computed tomography.
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Figure 2 DNA from both the clear cell carcinoma and choriocarcinoma compared with smooth muscle tissue of the uterus. The repeat sizes for 16 short tandem repeat loci (the 16 loci are shown in Figure 2A, B and C, respectively) are identical in the choriocarcinoma component (CH), the clear cell tumor (CL), and the uterine smooth muscle (CT).

treatment of uterine neoplasms, systemic therapy should be considered in this condition. Referring to the experience of chemotherapy in the treatment of high-risk choriocarcinoma, induction chemotherapy with low-dose etoposide-cisplatin was given to this patient instead of full-dose chemotherapy. This is because the tumor volume in both lungs was substantial and it was proved that, in this condition, induction chemotherapy may lead to a more gradual reduction of tumor burden, lessen the risk of significant hemorrhage in the thorax, and thus minimize the probability of early death induced by treatment.

Dr Zhang: What was the response to the induction chemotherapy and how was the patient treated after induction chemotherapy?

From September 2017, low-dose etoposide-cisplatin was administered as the induction chemotherapy (Figure 3). After three cycles of this regimen, the β-hCG level decreased to 497 mIU/mL with a significant improvement in hemoptysis. The pelvic MRI scans with contrast showed a heterogeneous soft tissue mass 4 cm in diameter in the uterine cavity involving the anterior wall of the uterus (Figure 4A) without enlarged lymph nodes in the pelvic or para-aortic area. She underwent a laparoscopic total hysterectomy.
Table 1  Cases of endometrial clear cell carcinoma combined with choriocarcinoma in post-menopausal women

<table>
<thead>
<tr>
<th>Current case</th>
<th>Bradley et al</th>
<th>Ashton et al</th>
<th>Black et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60</td>
<td>68</td>
<td>54</td>
</tr>
<tr>
<td>Gravity/parity</td>
<td>2/1</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>Symptoms</td>
<td>PMB</td>
<td>PMB</td>
<td>AUB for 1 year</td>
</tr>
<tr>
<td>Pre-treatment βhCG level</td>
<td>192193 mIU/mL</td>
<td>95 mIU/mL</td>
<td>2300 mIU/mL</td>
</tr>
<tr>
<td>Pre-treatment CA125 level</td>
<td>Normal mIU/mL</td>
<td>93 mIU/mL</td>
<td>88 mIU/mL</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>LH+BSO following EP induction</td>
<td>TH+BSO+omentectomy+pelvic and para-aortic lymph node dissection</td>
<td>TH+BSO+sigmoidectomy</td>
</tr>
<tr>
<td>Pathology</td>
<td>Endometrial clear cell carcinoma with choriocarcinomatous differentiation</td>
<td>Grade 3 endometrioid adenocarcinoma, foci of syncytiotrophoblast cells, clear cell component (approximately 20% of the tumor), a minor papillary serous component. Both pelvic and para-aortic lymph nodes are positive with serous component</td>
<td>Endometrioid adenocarcinoma, endometrial clear cell carcinoma, with trophoblastic differentiation. Involvement of sigmoid</td>
</tr>
<tr>
<td>Post-operative treatment</td>
<td>TP/TE×2 cycles, TC/TE×3 cycles, TC×1 cycle (Figure 3), Concurrent pelvic radiation</td>
<td>Megestrol acetate160 mg/day×6 weeks, TC (platinum 135 mg/m², carboplatin AUC=5)x6 cycles</td>
<td>EMA/CO, EMA/EP, EMA/EC, no specific description of cycles. Chemotherapy was ceased due to poor tolerance</td>
</tr>
<tr>
<td>FIGO stage</td>
<td>IV</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Lung (prior treatment )</td>
<td>No</td>
<td>Lung, brain (after surgery )</td>
</tr>
<tr>
<td>Pathology of distant metastasis</td>
<td>Choriocarcinoma</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Prognosis</td>
<td>NED 5 years after diagnosis (3.5 years after last chemotherapy, 5 years after surgery)</td>
<td>NED16 months after diagnosis</td>
<td>Died of cerebral metastasis15 months after diagnosis</td>
</tr>
</tbody>
</table>

*Autopsy was not performed and whether there was relapse at the time of death was not confirmed.

AUB, abnormal uterine bleeding; EC, etoposide combined with carboplatin; EMA/CO, etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine chemotherapy; EP, etoposide combined with cisplatin; LH+BSO, laparoscopic hysterectomy with bilateral salpingo-oophorectomy; N, not mentioned; NED, no evidence of disease; PMB, post-menopausal bleeding; TH+BSO, trans-abdominal hysterectomy+bilateral salpingo-oophorectomy; TP(C)/TE, paclitaxel/cisplatin (carboplatin) alternating with paclitaxel/etoposide chemotherapy; β-hCG, β-human chorionic gonadotropin.
with bilateral salpingo-oophorectomy. Intra-operative exploration revealed no enlargement of the lymph nodes.

**Dr Jing Wang:** What was the pathologic finding after the surgery?

The post-operative histopathology showed extensive hemorrhage and necrosis in both endometrial tissue and myometrium, with scant degenerated endometrial clear cell carcinoma and trophoblastic tumor differentiation outside the above necrotic and hemorrhagic tissue. There was no extension of parametrial tissue or metastasis of bilateral adnexa. Immunohistochemically, the clear cell carcinoma component showed positive staining for HNF1B, PAX-8, P53 and the Ki-67 index was 40%. The choriocarcinomatous component was positive for β-hCG (Figure 4B–D).

**Dr Feng:** How did you choose the post-operative treatment in this case?

Based on the pathologic findings, an ultimate diagnosis of International Federation of Gynecology and Obstetrics (FIGO) stage IVB endometrial clear cell carcinoma with non-gestational choriocarcinoma differentiation was made. Post-operatively, for stage IV endometrial clear cell tumor, systemic chemotherapy was recommended. The optimal regimen given should consider both choriocarcinoma and the clear cell cancer component. Full-dose paclitaxel/cisplatin alternating with paclitaxel/etoposide chemotherapy was given 3 days post-operatively instead of etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine (EMA/CO) (Figure 3). This was because paclitaxel/cisplatin alternating with paclitaxel/etoposide chemotherapy is a salvage regimen for non-gestational choriocarcinoma, and also platinum combined with paclitaxel is the preferred regimen in the post-operative chemotherapy of high-risk uterine neoplasm.²

Considering that the patient had the risk factors of advanced age and a relatively large intra-uterine mass, 6 weeks after the surgery concurrent pelvic radiotherapy including 28 courses of external beam radiotherapy (50.4 Gy) and two courses of brachytherapy (10 Gy) was given for 6 weeks.

**Dr Zhang:** Did the patient tolerate the chemotherapy well and what was the patient’s response to treatment?

After two cycles of paclitaxel/cisplatin alternating with paclitaxel/etoposide chemotherapy she developed grade II renal toxicity (glomerular filtration rate decline from 69 mL/min to 51 mL/min) and the cisplatin was then substituted with carboplatin (AUC=4). After three cycles of post-operative chemotherapy, the β-hCG level was normalized to 4.3 mIU/mL on January 9, 2018 (Figure 3). An additional three cycles of consolidation chemotherapy were given, the third cycle of which was changed to 3-weekly paclitaxel/carboplatin chemotherapy (paclitaxel 175 mg/m² and carboplatin AUC=5) due to grade IV myelosuppression. After stopping chemotherapy, the chest CT scan indicated that the original pulmonary lesions had disappeared (Figure 1B1, B2). Unfortunately, in June 2018 the β-hCG level rose to 73 mIU/mL, 9 weeks after stopping chemotherapy (Figure 3).

**Dr Cui:** Were there any new imaging findings at recurrence?

A positron emission tomography-computed tomography (PET-CT) scan was performed at this stage to detect any recurrence. Multiple new nodules measuring 0.5–1.2 cm in diameter in both lungs were found (Figure 1C1, C2), which implied that the patient had multiple recurrent lung nodules.

**Dr Feng:** What would be the treatment considerations at the time of this recurrence?

On recurrence, as the patient presented with an elevated β-hCG combined with pulmonary lesions, we suspected the main histologic component of recurrent lesion should be non-gestational. Therefore, the patient was treated with etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine (EMA/CO) chemotherapy. The patient achieved serum partial response after 11 cycles. However, the pulmonary lesion enlarged inside the right lung (Figure 1D). This supported the conventional idea that non-gestational choriocarcinoma would not respond to methotrexate chemotherapy as gestational choriocarcinoma did.²₄ Fortunately, most of the small recurrent lesions of the lung were treated by EMA/CO chemotherapy. The patient had one isolated recurrent pulmonary lesion after 11 cycles of EMA/CO.
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This would enable radiation and surgical removal.

**Dr Zhang: What was the subsequent treatments?**

Intensity modulated radiotherapy of the pulmonary lesions was added following the above chemotherapy. Ten days after the thoracic radiotherapy the β-hCG level was normalized but, 3 weeks after the radiotherapy, the β-hCG level increased to 7.9 mIU/mL and the chest CT scan indicated residual lesions in the right lung (Figure 1E). Thoracoscopic resection of the right middle lobe lesion was performed and chemotherapy with dactinomycin-etoposide regimen was given to prevent the tumor cells from disseminating into other sites during the peri-operative period. The resected pulmonary lesion consisted of cytotrophoblasts and syncytiotrophoblasts.

One week after surgery the patient achieved normalization of the β-hCG level and two additional cycles of EMA/CO were then given as consolidation therapy. This is consistent with other studies which found that multiple-drug chemotherapy combined with surgical

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**Figure 4** Pre-operative pelvic MRI, the gross and microscopic pathology of the endometrial lesion. (A) Pre-operative pelvic MRI with contrast showing intra-uterine lesion involving the anterior myometrium. (B) Gross pathology of the uterus and bilateral adnexa demonstrating delicate sallow tissue (7×5×3 cm) in the uterine cavity. (C) Clear cell cancer component of the endometrial carcinoma with microscopic papillary structure. (D) Choriocarcinoma component. (C1–5) Positive immunohistochemical staining for HNF1B, PAX-8, P53, P16 and Ki-67 in the clear cell component. (D1) Positive immunohistochemical staining for β-human chorionic gonadotropin in trophoblast.
 treatment might provide the optimal prognosis for patients with non-gestational choriocarcinoma.8

Dr Feng: Was there any choice of maintenance treatment for this patient?

Targeted therapy has not been reported in patients with endometrial carcinomas with choriocarcinoma differentiation while, in the treatment of endometrial carcinomas, the PI3K/AKT/mTOR signaling pathway is suggested to represent a potential target for targeted therapy.9 In order to detect any possible targeted treatment for this patient, whole-exon sequencing of the uterine tumor was performed and revealed mutations of PIK3CA, PTEN, p53 and KDR, suggesting that rapamycin might be effective. Inhibition of the PI3K/AKT/mTOR pathway is of therapeutic interest, and preclinical studies prove that loss of PTEN or genetic alteration of PIK3CA may be indicators of sensitivity to PI3K/AKT/mTOR pathway inhibition.9 Rapamycin is an inhibitor of the mTORs10 and an available inhibitor of the PI3K/AKT/mTOR pathway in China.

Since there is no consensus on the treatment of endometrial carcinomas with choriocarcinoma differentiation, after informed consent was signed by the patient, 1 mg of oral rapamycin daily was chosen as maintenance treatment on August 28, 2019 when rapamycin was off-label for treating endometrial cancer.

It has been 3.5 years since her onset of rapamycin after stopping chemotherapy. Up to the writing date of the report, the patient still remained disease-free. The response to this agent by this patient indicates that patients with a somatic PTEN and PIK3CA mutation may benefit from rapamycin maintenance treatment.

CONCLUSION

About 30 cases of endometrial carcinoma with choriocarcinomatous differentiation have been reported in the literature, and it is believed to have an aggressive clinical course and poor prognosis.8 Only three cases had endometrial carcinoma with concurrent clear cell carcinoma and choriocarcinoma.4 6 7 Since endometrial clear cell carcinoma is more aggressive than endometrioid adenocarcinoma, the prognosis of clear cell endometrial carcinoma combined with choriocarcinoma is believed to be even worse and the treatment is challenging. Two of the reported patients died within 16 months after the diagnosis or 18 months after the surgery.4 7 We report the successful treatment of a case diagnosed with endometrial clear cell carcinoma and non-gestational choriocarcinoma differentiation by short tandem repeat analysis. The patient has reached an overall survival of more than 3.5 years without disease, which is the longest survival of a patient with this cancer documented to date.

We conclude that, for patients with endometrial clear cell carcinoma with choriocarcinoma differentiation, gene typing should be performed at an early stage to recognize the nature of the mixed choriocarcinomatous component in order to choose the most suitable treatment. Whole exon sequencing of the tumor could be used in this rare disease to identify the possible treatment target. We speculate that the long-term progression-free survival of our patient may support the benefit of rapamycin maintenance therapy targeting somatic PTEN and PIK3CA mutation.

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Contributors ZhZ and FF participated in the design and plan of the study. ZhZ drafted the manuscript, JW provided and explained the pathology figures. RC provided imaging figures. ZZ contributed to collection of the data. FF revised the manuscript critically. All authors read and approved the final manuscript.

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Competing interests None declared.

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Ethics approval Ethics approval was obtained from The Institutional Review Board (IRB) of Peking Union Medical College Hospital, JS-1525. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES