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# From ectopic pregnancy to high-risk gestational trophoblastic neoplasia: Multimodal management of a rare metastatic case

***Corresponding Author: Rona Ting**
Logan Hospital, Australia.
Email: ronatingsh@gmail.com

## Abstract

Gestational Trophoblastic Neoplasia (GTN) is a rare malignancy arising from placental trophoblastic tissue, including choriocarcinoma, Placental-Site Trophoblastic Tumor (PSTT), and Epithelioid Trophoblastic Tumor (ETT). While most cases respond well to chemotherapy, delayed diagnosis or incomplete prior therapy can result in metastatic disease, complicating management.

We present a 33-year-old G6P5E1 woman with a prior ectopic pregnancy treated with methotrexate who was lost to follow-up. One year later, she developed persistent abnormal uterine bleeding and markedly elevated serum β-Human Chorionic Gonadotropin (β-hCG) levels (13,700 IU/L). Imaging revealed multiple pulmonary nodules without intrauterine pregnancy. She was staged as FIGO stage III, WHO prognostic score 9. She underwent total laparoscopic hysterectomy with bilateral salpingectomy, followed by multi-agent chemotherapy (EMA-EP: etoposide, methotrexate, actinomycin-D, cisplatin, vincristine). β-hCG levels declined significantly, and she continues treatment aiming for complete remission.

This case underscores the importance of early recognition, accurate risk stratification, and tailored multidisciplinary management in GTN. Although chemotherapy remains the mainstay, surgical intervention may be a valuable adjunct in selected high-risk or chemoresistant cases.

Timely diagnosis, appropriate staging, and combined modality management are critical for achieving remission in patients with high-risk or metastatic GTN. Multidisciplinary care and ongoing β-hCG monitoring are essential to optimize outcomes.

**Keywords:** Gestational trophoblastic neoplasia; β-hCG; Metastasis; Hysterectomy; Chemotherapy; EMA-EP.

## Introduction

Gestational Trophoblastic Neoplasia (GTN) is an uncommon malignancy arising from trophoblastic cells of the placenta. It includes choriocarcinoma, Placental-Site Trophoblastic Tumor (PSTT), and Epithelioid Trophoblastic Tumor (ETT) [1,2]. These tumors are characterized by abnormal trophoblastic proliferation

and elevated β-human Chorionic Gonadotropin (β-hCG), which serves as a sensitive biomarker for diagnosis, treatment monitoring, and follow-up [3]. Most GTNs respond exceptionally well to chemotherapy, making early detection essential for achieving complete remission [1,4].

Although GTN typically originates in the uterus, delayed diagnosis, chemoresistant disease, or metastatic spread presents significant clinical challenges [5,6]. Surgical management, such as hysterectomy, may serve as an adjunct for patients with localized disease resistant to chemotherapy, severe hemorrhage, or those who have completed childbearing [7-9].

We report a case of metastatic GTN in a 33-year-old woman following incomplete methotrexate therapy for ectopic pregnancy, highlighting the importance of early diagnosis, multidisciplinary management, and individualized treatment strategies to optimize outcomes.

## Case Report

A 33-year-old G6P5E1 woman presented with a one-year history of persistent abnormal uterine bleeding. Her obstetric history included five term deliveries and an ectopic pregnancy in March 2024, treated with two doses of methotrexate. She was lost to follow-up and did not undergo serial β-hCG testing; the last recorded value in April 2024 was 599 IU/L.

Over the following year, she experienced irregular, heavy, and intermenstrual bleeding but did not seek medical evaluation. Her general health was otherwise unremarkable, and she reported being sexually active without contraception.

In April 2025, she presented to her general practitioner. Laboratory investigations revealed a markedly elevated serum β-hCG of 13,700 IU/L. Transvaginal ultrasound showed no intrauterine or extrauterine pregnancy. She was referred to the emergency department for further assessment. On presentation, she was alert, hemodynamically stable, with minimal vaginal bleeding. Pathology testing showed serum β-hCG was 36,477 and free β-hCG tumour marker was 171 IU/L (Table 1). Repeat ultrasound demonstrated a 474 cc anteverted uterus with heterogeneous echotexture and endometrial thickness of 11 mm.

The patient underwent comprehensive staging, including contrast-enhanced Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). CT pelvis revealed heterogenous mass measuring 82×66×92 mm at the uterine fundus. From the CT chest, several pulmonary nodules were identified, the largest located in the right upper lobe, measuring 35×24×33 mm in a subpleural location. Additional nodules were present in the right upper lobe adjacent to the oblique fissure (12 mm) and in the anterior lingula (12 mm). Magnetic Resonance Imaging (MRI) of the pelvis supported the CT findings which demonstrated large heterogenous mass measuring 93×80×122 mm centered within the fundal myometrium. MRI of the brain showed no intracranial metastases.

**Table 1:** Pathology results.

| Lab results | Normal range | |
|---|---|---|
| Haemoglobin | 115-160 | 113 |
| White Cell Count | 4.0-11.0 | 11.0 |
| Platelet Count | 140-400 | 424 |
| Sodium Level | 135-145 | 138 |
| Potassium Level | 3.5-5.2 | 3.9 |
| Alkaline Phosphatase | 30-110 | 56 |
| Gamma-GT | <38 | 21 |
| Alanine Transaminase | <34 | 12 |
| Aspartate Transaminase | <31 | 19 |
| Lactate Dehydrogenase | 120-250 | 255 |
| Calcium Level (alb. Corr.) | 2.10-2.60 | 2.41 |
| Phosphate Level | 0.75-1.50 | 0.84 |
| Magnesium Level | 0.70-1.10 | 0.63 |
| Free Beta HCG tumour Marker | 0.01-0.23 | 171.00 |
| hcg (Total) | 0.1-0.6 | 36477 |
| hcg (Pregnancy) | <3.0 | 36477 |

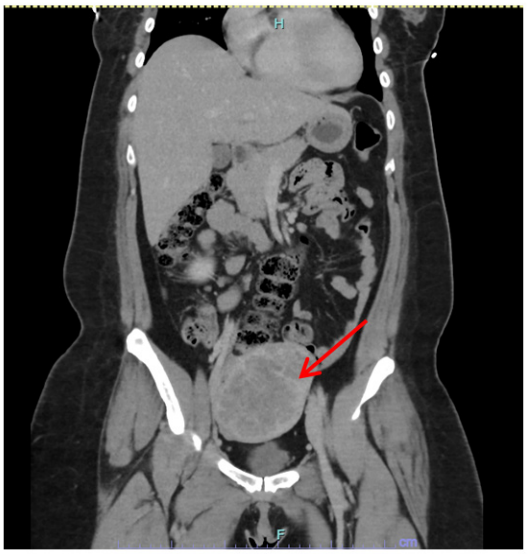

**Figure 1:** CT abdo-pelvis with contrast showed heterogenous mass at the uterine fundus (red arrow).

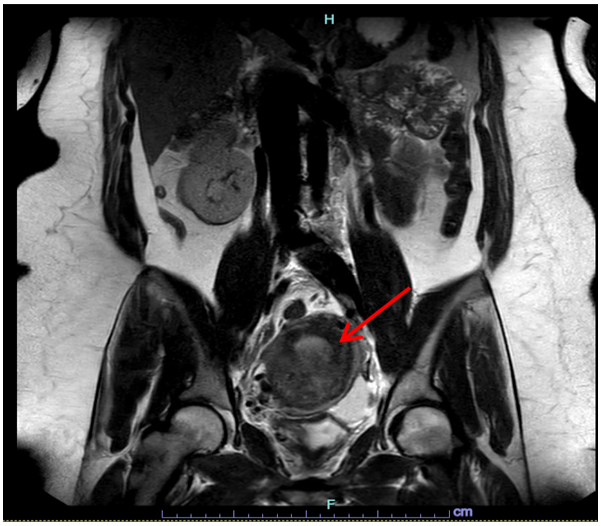


**Figure 2:** MRI pelvis showed heterogeneous mass centered within the fundal endometrium (red arrow).

Based on these findings, the patient was diagnosed with high-risk GTN, likely arising from her prior ectopic pregnancy, classified as FIGO stage III with a World Health Organization (WHO) prognostic score of 9 [1,9]. Given her completed family planning and the localized nature of the uterine lesion, she underwent a total laparoscopic hysterectomy with bilateral salpingectomy. Postoperatively, her WHO prognostic score decreased to 6, and multi-agent chemotherapy with EMA-EP (Etoposide, Methotrexate, Actinomycin-D, cisplatin, vincristine) was initiated.

Following initiation of chemotherapy, the patient demonstrated a substantial decline in β-hCG levels. She tolerated the regimen well, with mild transient side effects including fatigue and nausea, managed conservatively. At present, she continues receiving chemotherapy under close monitoring, with the aim of achieving complete remission. Multidisciplinary follow-up involving gynecologic oncology, medical oncology, and radiology is ongoing to monitor treatment response and detect any potential recurrence.

## Discussion

Gestational Trophoblastic Neoplasia (GTN) is an uncommon malignancy, comprising fewer than 1% of female reproductive tract tumors [1,2]. Its metastatic form is often misdiagnosed due to nonspecific symptoms, but persistently elevated serum β-Human Chorionic Gonadotropin (β-hCG) levels are a key diagnostic marker [3]. Despite its rarity, GTN generally has a favorable prognosis, with cure rates reaching 90-100%, even in cases with metastases [4].

The lungs, vagina, and pelvis are the most frequent metastatic sites, reported in approximately 80%, 30%, and 20% of cases, respectively. Less commonly, metastases involve the liver and brain (around 10% each), while unusual sites such as the gums and pancreas have also been documented [3,5-7]. Recognizing both typical and atypical presentations is essential for early detection and improved patient outcomes.

Multiple genetic alterations may contribute to GTN pathogenesis, and several epidemiologic factors are associated with increased risk. These include advanced maternal age (approximately 40 years), prior molar pregnancy, teenage pregnancy, blood group A, and Asian ethnicity [2]. Differential diagnoses often include ectopic pregnancy, incomplete abortion, cornual pregnancy, and β-hCG–producing germ cell tumors [1]. A thorough clinical and pathological evaluation is critical, particularly in patients with persistent or abnormal bleeding, history of extrauterine pregnancy without histologic confirmation, or delayed normalization of β-hCG [2,3].

Patients may present with a variety of symptoms, depending on tumor location and disease burden. Vaginal bleeding is the most common manifestation, either from a uterine primary lesion or from metastatic deposits such as pulmonary nodules, which can cause hemoptysis [1,2]. Importantly, histopathologic confirmation is not always necessary to initiate treatment when clinical suspicion is high [8].

**Table 2:** FIGO[a] staging system for gestational trophoblastic neoplasia.

| Stage | |
|---|---|
| 1 | Lesion confined to the uterus |
| 2 | Lesion extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament) |
| 3 | Lesions are seen in the lungs |
| 4 | All other metastatic sites |

[a](FIGO: International Federation of Gynecology and Obstetrics)

**Table 3:** WHO prognostic scoring system.

| Risk factor | 0 | 1 | 2 | 4 |
|---|---|---|---|---|
| Age (Years) | <40 | >40 | - | - |
| Antecedent pregnancy | Mole | Abortion | Term | - |
| The interval from last pregnancy (months) | 4 | 4 to 6 | 7 to 12 | >12 |
| Pre-treatment serum hCG (IU/L) | <1000 | 1000 to 10000 | 10000 to 100000 | >100000 |
| Largest tumour size | <3 cm | 3 to 4 cm | >5 cm | - |
| Site of metastasis | Lung | Spleen, kidney | GI tract | Brain, liver |
| No of metastasis | - | 1 to 4 | 5 to 8 | >8 |
| Prior failed chemotherapy | - | - | 1 drug | >/= 2 drugs |

The World Health Organization (WHO) prognostic scoring system is widely used to classify GTN risk. Factors considered include patient age, type and interval of antecedent pregnancy, pre-treatment β-hCG, largest tumor size, metastatic sites and number, and prior chemotherapy exposure [5]. Scores below 7 indicate low-risk disease, while scores of 7 or higher define high-risk GTN, warranting prompt multi-agent chemotherapy [5].

Management of low-risk GTN typically involves single-agent chemotherapy, most often methotrexate or dactinomycin [4,9]. Methotrexate remains the preferred first-line therapy due to its tolerability and ease of administration, despite evidence suggesting slightly higher efficacy of dactinomycin in certain studies [9].

High-risk GTN, defined by a WHO score of 7 or higher, is treated with combination chemotherapy. The standard EMA-CO regimen—comprising etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine—has been established for over twenty years and yields response rates around 93%, with mortality reduced to approximately 9% [4,9]. Nonetheless, 30-40% of patients may demonstrate a rise in β-hCG following EMA-CO completion. In such cases, salvage therapy with EMA-EP (etoposide, methotrexate, actinomycin-D, cisplatin, vincristine) achieves an overall response rate of approximately 85% [4].

Surgery, particularly hysterectomy, is generally reserved for select situations because chemotherapy alone is highly effective and preserves fertility [6-8]. Indications for surgical intervention include chemotherapy-resistant tumors, significant hemorrhage, or patients who have completed childbearing, especially when disease is confined to the uterus [7,8]. Studies indicate that hysterectomy can decrease the total number of chemotherapy cycles required and accelerate β-hCG normalization in carefully selected low-risk patients [7]. In PSTT and ETT, which respond less predictably to chemotherapy, hysterectomy is frequently the primary therapeutic approach [6,7].

## Conclusion

Gestational trophoblastic neoplasia, though rare, is highly curable with prompt recognition and appropriate management. Early measurement of β-hCG, accurate staging, and risk stratification are vital to guide therapy. Chemotherapy remains the cornerstone of treatment, but surgical intervention can be a useful adjunct in selected patients with chemoresistant disease, hemorrhage, or less chemosensitive tumor subtypes such as PSTT and ETT. Close monitoring, individualized multidisciplinary care, and ongoing β-hCG surveillance are essential to ensure remission and prevent recurrence.

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**Authors Information:** Rona Ting*
Logan Hospital, Australia.

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