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Acute cardiopulmonary failure in a young woman with high-risk gestational trophoblastic neoplasia: A case of induction chemotherapy during extracorporeal membrane oxygenation

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1. Introduction

Gestational trophoblastic neoplasia (GTN) includes choriocarcinoma, placenta site trophoblastic tumor, epithelioid trophoblastic tumor, and invasive moles, and is comprised of the growth of abnormal placental trophoblastic tissue (Brown et al., 2017). Based on the World Health Organization (WHO) prognostic score, 81% of patients have low-risk disease (WHO score of ≤ 6), 18% have high-risk disease (WHO score > 6), and 1% have placental site trophoblastic tumor (Braga et al., 2000). Metastatic sites commonly involve the vagina and lung. This malignancy is very chemo-responsive.

GTN is most often diagnosed following abnormal pregnancies, persistent vaginal bleeding, or an increasing or plateau in beta-human chorionic gonadotropin (HCG) levels, but cases of respiratory symptoms alone as the presenting symptom have been reported (Kelly et al., 1990; Staples et al., 2019; Multani et al., 2015). For example, Kelly *et al.* described 135 patients over a 28 year period whose initial complaint was shortness of breath (Kelly et al., 1990). Staples *et al.* reported on two patients treated with video assisted thoracoscopic surgery for lung mass and lung nodule, one of whom presented with chest tightness and dyspnea (Staples et al., 2019). Finally, Multani *et al.* reported a case of intermediate trophoblastic tumor that presented as recurrent pneumothorax (Multani et al., 2015). While more rare, respiratory symptoms should not be overlooked as the presenting complaint in GTN. Here we describe a case of GTN presenting as severe acute respiratory distress syndrome (ARDS) with right ventricular failure. The use of extracorporeal membrane oxygenation (ECMO) with concomitant induction chemotherapy and the clinical considerations encountered during this patient's initial course make this case unique and highlights the benefit of a multidisciplinary approach to critical care in treating high-risk GTN. The patient provided written consent for publication of her case.

2. Case

A 20-year-old G1P1001 presented to an outside hospital with cough, worsening shortness of breath, a 15-month history of amenorrhea since a vaginal delivery in October 2019, and two months of "morning sickness." Evaluation for pulmonary embolism was negative as were infectious etiologies (Influenza A and B negative, SARS-CoV-2 (COVID-19) negative). She was incidentally found to have a beta-HCG of approximately 900,000 mIU/mL, an adnexal mass, and bilateral diffuse pulmonary nodules. The patient was intubated due to hypoxemia, and empiric antibiotics were started for presumed septic shock. Over the

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succeeding several hours her ventilatory requirements increased with an FiO_2/PaO_2 ratio of 69 on 100% FiO_2, hypercarbia to 80 mmHg, and increasing positive end-expiratory pressure despite lung-protective ventilatory strategies and paralysis. The patient was promptly evaluated by our institution's multidisciplinary team and transferred for ECMO cannulation.

Upon arrival, transesophageal echocardiogram revealed acute right ventricular failure with severe tricuspid regurgitation, a dilated right ventricle with moderate to severe systolic dysfunction and intra-atrial septal bowing from right to left. Due to right ventricular failure, she underwent cannulation with dual-lumen percutaneous right ventricular assist device (RVAD) (TandemLife Protek Duo™, LivaNova, UK) in conjunction with an ECMO circuit (Cardiohelp™, Getinge, Gothenburg, SE). While in the hybrid operating suite, she underwent dilation and curettage in an attempt to obtain a histologic diagnosis related to elevated beta-HCG. She was started on a heparin infusion and was weaned from vasopressors within three hours of admission to the intensive care unit postoperatively.

Beta-HCG at our institution was 917,929 mIU/mL supporting a clinical diagnosis of GTN, presumed FIGO stage III due to the presence of pulmonary lesions. Her WHO score was 14. On hospital day (HD) 1, the patient was started on induction chemotherapy of cisplatin 20 mg/m^2 and etoposide 100 mg/m^2 which she received on HD 1 and 2. On HD 2 her beta-HCG fell to 707,706 mIU/mL. Additional tumor markers were alpha fetoprotein (AFP) less than 0.6 ng/mL, LDH 670 U/L, and inhibin B 20 (pg/mL). The patient was extubated on HD 2. She suffered an ECMO circuit complication on HD 2 following chemotherapy administration due to acute oxygenator failure, which manifested clinically as acute tachycardia, hypoxia, and hypotension requiring vasopressor support. The ECMO circuit showed no signs of obstruction, and no visible fibrin deposition was observed in the oxygenator, but due to a high transoxygenator pressure gradient, a clinical diagnosis of oxygenator failure due to suspected etoposide sequestration was made. The circuit was exchanged entirely with immediate improvement in the patient's clinical condition. Reintubation was successfully avoided. The patient continued to clinically improve on ECMO support.

Final pathology from the dilation and curettage demonstrated no chorionic villi, fetal parts, implantation site or neoplasm, and gestational type endometrium with breakdown. Given the outside hospital ultrasound revealed a complex multi-cystic left adnexa measuring 7.5 x 5.4 x 8.0 cm, a CT-guided biopsy of the pelvic mass was completed on HD 6 in an attempt to rule out a primary ovarian choriocarcinoma. Final pathology demonstrated fragments of a corpus luteum cyst. The patient's final oncologic plan was to continue induction chemotherapy while the patient remained hospitalized with transition to Etoposide, Methotrexate, d-Actinomycin, Cyclophosphamide, and Vincristine (EMA-CO) chemotherapy once the patient was stable and discharged.

The patient's remaining hospital course was complicated by thrombocytopenia while on ECMO (nadir, 33 10^3/uL) and neutropenia (absolute neutrophil count [ANC] nadir 35 10^3/uL), both of which delayed subsequent doses of induction chemotherapy and were believed to be multifactorial in etiology (i.e. chemotherapy and ECMO). Despite a delay in chemotherapy, her beta-HCG continued to fall (Fig. 1). Magnetic resonance imaging of her brain was negative for metastatic lesions. Her respiratory status continued to improve and she was successfully decannulated from ECMO on HD 10 with a clot noted on the distal tip of the cannula. A transthoracic echocardiogram that day revealed a mobile echodensity on the tricuspid valve, a differential diagnosis for which included tumor, thrombus, or vegetation. At this point her beta-HCG had fallen to 60,862 mIU/mL.

On HD 12 she was transferred out of the ICU. Her platelet counts and ANC improved significantly after ECMO decannulation and she received cycle 2 of induction chemotherapy on HD 16 and 17 without significant toxicity. A repeat echocardiogram was performed revealing, "1.1 cm mobile echodensity on tricuspid valve… compared to prior echo, appears thinner." Therapeutic enoxaparin was initiated and the patient maintained respiratory status on room air. She was discharged home on HD 18.

Thirty days from patient's initial presentation, she returned for cycle 1 day 1 of EMA-CO. She received etoposide 100 mg/m^2, methotrexate 300 mg/m^2, and dactinomycin 0.5 mg on day 1, etoposide 100 mg/m^2 and dactinomycin 0.5 mg on day 2, and cyclophosphamide 600 mg/m^2 and vincristine 1 mg/m^2 on day 8. Cycles were 14 days long and the patient's beta-HCG normalized to less than 5 mIU/mL after 3 cycles of EMA-CO (Fig. 1). The patient received filgrastim marrow support 300 mcg daily for 4 days (cycle day 9–12). She received 3 additional cycles of

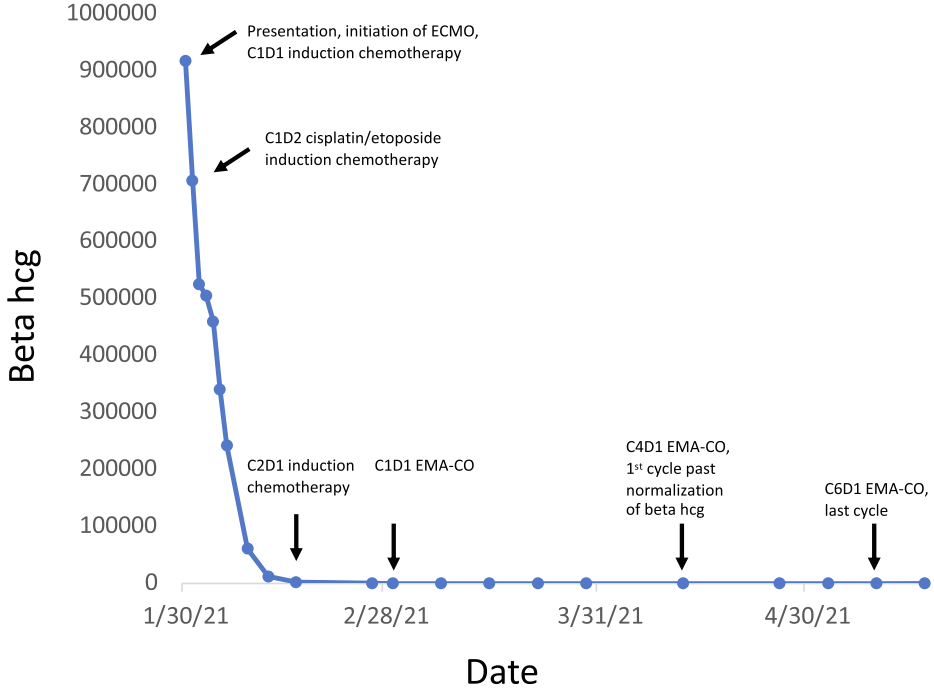

Fig. 1. Trend of beta-HCG compared to administration of chemotherapy.

EMCA-CO after beta-HCG normalized. She is currently under surveillance and doing well.

3. Discussion

Several aspects of this patient's presentation and care make this case unique. First, her presenting beta-HCG of >900,000 mIU/mL and antecedent pregnancy of a term vaginal delivery 15 months prior contributed to her high-risk GTN diagnosis. This patient's treatment with a multidisciplinary team of oncologic and cardiovascular subspecialists, however, allow this case to serve as an example in the care of patients with the competing medical needs of malignancy and acute cardiopulmonary failure.

Consideration for ECMO in our patient was initiated prior to a formal diagnosis of GTN. The patient's presentation with acutely worsening respiratory symptoms, hypoxia, and temporal relationship to the winter 2021 peak in COVID-19 cases perhaps led to the outside hospital emergency department's initiation of the transfer to a center with ECMO capabilities as COVID-19 was an initial part of this patient's differential diagnosis. When her hypoxia increased despite lung-protective ventilation and permissive hypercarbia, ECMO was initiated. Early use of ECMO in GTN with pulmonary lesions has been recommended as a treatment consideration (Kelly et al., 1990; Montrief et al., 2020), as positive pressure ventilation in patients with pulmonary tumor burden can lead to barotrauma and pulmonary hemorrhage (Kelly et al., 1990). Our patient stabilized quickly once ECMO was initiated. This allowed for consideration of early chemotherapy for treatment of her suspected GTN.

Use of chemotherapy for treatment of GTN while on or in close proximity to ECMO is limited to few case reports (Sekandarzad et al., 2020; Chung et al., 2017). Chung *et al.* described administration of one cycle of EMA-CO while a patient was on ECMO after pulmonary embolectomy for choriocarcinoma tumor embolus (Chung et al., 2017). Sekandarzad *et al.* presented a case of postpartum choriocarcinoma in which EMA-CO was initiated and the patient subsequently developed dyspnea, hypoxemia, was intubated and suffered a pulmonary hemorrhage. Due to persistent hypoxemia, the patient underwent cannulation for ECMO and was restarted on EMA-CO after a delay of six days. This patient required re-initiation of ECMO for 21 days during the second and third cycles of chemotherapy (Sekandarzad et al., 2020).

Compared to these aforementioned cases, our patient underwent induction chemotherapy with etoposide and cisplatin within 12 hours after initiation of ECMO, which to our knowledge has not been previously described. This induction chemotherapy regimen has been successfully used for patients with a WHO score > 12 due to significant risk for hemorrhage with a large burden of metastatic disease (Alifrangis et al., 2013). A reduction in death within the first four weeks of treatment in high-risk patients has been attributed to induction chemotherapy, as a gradual decrease in tumor volume in the lungs is believed to be associated with a decreased risk of pulmonary hemorrhage and subsequent mortality (Alifrangis et al., 2013). Our patient tolerated the etoposide and cisplatin well, receiving day 1 while on ECMO and mechanically ventilated, and day 2 while on ECMO after being extubated several hours earlier. She received aprepitant and dexamethasone on day 1 and did not experience significant nausea. This initial cycle of induction chemotherapy led to a decline in beta-HCG from 917,929 to 525,327 mIU/mL.

While a definitive cause for the ECMO oxygenator failure in our patient was not determined, etoposide was the suspected culprit given the propensity of lipophilic, protein-bound agents to sequester in ECMO circuits, and the temporal proximity of etoposide administration to the oxygenator failure. There is a paucity of data on chemotherapy administration in patients on ECMO. One case of etoposide administration during ECMO was provided without issue to a nine-year-old with hemophagocytic lymphohistiocytosis in combination with doxycycline and dexamethasone (Cheng et al., 2016). Circuit factors, patient factors, and drug interactions have all been shown to affect drug pharmacokinetics in ECMO patients (Shekar et al., 2012). ECMO circuits influence the pharmacokinetics of various drugs because of hemodilution, circuit sequestration, and drug inactivation. In our patient, timely replacement of the entire circuit—oxygenator and circuit—led to cardiopulmonary stabilization and avoidance of re-intubation. Consideration of use of an ECMO circuit with an oxygenator that could be exchanged independent of replacement of the entire circuit may be a useful consideration for future cases where chemotherapy or other less commonly used drugs are anticipated to be utilized while a patient is on ECMO given the limited knowledge and unpredictability of how these drugs may interact with the ECMO circuit.

Close collaboration between the gynecology oncology service and cardiac intensivist team, comprised of cardiothoracic surgery and anesthesia intensivists, undoubtedly contributed to the expedient stabilization and clinical improvement in our patient. Several multidisciplinary treatment conversations occurred while treating this patient: deciding when to initiate chemotherapy, concerning the oxygenator failure, the timing of de-cannulation, and treating the tricuspid thrombus. The expertise of our team of providers from several different subspecialties can be used as an example for other oncologists who may encounter the need to treat patients with coexisting malignancy and cardiopulmonary failure requiring ECMO.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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