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A Biologically Dominant Trophoblastic Component Guiding Neoadjuvant EMA/CO in Endometrial Carcinoma: A Clinical Case Report

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ABSTRACT

Endometrial carcinoma with choriocarcinomatous components (ECCC) is a rare and aggressive malignancy for which optimal management remains undefined. We report a case illustrating how preoperative identification of a biologically dominant trophoblastic component can guide treatment sequencing and achieve durable remission. A 61-year-old postmenopausal woman presented with abnormal uterine bleeding. Endometrial biopsy revealed a mixed tumor composed predominantly of choriocarcinomatous elements with a minor grade 1 endometrioid carcinoma component. Despite only superficial myometrial invasion, imaging demonstrated multiple pulmonary nodules, and serum human chorionic gonadotropin (hCG) was markedly elevated (46,538 mIU/mL). This clinicopathological incongruity suggested that the trophoblastic component, rather than the low-grade endometrioid carcinoma, was driving disease progression. Neoadjuvant EMA/CO chemotherapy was therefore prioritized to achieve rapid systemic control. After six cycles, serum hCG normalized and pulmonary lesions completely resolved. The patient subsequently underwent total hysterectomy and bilateral salpingo-oophorectomy, which revealed no residual choriocarcinoma. She remains disease-free more than two years after completion of treatment. This case highlights the importance of recognizing clinicopathological incongruity and identifying the biologically dominant tumor component when determining treatment sequencing in rare mixed malignancies.

1 | Introduction

Endometrial carcinoma with choriocarcinomatous components (ECCC) is an exceptionally rare entity characterized by aggressive clinical behavior and poor prognosis. Since its first description, only a limited number of cases have been reported in the literature, most of which demonstrated early hematogenous dissemination and unfavorable outcomes [1, 2].

Histologically, ECCC consists of both trophoblastic and epithelial components, which may arise either through synchronous coexistence or through trophoblastic differentiation from an epithelial carcinoma [3, 4]. Distinguishing between these patterns is clinically relevant, as trophoblastic differentiation is often associated with more aggressive behavior and resistance to conventional chemotherapy [5]. Because of its rarity, standardized treatment strategies for ECCC have not been established.

Key Clinical Message

In endometrial carcinoma with choriocarcinomatous components, early recognition of the predominant histologic component and tailored integration of local and systemic therapies may be critical for optimizing patient outcomes.

Most reported cases have been diagnosed postoperatively and managed with upfront surgery followed by adjuvant chemotherapy [2, 4–6]. However, when different tumor components demonstrate discordant biological behavior, treatment decisions based solely on anatomical staging may be suboptimal. In such situations, identifying the component that predominantly drives disease progression may be critical.

Here, we present a case of ECCC in which careful preoperative interpretation of pathological, biochemical, and radiological findings suggested that the trophoblastic component represented the biologically dominant component. Based on this clinicopathological interpretation, neoadjuvant trophoblastic-directed chemotherapy was prioritized, resulting in durable remission.

1.1 | Case History and Examination

A 61-year-old woman (gravida 2, para 2), postmenopausal since the age of 50, presented with abnormal uterine bleeding. She had no significant medical or family history. Transvaginal ultrasonography revealed an intrauterine mass measuring approximately 1 cm. Endometrial biopsy demonstrated a mixed tumor composed predominantly of choriocarcinomatous elements with a minor component of grade 1 endometrioid carcinoma (Table 1; Figure 1A,B).

Laboratory evaluation revealed a markedly elevated serum human chorionic gonadotropin (hCG) level of 46,538 mIU/mL, while CA-125 was within normal limits. Pelvic magnetic resonance imaging showed a 12 × 10 mm enhancing intrauterine lesion with superficial myometrial invasion (Figure 2A). Computed tomography and positron emission tomography–CT revealed multiple bilateral pulmonary nodules (Figure 2B).

Because the pulmonary nodules were located in anatomically challenging areas, histological confirmation by bronchoscopy or image-guided biopsy was considered technically difficult and unlikely to provide sufficient diagnostic benefit. In addition, given the aggressive clinical behavior previously reported in ECCC, delaying treatment initiation to pursue additional invasive or molecular diagnostic procedures, including liquid biopsy or ctDNA analysis, was considered potentially detrimental. Because the endometrial biopsy specimen was predominantly composed of trophoblastic components together with markedly elevated serum hCG levels and FDG-avid pulmonary nodules, early initiation of trophoblastic-directed chemotherapy was prioritized.

TABLE 1 | Clinical timeline of the present case.

Time	Clinical course
April year X	Onset of abnormal uterine bleeding
July year X	Initial evaluation at local clinic
August year X	Referral to our hospital
August year X	Serum hCG: 46,538 mIU/mL; pulmonary nodules detected
August–December year X	Six cycles of neoadjuvant EMA/CO chemotherapy
December year X	Normalization of serum hCG and disappearance of pulmonary lesions
January year X+1	Total abdominal hysterectomy with bilateral salpingo-oophorectomy
January–March year X+1	Three additional postoperative EMA/CO cycles
Follow-up	Complete remission maintained for more than 2 years

1.2 | Differential Diagnosis, Investigations, and Treatment

Histologically, the biopsy specimen showed sheets of pleomorphic trophoblastic cells resembling syncytiotrophoblasts and cytotrophoblasts, with a clear transitional zone to the endometrioid carcinoma component, supporting presumed trophoblastic differentiation (Figure 1A,B). Immunohistochemical staining demonstrated strong hCG expression in the choriocarcinomatous component, supporting trophoblastic differentiation. Considering the minimal uterine invasion, low-grade epithelial component, markedly elevated hCG level, and presence of pulmonary nodules, the metastatic disease was considered most consistent with metastasis from the trophoblastic component.

Neoadjuvant chemotherapy with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) was initiated, and six cycles were administered prior to surgery. EMA/CO chemotherapy consisted of intravenous etoposide (100 mg/m^2), methotrexate (300 mg/m^2), and actinomycin D (0.5 mg) on Days 1 and 2, followed by intravenous cyclophosphamide (600 mg/m^2) and vincristine (1 mg) on Day 8, administered according to standard protocols. Serum hCG levels initially increased transiently (163,337 mIU/mL) but then rapidly declined, normalizing after six cycles (Figure 3). Imaging confirmed complete resolution of the pulmonary lesions and marked regression of the uterine tumor (Figure 4A,B). The patient subsequently underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Histopathological examination revealed no residual choriocarcinoma; only a small focus of grade 1 endometrioid carcinoma remained, without myometrial invasion or lymphovascular space involvement (Figure 5A,B). Three

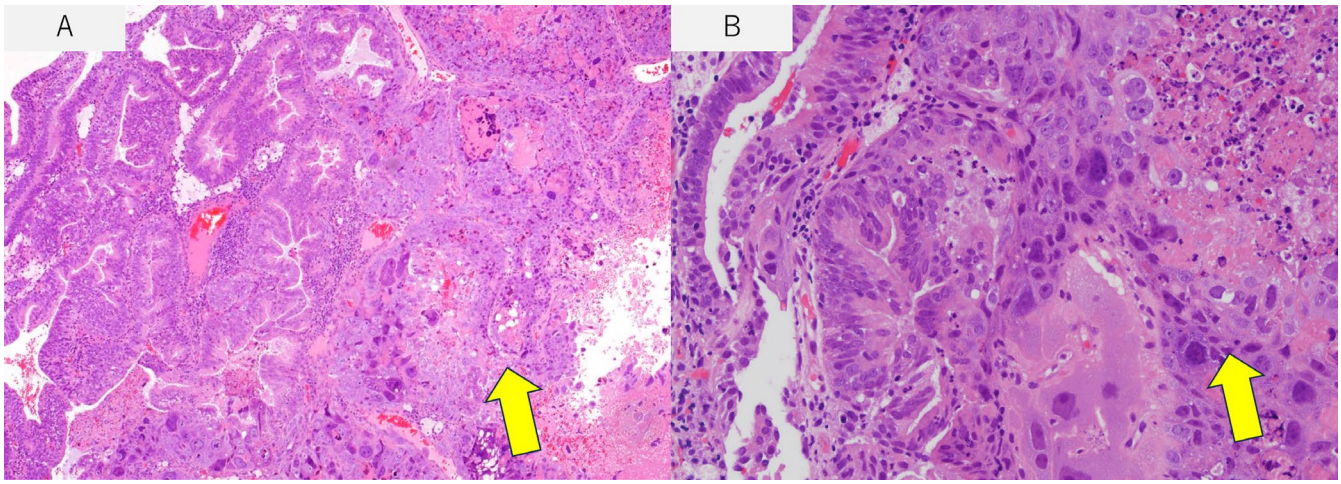

FIGURE 1 | Histopathological findings of the endometrial biopsy. (A) Low-power view. (B) High-power view. Endometrioid carcinoma (left) and trophoblastic (choriocarcinomatous) components (right) coexist, with a transitional area between the two. The endometrioid carcinoma component exhibited atypical columnar epithelium with glandular and papillary proliferation as well as focal squamous differentiation, whereas the choriocarcinomatous component showed sheets of pleomorphic trophoblastic cells with marked atypia. A clear transitional area between these components was identified, supporting the diagnosis of endometrial carcinoma with choriocarcinomatous components.

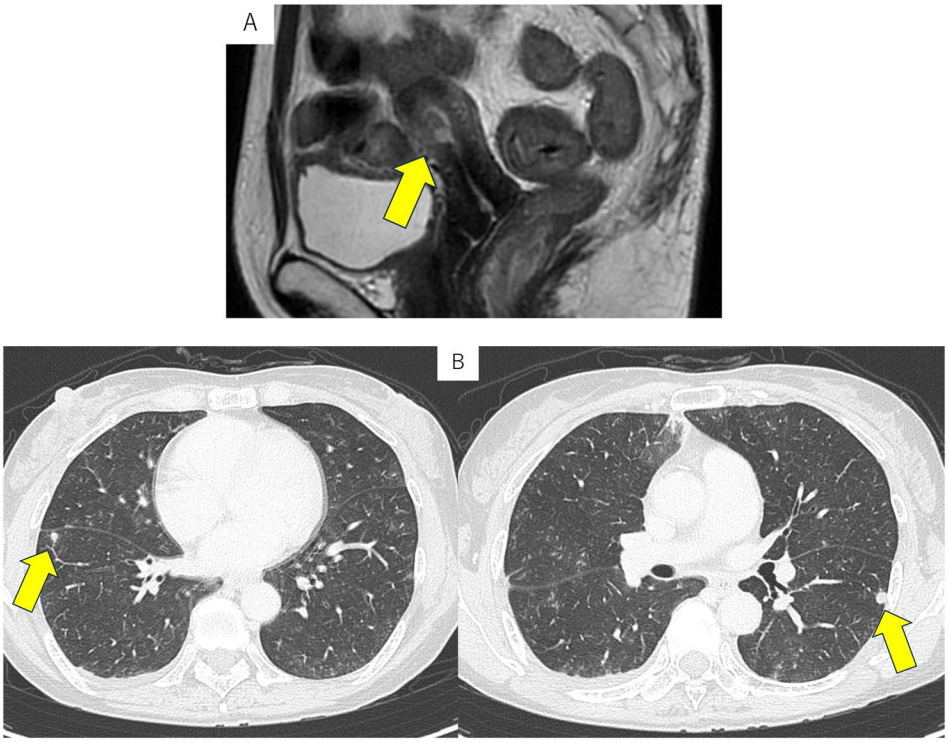

FIGURE 2 | Pretreatment pelvic MRI and contrast-enhanced CT. (A) Pelvic MRI shows a solid intrauterine mass measuring 12×10 mm with superficial myometrial invasion and strong enhancement. (B) Contrast-enhanced CT reveals multiple bilateral pulmonary metastases.

additional postoperative cycles of EMA/CO were administered as consolidation therapy. EMA/CO chemotherapy was generally well tolerated. The patient experienced only mild nausea during treatment, and no grade 3 or higher hematologic or non-hematologic adverse events were observed.

1.3 | Conclusion and Results (Outcome and Follow-Up)

The patient has remained in complete remission for more than two years.

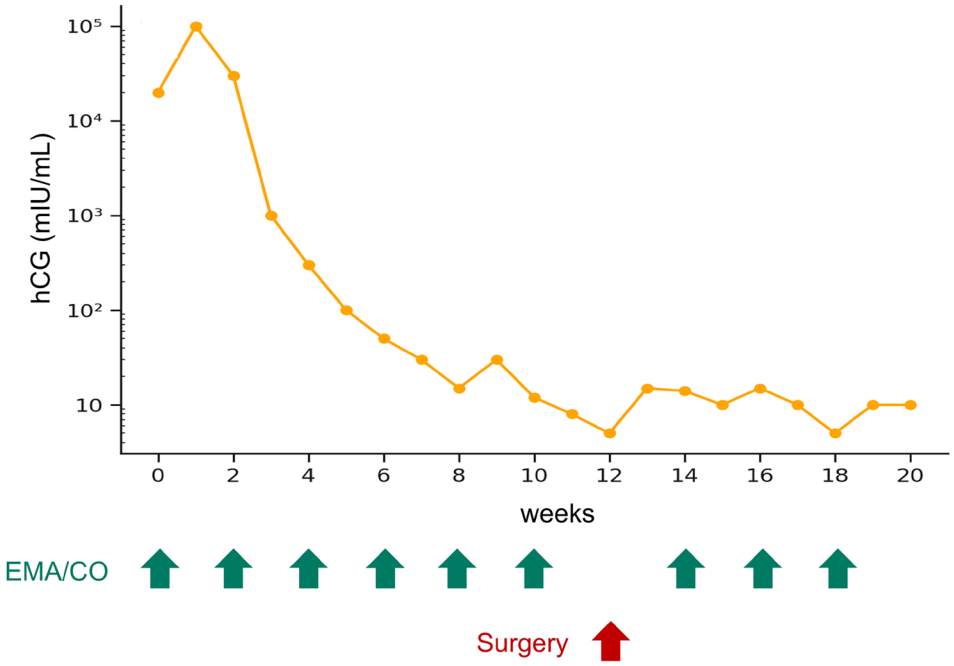

FIGURE 3 | Serum hCG trend during treatment. Serum hCG levels showed a transient increase immediately after initiation of EMA/CO chemotherapy, followed by rapid decline and normalization before surgery.

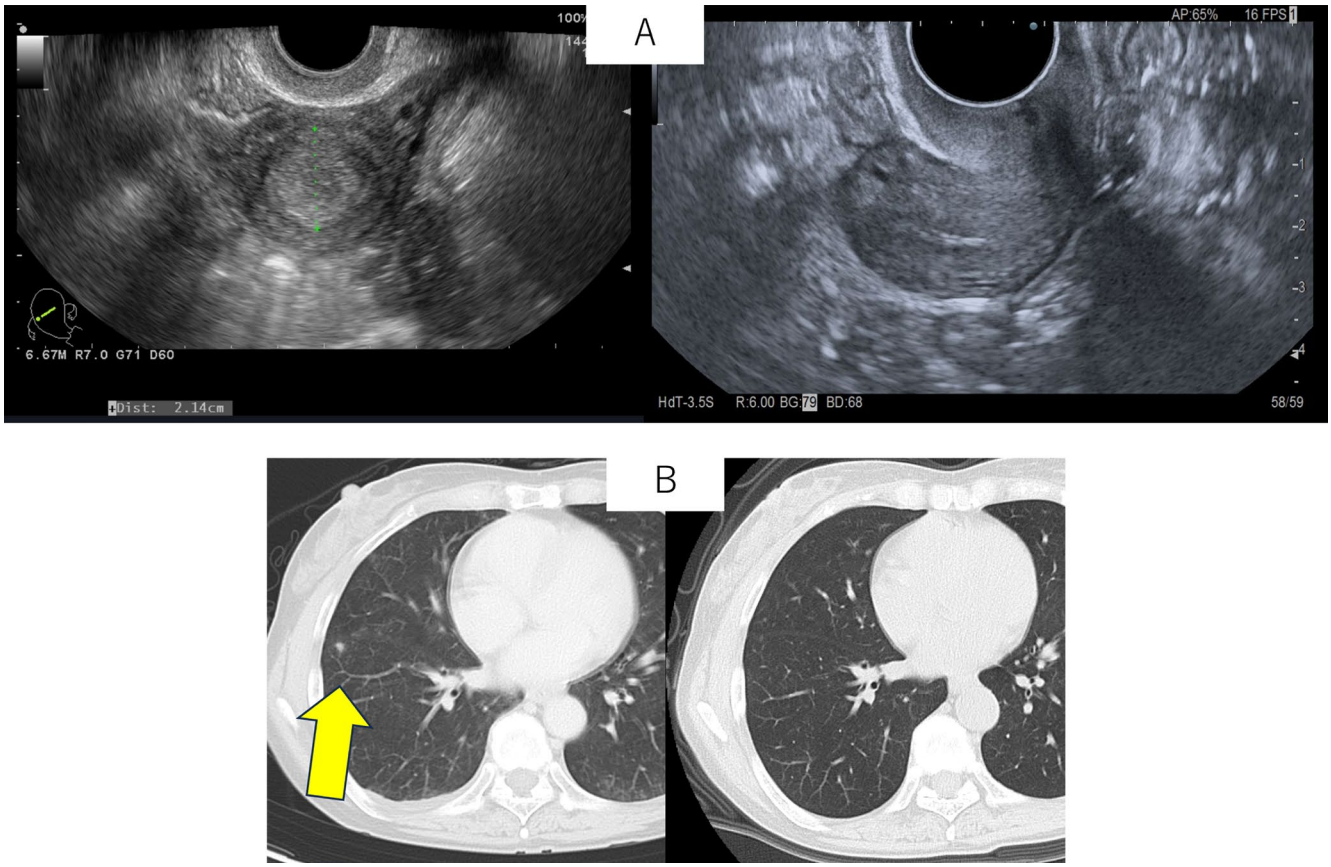

FIGURE 4 | Imaging findings before treatment and prior to surgery. (A) Transvaginal ultrasonography before treatment (left) and prior to surgery (right), showing marked reduction of the intrauterine mass. (B) Chest CT before treatment (left) and prior to surgery (right), showing resolution of pulmonary metastases with residual scar-like opacity.

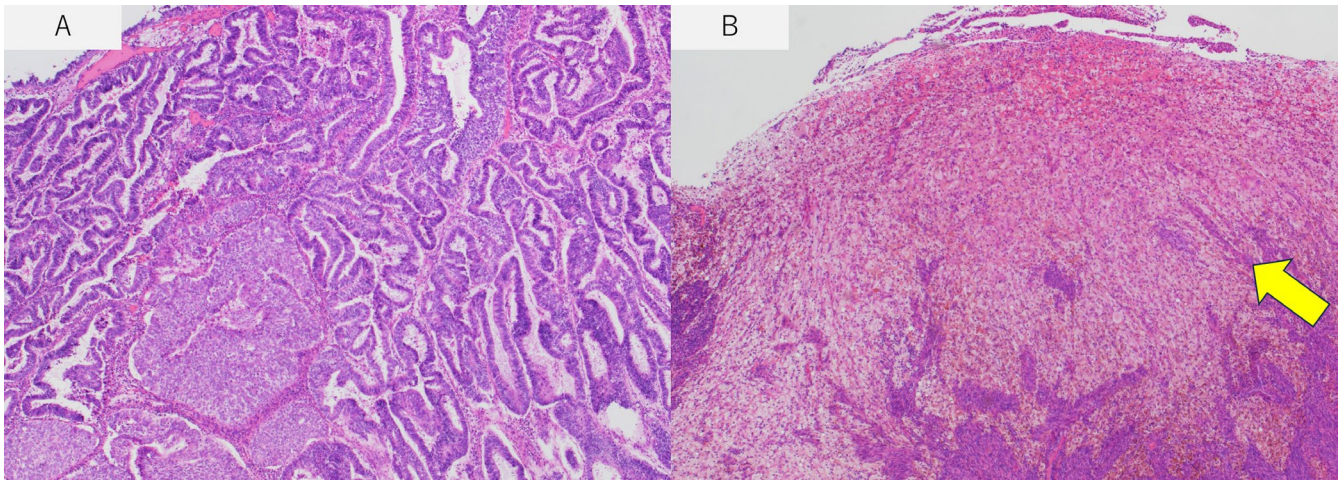

FIGURE 5 | Pathological findings of the resected uterus. (A) Residual focus of endometrioid carcinoma. Only a small focus of grade 1 endometrioid carcinoma remained, with no evidence of lympho-vascular space invasion or other high-risk pathological features. (B) In the area where choriocarcinoma was initially present, hemosiderin-laden macrophages were observed, indicating complete regression of the trophoblastic component.

2 | Discussion

This case illustrates the clinical importance of identifying the biologically dominant tumor component when managing rare mixed malignancies such as ECCC. Although ECCC is defined by the coexistence of trophoblastic and epithelial elements, these components do not necessarily contribute equally to disease behavior or prognosis.

A key feature of this case was the marked clinicopathological incongruity: a superficially invasive, low-grade endometrioid carcinoma accompanied by multiple pulmonary nodules and extremely elevated serum hCG levels. Hematogenous lung metastases are exceedingly rare in grade 1 endometrioid carcinoma but are characteristic of choriocarcinoma [1, 2]. These findings suggested that the trophoblastic component may have represented the primary driver of disease progression.

In previously reported cases, the majority of patients with ECCC were managed with upfront surgery followed by adjuvant chemotherapy, regardless of disease distribution at diagnosis (Table 2) [2, 4–12]. Review of the available literature indicates that neoadjuvant chemotherapy has rarely been employed, and durable disease-free survival has been uncommon, particularly in cases presenting with distant metastases. Even in reports describing the use of trophoblastic-directed chemotherapy, treatment was typically administered postoperatively.

In this context, the present case adds to the literature by demonstrating that treatment sequencing based on biological dominance—rather than anatomical extent alone—may contribute to durable remission. The novelty of this case therefore lies not in the chemotherapy regimen itself, but in the preoperative decision to prioritize systemic control of the biologically dominant component before surgical intervention.

Most previously reported cases of ECCC were treated with upfront surgery, followed by adjuvant chemotherapy. In contrast, we prioritized neoadjuvant EMA/CO to achieve rapid systemic disease control before surgical intervention. A transient increase in serum hCG levels was observed immediately after initiation of chemotherapy, which may have reflected rapid destruction of highly active trophoblastic tumor cells with temporary release of intracellular hCG into the circulation before subsequent rapid decline. The dramatic biochemical and radiological response further supported the appropriateness of this sequencing and allowed definitive surgery to be performed after eradication of the life-threatening metastatic burden. Although complete radiological and pathological response was achieved, three additional postoperative cycles of EMA/CO were administered as consolidation therapy. This strategy was based on established treatment principles for gestational trophoblastic neoplasia and choriocarcinoma, in which additional chemotherapy cycles are commonly administered after normalization of serum hCG levels to reduce the risk of recurrence.

Although ECCC is rare, the clinical principle illustrated in this case may be applicable to other mixed malignancies in which one histological component exhibits disproportionate biological aggressiveness. Careful integration of pathological findings, tumor markers, and metastatic patterns may allow clinicians to identify the dominant driver of disease and tailor treatment sequencing accordingly. When clinicopathological incongruity is present—such as aggressive metastatic behavior arising from an anatomically low-risk primary lesion—early prioritization of systemic therapy targeting the dominant component should be considered, even if this requires deferral of immediate surgical management.

This report has limitations inherent to a single-case observation. Pulmonary metastases were not histologically confirmed, and molecular analyses demonstrating clonal origin were not performed. Definitive distinction between synchronous coexistence and true trophoblastic differentiation often requires genomic analysis, which was not available in this case [5]. Therefore, this case should be regarded as hypothesis-generating. Nevertheless, the sustained complete response supports the clinical interpretation.

TABLE 2 | Summary of previously reported cases of ECCC, including treatment regimens and clinicopathological findings.

References	Age (year)	Primary therapy	Chemotherapy details	Trophoblastic component (%)	Non-trophoblastic component(s)	2009 FIGO stage	Follow-up status/ duration (months)
Horn (2006) [3]	61	TH + BSO + LY	EMA-CO	33	ESC	II	DOD (2)
Yamada (2009) [4]	58	TH + BSO + LY	CTP (cycles NR)	50	EEC grade1	I	NED (50)
Wakahashi (2012) [7]	85	TH + BSO	None	< 50	EEC + ESC	III	AWD (5)
Ishida (2013) [6]	59	TH + BSO + LY	None	20	EEC grade3	III	NED (2)
Seki (2014) [8]	54	TH + BSO + LY	Unknown	5	EEC grade3	IV	DOD (12)
Ashton (2014) [5]	54	TH + BSO	Unknown	30	EEC grade2 +CCC	III	DOD (15)
Carta (2014) [9]	50	TH + BSO	None	< 5	EEC grade1	I	NED (24)
Ji (2016) [10]	54	TH + BSO + LY	TC (cycles NR)	60	Adenocarcinoma	III	AWD (5)
Rawish (2018) [11]	72	TH + BSO + LY + OMT	EMA/CO + TC (cycles NR)	40	DDC	III	DOD (7)
Rawish (2018) [11]	77	TH + BSO + LY + OMT	EMA/EP (cycles NR)	40	EEC grade1	III	DOD (11)
Rawish (2018) [11]	62	TH + BSO + LY	EMA/CO + TC (cycles NR)	20	DDC	III	DOD (16)
Xie (2022) [12]	39	MTX + VP-16, EMA-CO (neoadjuvant)	MTX + VP-16 × 1, EMA/ CO × 8 (neoadjuvant)	85	EEC grade1	IV	NED (33)
Present patient	61	EMA-CO (neoadjuvant)	EMA/CO × 6 (neoadjuvant) + EMA/ CO × 3 (postoperative)	> 90	EEC grade1	IV	NED (26)

Abbreviations: AWD, alive with disease; BSO, bilateral salpingo-oophorectomy; CCC, clear cell carcinoma; CO, cyclophosphamide + vincristine; CTP, carboplatin + cyclophosphamide; DDC, dedifferentiated endometrial carcinoma; DOD, dead of disease; EEC, endometrioid endometrial carcinoma; EMA, etoposide + methotrexate + actinomycin D; EP, etoposide + cisplatin; ESC, endometrial serous carcinoma; LY, lymphadenectomy; MTX + VP-16, methotrexate + vincristine; NED, no evidence of disease; OMT, omentectomy; TC, paclitaxel + carboplatin; TH, total hysterectomy; TP-TE, paclitaxel + cisplatin, followed by paclitaxel + etoposide.

Distinguishing ECCC from gestational choriocarcinoma is clinically vital. In our patient, the postmenopausal status (11 years since menopause), absence of recent pregnancy, and the histological "transitional zone" between the endometrioid and choriocarcinomatous components were considered supportive of a presumed non-gestational tumor with trophoblastic differentiation based on clinicopathological findings.

3 | Conclusion

Preoperative identification of a biologically dominant trophoblastic component can fundamentally influence treatment sequencing and outcome in ECCC. Recognizing clinicopathological incongruity and prioritizing systemic control of the dominant component may represent an important management principle for this rare and aggressive malignancy. Further accumulation of similar cases will be necessary to validate this treatment strategy.

Author Contributions

Shinsuke Shirakawa: writing – original draft. **Shoji Nagao:** writing – original draft, writing – review and editing. **Yui Tanaka:** resources. **Atsushi Fujikawa:** resources. **Ryoko Imatani:** resources. **Momoko Tanioka:** resources. **Yoshinori Tani:** resources. **Hanako Sugihara:** resources. **Kazuhiro Okamoto:** resources. **Naoyuki Ida:** resources. **Hirofumi Matsuoka:** resources. **Junko Haraga:** resources. **Chikako Ogawa:** resources. **Keiichiro Nakamura:** resources. **Hiroyuki Yanai:** supervision, writing – review and editing. **Hisashi Masuyama:** supervision.

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Ethics Statement

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data relevant to this case report is included in the article.

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