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Case Report

Metastatic Gestational Trophoblastic Neoplasia Leading to Acute Respiratory Failure and Death: A Case Report – About a Particularly Challenging Management in the Intensive Care Unit, and Exploring the Potential of Pembrolizumab in Treating Frail, Pretreated Gestational Trophoblastic Neoplasia

Michel Meyers[a] Ahmad Awada[a] Marine Najmaoui[b] Maxime Ilzkovitz[b] Martina Pezzullo[c] Julia Chaves[d] Jacques Deviere[d] Katarina Halenarova[e] Aspasia Georgala[f] Maxime Fastrez[g] Frédéric Goffin[h, i] Laura Polastro[a]

[a]Department of Medical Oncology, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [b]Department of Internal Medicine, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [c]Department of Radiology, Hôpital Erasme, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [d]Department of Gastroenterology, Hôpital Erasme, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [e]Department of Intensive Care, Hôpital Erasme, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [f]Department of Infectious Disease, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [g]Department of Gynecology, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [h]Department of Gynecology, Centre Hospitalier Universitaire de Liège, Liège, Belgium; [i]Belgium Registery and Reference Center for Gestational Trophoblastic Diseases, Liège, Belgium

Keywords

Choriocarcinoma · Gestational trophoblastic disease · Extracorporeal membrane oxygenation · Acute respiratory distress syndrome · Immunotherapy

Abstract

Introduction: Gestational trophoblastic disease (GTD) includes rare tumors from abnormal fertilization, ranging from benign hydatidiform moles to malignant choriocarcinomas (CCs) and rare placental-site trophoblastic tumors. Management of GTD depends on FIGO scoring, with

Correspondence to:
Michel Meyers, michel.meyers@outlook.com

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low-risk cases treated conservatively and high-risk or ultra-high-risk cases requiring multi-agent chemotherapy, often EMA-CO, with induction therapy recommended for patients at very high risk of early death. ***Case Presentation:*** We present the case of a 37-year-old female patient who developed an acute respiratory failure, requiring mechanical ventilation, 2 months after term delivery by cesarean section. The diagnosis of gestational trophoblastic neoplasia (GTN) was suspected due to high level of HCG in postpartum period and thoracic imaging suggesting multiple pulmonary metastases. No biopsy was available. She subsequently developed ventilator-associated pneumonia with severe acute respiratory distress syndrome (ARDS), requiring veno-venous extracorporeal membrane oxygenation support alongside concurrent polychemotherapy. After spending 61 days in the intensive care unit, and achieving biological complete remission based on HCG monitoring, the patient was transferred to the oncology ward. Due to prolonged hypoperfusion and hypoxemia, the patient developed ischemic cholangiopathy, severely constraining further therapeutic options. After 4 months of biological remission, the patient experienced a recurrence based on HCG rising and reappearing of pulmonary lesions on thoracic imaging in the lungs. In second line, the patient was treated with carboplatin, with no significant response. In third line, pembrolizumab was used, and the patient experienced a significant decrease in HCG. However, due to hematologic toxicity, we discontinued the treatment. Subsequently, the HCG level raised and the patient rapidly developed hemorrhagic cerebral metastasis and succumbed shortly thereafter. ***Conclusion:*** This case underscores the importance of prompt recognition and timely intervention in the management of patients with ARDS during the early postpartum period. GTN with lung involvement should be considered after excluding the other more frequent causes of ARDS. It also highlights how ECMO support enables the continuation of chemotherapy and the achievement of remission in CC. Furthermore, due to the inability to initiate the desired chemotherapy, immunotherapy was introduced as a possible treatment modality. Therefore, this case underscores the importance of adaptability in treatment plans based on patient-specific clinical conditions and collaborative decision-making with specialized centers. Finally, it emphasizes the efficacy of pembrolizumab, even as a monotherapy, in pretreated CC cases.

Introduction

Gestational trophoblastic disease (GTD) forms a group of rare tumors that account for <1% of all gynecologic cancers and encompasses a spectrum of disorders that occur from abnormal fertilization events. This group includes premalignant conditions such as complete and partial hydatidiform moles (HMs) and malignant conditions such as invasive moles, CCs, and the exceptionally rare placental-site trophoblastic tumors or epithelioid trophoblastic tumors [1].

In Europe and North America, CC affects approximately 1 in 40,000 pregnancies and 1 in 40 HMs [2, 3]. Overall, higher frequencies are reported in Asia, the Middle East, and Africa [4].

Since 2002, management of CC is defined by the Federation of Gynecology and Obstetrics (FIGO) score which is based on a prognostic scoring and anatomic staging systems [1, 5]. Approximately 95% of patients diagnosed with gestational trophoblastic neoplasia (GTN) following HMs are classified as low risk, with scores ranging from 0 to 6. Patients with high-risk GTN, with a score higher or equal to 7, are treated with multi-agent chemotherapy. Currently, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine (EMA-CO) is the standard of care in this setting. Several other multi-agent chemotherapies exist, but to date, it is not clear which combination is the most effective [6].

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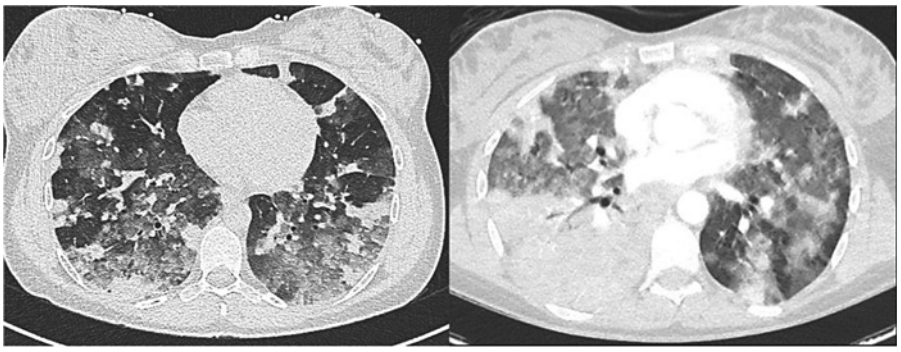

Fig. 1. Multidetector computed tomography (MDCT) of the chest (lung window): evolution of the pulmonary lesions over 7 days showing coalescence of the pulmonary opacities and development of a consolidation of the right inferior lobe. Neither pulmonary embolism nor mediastinal adenopathies are found (performed upon admission to the emergency room).

Ultra-high-risk GTN includes patients with a FIGO score of 13 and above, who have an increased risk of early death within 4 weeks of starting chemotherapy or late death. Associated factors include very advanced disease, liver and/or brain metastasis, an interval from the end of the causative pregnancy >2.8 years. Early deaths can be avoided by using induction chemotherapy with low-dose etoposide and cisplatin, followed by EMA-CO or etoposide/methotrexate/actinomycin D – etoposide/cisplatin (EP-EMA) [7, 8]. GTN metastases occur most commonly in the lungs (80–85%), followed by the vagina (30%), with less frequent metastases to the central nervous system and liver (10% each), typically involving concurrent pulmonary and/or vaginal sites in central nervous system cases [9, 10].

Lung metastases can cause dyspnea, chest pain, cough, or hemoptysis, with symptoms varying based on the stage of detection. In a study of 131 patients with metastatic GTN, 75 patients presented pulmonary metastases, 33% had >50% lung opacification, 48% had prominent pleural effusion, and 11% developed respiratory failure requiring mechanical ventilation within 1 month of presentation [11]. Trophoblastic emboli can lead to pulmonary arterial occlusion, right heart strain, and pulmonary hypertension, potentially resulting in a misdiagnosis of primary pulmonary disease, especially with distant antecedent pregnancies and minimal gynecologic symptoms [12].

We present the case of a 37-year-old female who developed acute respiratory failure, requiring veno-venous extracorporeal membrane oxygenation (VV-ECMO) and poly-chemotherapy for GTN with pulmonary metastases, highlighting the challenges of intensive care unit (ICU) management and exploring the potential of pembrolizumab in treating frail, pretreated patients.

Case Presentation

A 37-year-old woman without any notable medical history developed preeclampsia, necessitating an emergency cesarean section at 36 weeks of gestation. Two months post-partum, the patient developed progressive dyspnea and hemoptysis. She was admitted to the emergency department of a primary hospital on February 2022 and underwent a thoracic CT scan, which revealed multiple ground-glass infiltrates in both lung fields, suggestive of COVID-19 infection (Fig. 1).

Despite conducting an exhaustive bacteriological, virological, and immunological assessment, no definitive diagnosis was found. Empirical antibiotic treatment was initiated. In

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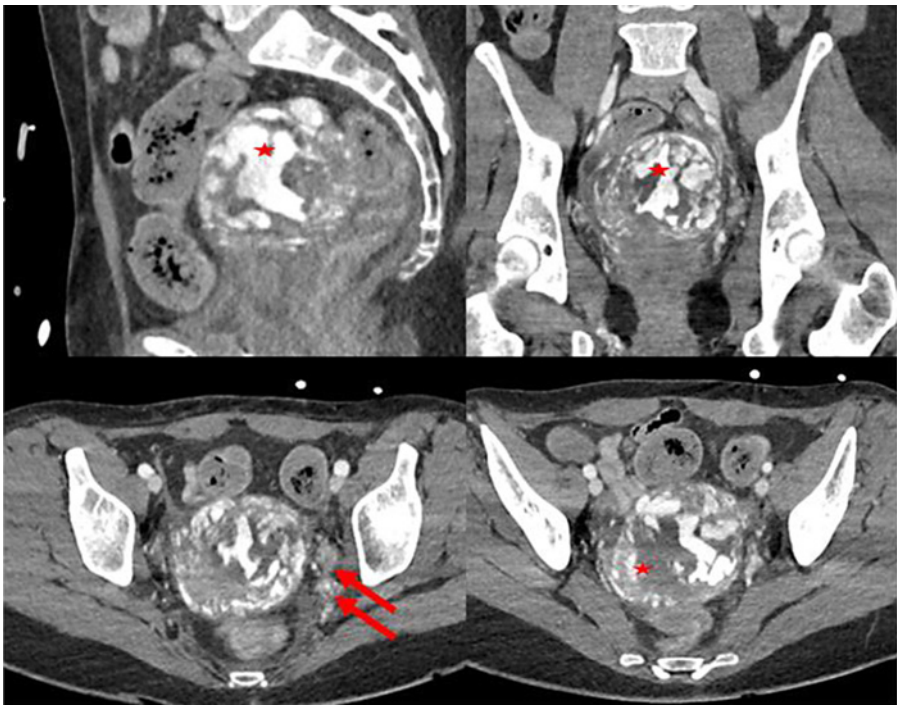

Fig. 2. MDCT of the abdomen after iodine contrast medium injection in portal venous phase showing an heterogeneous partially hemorrhagic and globally highly enhancing mass (70 × 71 × 80 mm) within the uterine cavity (asterisk) and multiples enlarged and heterogeneously enhancing lymph nodes in the internal iliac chains (arrow) (performed during the work-up for the stay in the ICU). MDCT, multidetector computed tomography.

Table 1. FIGO score [6]

Score	0	1	2	4
Age, years	≤39	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Interval from index pregnancy, months	<4	4–6	7–12	>12
Pretreatment serum HCG, IU/L	<1,000	1,000–10,000	10,000–100,000	>100,000
Largest tumor size (including uterus), cm	–	3–4	>5	–
Site of metastases	Lung	Spleen/kidney	GI	Liver/brain
Metastases, *n*	–	1–4	5–8	>8
Previous failed chemotherapy			Single drug	2 or more drugs

parallel, intravenous methylprednisolone was administered at a dose of 40 mg and was later escalated to 60 mg/day (1 mg/kg).

The patient was transferred to the ICU of a tertiary care hospital for management of hypoxemic bilateral pneumopathy of unclear etiology. After 3 days, her respiratory status deteriorated, necessitating endotracheal intubation. Corticosteroids were continued, and antibiotic treatment was adjusted based on current microbiological findings. The patient did not present any gynecological symptoms.

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Fig. 3. Evolution of b-HCG concentration during the hospitalization and administration of chemotherapy.

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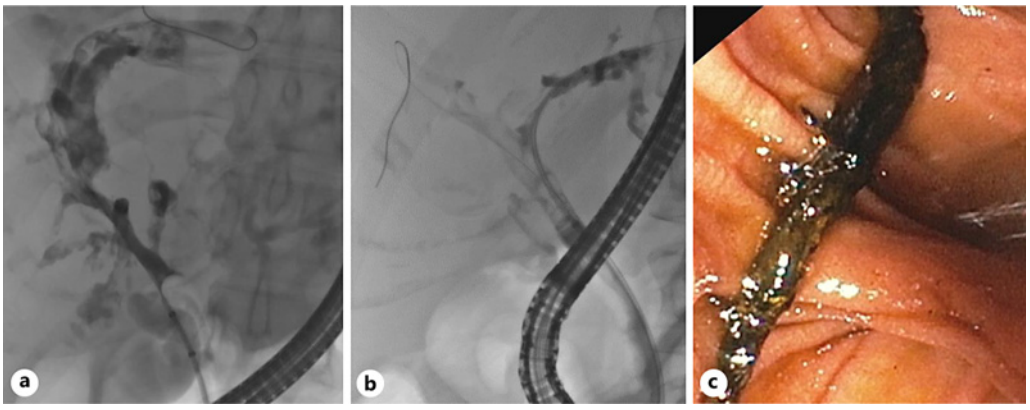

Fig. 4. First ERCP performed at the time of recovery from septic shock and ARDS. Disclosure of massive hemobilia with blood clots filling all intrahepatic ducts. Biliary endoscopic sphincterotomy was performed followed by balloon extraction of the clots. Biliary communication with portal vein was demonstrated during maneuver. **a** Follow-up ERCP was performed with balloon extraction of residual sludge and placement of two plastic stents. No more bilio-portal leak was demonstrated but significant abnormalities were present on the secondary bile ducts. **b** During ERCP, we found intrabiliary black material (CAST). **c** The first ERCP was performed during the stay in the ICU; the subsequent ones were organized over the following half year.

Concomitantly, laboratory investigations revealed elevated human chorionic gonadotropin (HCG) levels, increasing from 14,391 IU/L to 18,703 IU/L over a 4-day interval. This finding led to the hypothesis of GTD with pulmonary metastases, although no histological analysis was available.

Subsequent gynecological ultrasound examination identified a heterogeneous posterior fundal intramyometrial mass measuring 65 mm in its longest axis. Furthermore, contrast-enhanced abdominal computed tomography (Fig. 2) showed the presence of a heterogeneous, partially hemorrhagic, enhancing mass.

Pulmonary biopsy was not performed due to the elevated risk of hemorrhage and the potential adverse impact it could have on the patient's respiratory function. A retrospective anatomopathological examination of the patient's placenta did not show any signs of malignancy.

Since pulmonary metastases were radiologically documented, a cerebral MRI was requested, which ruled out cerebral metastases. In this context, the diagnosis of GTD, stage III, high risk (FIGO score 10), was proposed (Table 1).

The management strategy involved several key decisions due to unique clinical challenges. Although EMA-CO was the preferred treatment, the patient's respiratory insufficiency and associated risks – including potential exacerbation of her condition and tumor lysis syndrome – precluded its use. Therefore, an induction chemotherapy regimen consisting of weekly etoposide and cisplatin was implemented. This adjustment was thoroughly discussed and coordinated with reference centers in Belgium and France to ensure a consensus on the best course of action.

The chemotherapy was administered in three weekly cycles on May 17th, May 24th, and June 6th while the patient was intubated. Profound febrile neutropenia occurred after the two chemotherapy cycles given at 1-week intervals. This was managed with cefepime for 5 days. No identifiable infectious sources were detected, and prophylactic treatment with filgrastim was administered for febrile neutropenia.

Following the first round of chemotherapy, the patient experienced further respiratory deterioration with severe acute respiratory distress syndrome (ARDS) (P/F <80 mm Hg) due

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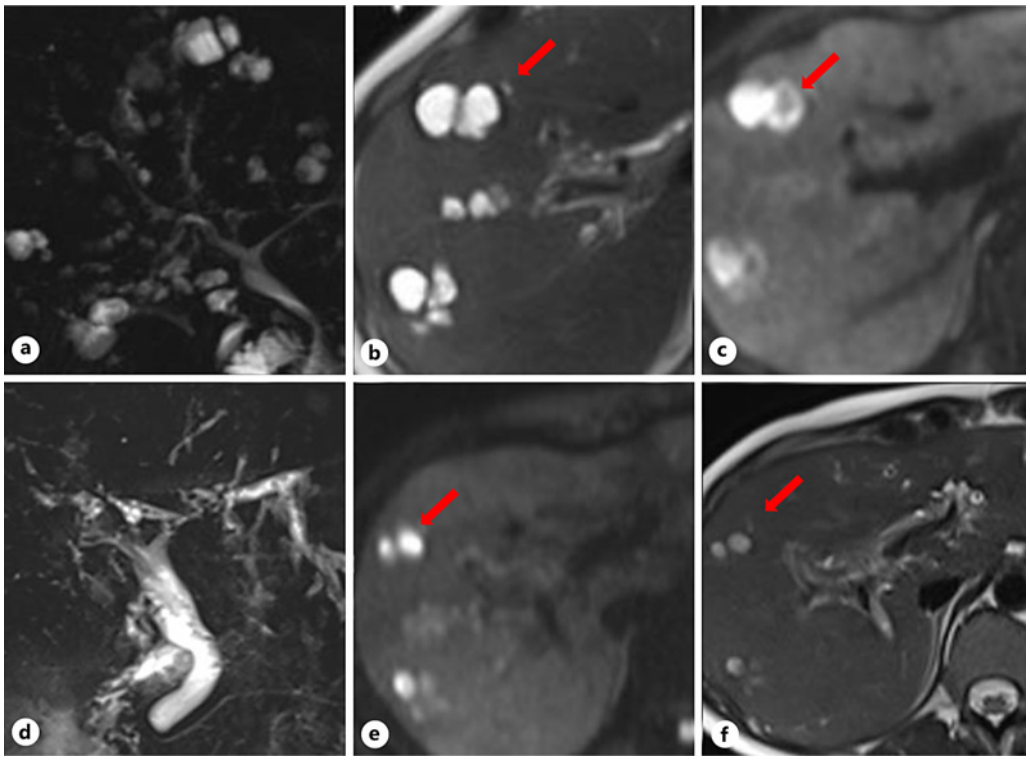

Fig. 5. MRI examination at two different time points. T2-w images (**b**, **f**) show several cystic (arrows) lesions with diffusion restriction (**c**, **e**), suggesting the diagnosis of liver abscesses for at least some of them in the appropriate clinical context and confirmed by the partial size regression in the follow-up exam (arrow in **e** and **f**), namely, in the right anterior sector (segment VIII-V). MRCP images in the coronal plane (**a**, **d**) also show the regression of the cystic lesions and the appearance of diffuse irregularities of the intrahepatic biliary ducts, demonstrating a cholangiopathy (the first MRCP was performed during the stay in the ICU; the subsequent ones were organized over the following half year).

to microbiologically documented pneumonia. This necessitated six sessions of prone positioning and support by VV-ECMO due to refractory hypoxemia. The second and third chemotherapy cycle were administered with ongoing VV-ECMO support. The patient was also treated with systemic corticosteroids at 2 mg/kg decreasing dose for late persistent ARDS [13]. After 4 weeks, the patient's condition improved, allowing for VV-ECMO weaning and extubation.

During VV-ECMO, the patient developed multiple hepatic abscesses with bacteremia caused by *Enterococcus faecium* due to an ischemic cholangitis resulting from prolonged liver hypoperfusion and hypoxemia. Weekly monitoring of HCG levels revealed a decreasing concentration to 76 IU/L at the time of discharge from the ICU, and they continued to drop further during hospitalization. Finally, the patient achieved a complete biological response (Fig. 3).

Over several months, the abscess and ischemic cholangitis were treated with multiple courses of antibiotics, repeated ERCP procedures involving several dilatations, and the placement of two stents that were subsequently removed (Fig. 4, 5). Despite all efforts, cholestasis could not be controlled, greatly limiting the therapeutic options for treating recurrent GTN. Furthermore, the patient was cachectic and presented with peripheral polyneuropathy after the ICU; therefore, EMA-CO was not an option for this patient, and carboplatin in monotherapy was administered over four cycles, yet it failed to yield substantial improvement (Fig. 3).

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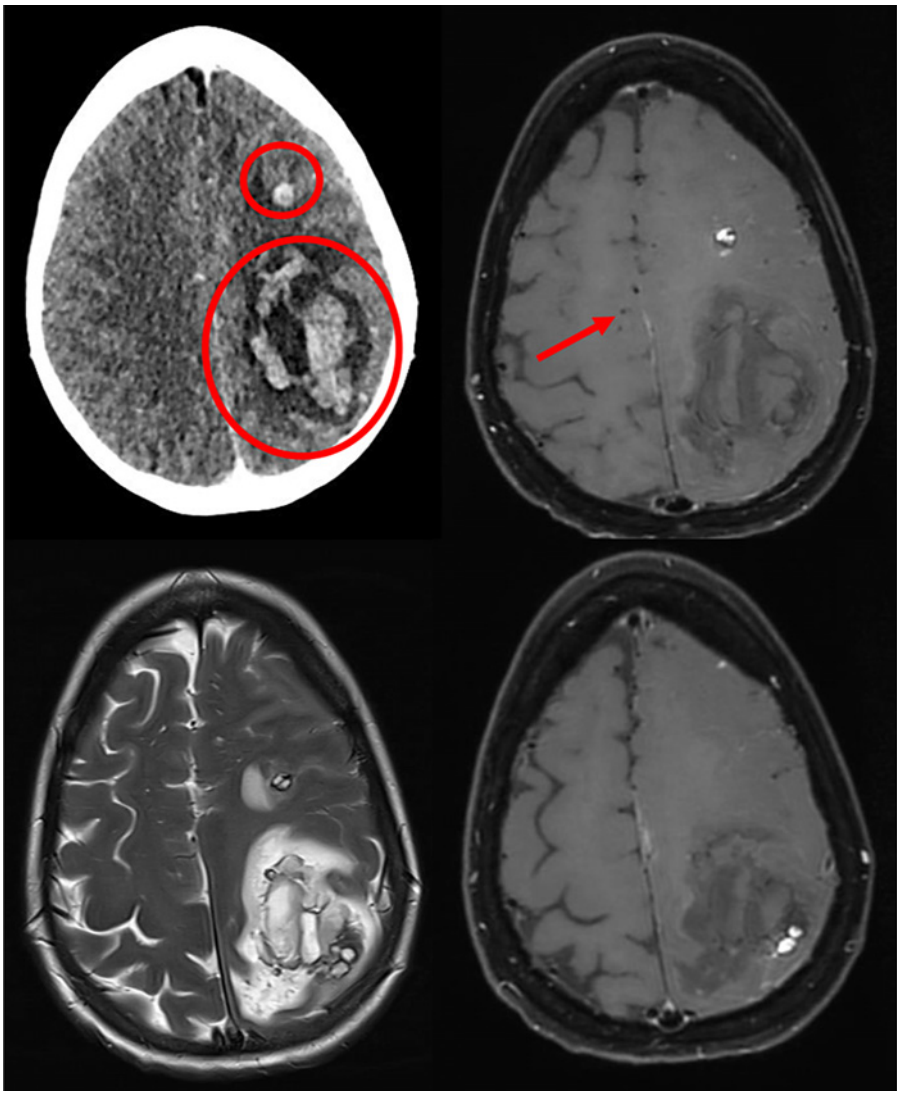

Fig. 6. On the CT scan, we found two hemorrhagic lesions (circles) with the presence of perilesional edema. The first lesion is located in the left parietal region and measures approximately 7 cm in its largest diameter. The second lesion is located anteriorly in the left frontal region and measures approximately 2 cm in its largest diameter. These two lesions cause diffuse cerebral edema associated with subfalcine herniation, with a deviation of the midline to the right by 9–10 mm (arrow), as well as a very slight protrusion of the left temporal uncus.

As third line, pembrolizumab was utilized off-label, exhibiting a notable efficacy in controlling the cancer, with an impressive biological response (Fig. 3). Pembrolizumab was not used earlier in combination with carboplatin as a second-line treatment due to off-label restrictions.

Unfortunately, the patient developed febrile bicytopenia (anemia and thrombocytopenia) consistent with hemophagocytic lymphohistiocytosis syndrome (H-score 70%), most likely induced by pembrolizumab. A bone marrow biopsy revealed pure red cell aplasia. Despite treatment with corticosteroids and intravenous immunoglobulin for pure red cell aplasia, the patient remained transfusion dependent [14].

There was no increase at the time of the development of cerebral metastasis; rather, the HCG levels plateaued (Fig. 3). She eventually passed away as a result of the progression of cerebral metastasis (Fig. 6). The patient and her family did not consent to an autopsy.

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Discussion

This case is particularly noteworthy due to the use of ECMO to enable the continuation of chemotherapy, resulting in complete biological remission. Recently, significant discussions have emerged about the use of ECMO in cancer patients. While terminal malignancy may be considered a reasonable contraindication, decision-making is more complex for other oncologic conditions [15].

With the development of ECMO technology and increase of its availability, recent studies report improved survival of oncologic patients with ECMO, which reflects improvements in cancer care. However, there remains a concern of increased complication rates with ECMO because of immunodeficiency, cytopenia, and coagulopathy [15, 16].

Recent reports confirm higher incidence of infection in oncologic population compared to one without cancer, but this finding does not impact on patients' outcome [17]. As suggested in these reports and observed in the case of our patient, ECMO use should not be prohibited because of the presence of malignancy only. Unfortunately, the patient developed ischemic cholangitis, which is a rare complication that has only been described in few case reports [18, 19].

Immunotherapy is becoming increasingly used in the treatment of recurrent, high-risk GTN patients. Recent studies found a strong expression of PD-L1 in GTN, and increasing amount of literature emphasizes that anti-PD-1 or anti-PD-L1 therapies could present a significant new treatment approach for managing chemoresistant/-refractory GTN [20–22].

In choriocarcinoma (CC), dual immunotherapy with anti-CTLA-4 and anti-PD-1 blockade has demonstrated promising response rates, with ongoing objective responses and a favorable safety profile observed in a phase II trial involving 4 GTN patients [19].

You et al. [22] demonstrated that single-agent immunotherapy showed favorable safety and efficacy in approximately 50% of patients with single-agent chemotherapy-resistant GTN, suggesting its potential as an alternative to combination chemotherapy [22]. The timing of pembrolizumab introduction in the treatment of high-risk GTN is still a matter of debates [23–29].

Goldfarb et al. [23] and Clair et al. [24] presented two case of multi-agent drug-resistant CC that responded to pembrolizumab, pointing to the potential of immunotherapy in overcoming resistance to conventional treatments underlining the efficacy of immune checkpoint as salvage therapy [23, 24]. Paspalj et al. [25] shared a case of long-term survival in multiresistant metastatic CC after pembrolizumab treatment, further reinforcing the potential of pembrolizumab as a viable option for challenging CC cases.

Conversely, Kazemi et al. [28] underscored a cautionary tale of hyperprogression in a case of non-gestational CC upon treatment with pembrolizumab, highlighting the need for deeper understanding and careful patient selection when considering immunotherapy. In case of recurrence of non-resectable disease after EMA-EP or taxol/etoposide – taxol/cisplatin (TE-TP), and if the surgical procedure does not lead to HCG normalization or if there is non-resectable disease, anti-PD-1 immunotherapy is indicated [30, 31].

This case illustrates the importance of early diagnosis and supports the early integration of pembrolizumab into the treatment strategy, either as a monotherapy or in combination with chemotherapy, due to the potential of chemotherapy to enhance the efficacy of immunotherapy and its favorable tolerability profile [32, 33]. Further studies are required to solidify the role of immunotherapy in combination with chemotherapy as a first- or second-line treatment. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543518).

Conclusion

This case highlights the critical importance of early recognition and timely intervention in managing patients with ARDS during the postpartum period. GTN with lung involvement should be considered after excluding other more common causes of ARDS. In cases of severe and unusual postpartum respiratory distress, it may be prudent to promptly consider GTN by simply measuring HCG levels.

It also highlights that ECMO support can enable the continuation of chemotherapy, allowing remission of CC. This case also underscores the efficacy of pembrolizumab, even as a monotherapy, in frail, pretreated patients with GTN, and suggests the integration of immunotherapy into earlier treatment lines, whether in combination or as a single agent, in the management of CC patients.

Acknowledgments

We would like to extend our sincere gratitude to the healthcare professionals involved in the challenging care and treatment of this patient.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images prior to their passing away. No patient-identifying information is included in this study. This research was conducted in accordance with the World Medical Association Declaration of Helsinki. This retrospective review did not require ethical approval in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Michel Meyers wrote the article, created the tables, discussed the case at the Belgian Multidisciplinary Immunotoxicity Board (BITOX) a national multidisciplinary council for immunotherapy-related adverse events and together with Marine Najmaoui, treated the patient during her hospitalization. Maxime Ilzkovitz treated the patient during her hospitalization and discussed the case at the BITOX. Martina Pezzullo performed and interpreted the MRI and CT scans, took the images, and annotated them for the case report. Chaves Julia and Jacques Deviere performed the endoscopic retrograde cholangiopancreatography, captured images, and annotated them for the case report. Katarina Halenarova managed the

patient's care during her stay in the ICU. Aspasia Georgala served as the treating infectiologist. Maxime Fastrez, a gynecologist-obstetrician specializing in gynecologic oncology, coordinated the patient's treatment with international multidisciplinary oncology conferences. Frédéric Goffin is a gynecologist-obstetrician specializing in gynecologic oncology and is the coordinator of the Belgium Registery and Reference Center for Gestational Trophoblastic Disease. Ahmad Awada, as head of the medical oncology department, oversaw the patient's care during hospitalization. Laura Polastro was the patient's medical oncologist. All authors discussed the results, proposed revisions at each stage, and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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