Gynecologic Oncology Reports 48 (2023) 101224

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Acute pulmonary complications in the setting of high risk gestational trophoblastic neoplasia and induction of chemotherapy

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A B S T R A C T

Gestational trophoblastic neoplasia (GTN) consists of rare malignancies of the placenta with a known propensity to metastasize to the lungs. GTN is treated with chemotherapeutic agents known to cause lung injury, further placing patients at risk for serious pulmonary events. In the literature, only a few reports of these complications and their management have been described. Here, we present two cases of GTN with pulmonary complications in the hopes of providing guidance in management. Management of these acute complications had to be balanced between continuation of life-saving therapy to reduce disease burden versus further exacerbation existing pulmonary disease. A review of the English language literature on pulmonary complications in GTN and chemotherapy was performed.

In these two cases, we identified key steps that were critical in management: inpatient chemotherapy, early intervention and transfer to an intensive unit when needed, multidisciplinary teams, and altering regimens to reduce lung toxicity. Sequelae of pulmonary injury secondary to chemotherapy can be similar to those secondary to metastases. Because consistent criteria for chemotherapy-induced lung injury has not been established, the true incidence of lung injury that is directly related to chemotherapy versus metastatic disease cannot always be parsed out, making management of these complications difficult. There is also a lack of centralized care for a rare disease like GTN and regional differences in incidence, which can lead to inconsistent treatment decisions. It therefore remains important to illuminate rarely seen complications and their management in the hopes of providing guidance to future clinicians.

1. Introduction

Gestational trophoblastic neoplasia (GTN) consists of rare malignancies of the placenta with known propensity to metastasize to the lungs, making these patients susceptible to various pulmonary complications such as pneumothorax (PTX), pulmonary artery pseudoaneurysms (PAP), and pulmonary arteriovenous malformations (PAVM). The proper management of these complications is crucial to optimize patient well-being and assure prompt, uninterrupted chemotherapy administration. As these pulmonary complications are potentially severe, and even deadly, it is important for the management team to be familiar with diagnosing and treating these conditions. In addition to the pathophysiology of GTN that leads to direct pulmonary toxicity, the chemotherapeutic agents used can also lead to significant lung toxicity due to massive tumor response, as well as from the agents themselves. Though patients with GTN have a uniquely high risk of serious pulmonary events, there is minimal published guidance on their management, as only a few cases of serious pulmonary complications in GTN have been reported. Here, we present two clinically complex cases of GTN associated with acute pulmonary events in the hopes of adding to the body of knowledge on management of these patients. Management of these acute complications had to be balanced between continuation of life-saving therapy that had the potential to reduce disease burden, versus the potential to further exacerbate existing pulmonary disease.

2. Case series

2.1. Case 1

A 33 year-old G3P3003 female with a history of chronic obstructive pulmonary disease (COPD) secondary to tobacco use presented with severe headache and was found to have right cerebellar and temporal lobe lesions concerning for metastatic cancer of unknown primary. She had a beta human chorionic gonadotropin (bHCG) level of 299 mIU/mL and her last pregnancy resulted in a term delivery > 12 months ago. A transvaginal ultrasound (TVUS) showed no intrauterine pregnancy. Gynecology was consulted for what was thought to be an ectopic pregnancy. She underwent a craniotomy and final pathology of the lesion demonstrated metastatic choriocarcinoma. She was diagnosed with stage IV choriocarcinoma, WHO score 13 with additional metastases to the lungs (Fig. 1A). She underwent low-dose induction etoposide and cisplatin (EP) for 1 cycle post-operatively and was discharged with plans

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https://doi.org/10.1016/j.gore.2023.101224
Received 26 April 2023; Received in revised form 30 May 2023; Accepted 5 June 2023
Available online 10 June 2023

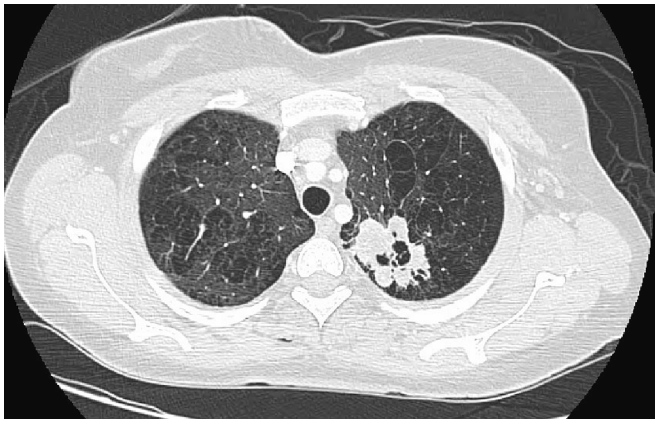

Fig. 1A. This staging chest computed tomography (CT) demonstrates pulmonary metastases in the left upper lobe measuring 4.3 × 3.8 cm. Additional metastases were noted in the right upper lobe (not pictured).

for full-dose therapy with etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (EMA-CO). However, shortly after discharge, she developed a large, spontaneous PTX requiring emergent chest tube placement (Fig. 1B). Treatment was continued with 2 cycles of EP, followed by full-dose EMA-CO for 1 cycle then stereotactic radiosurgery. Her chest tube was removed after 25 days and she was discharged with continuation of EMA-CO for 4 additional cycles. Her β-HCG levels initially decreased, then rose. She was switched to etoposide, methotrexate, actinomycin-D, etoposide, cisplatin (EMA-EP) for 5 cycles. Her β -HCG levels again rose. She was transitioned to alternating cycles of paclitaxel/etoposide and paclitaxel/cisplatin. Despite this, her lung and brain metastases worsened. After her second cycle of etoposide/paclitaxel, she developed acute respiratory failure requiring intubation. Etiology of her acute hypoxemia was unclear, but was likely multifactorial with her baseline COPD and acquired chemotoxicity. She was managed conservatively with breathing treatments and broad-spectrum antibiotics. She underwent repeat stereotactic radiosurgery for recurrent brain metastases and was switched to carboplatin/paclitaxel. She was then hospitalized again after developing severe thrombocytopenia with a platelet count of < 10,000/mcL. She was unresponsive to platelet transfusions. She subsequently developed respiratory distress and was intubated and transferred to the medical intensive care unit. A bronchoscopy noted diffuse alveolar hemorrhage. On hospital day 7, she developed bilateral fixed, blown pupils. No spontaneous breathing effort was noted on mechanical ventilator and a head computed tomography (CT) showed a large left occipital, parietal, and intraventricular hemorrhage with effacement concerning for herniation syndrome. After discussing these findings and lack of meaningful intervention for her condition with her family, the decision was made to withdraw care. She was terminally extubated and died the same day.

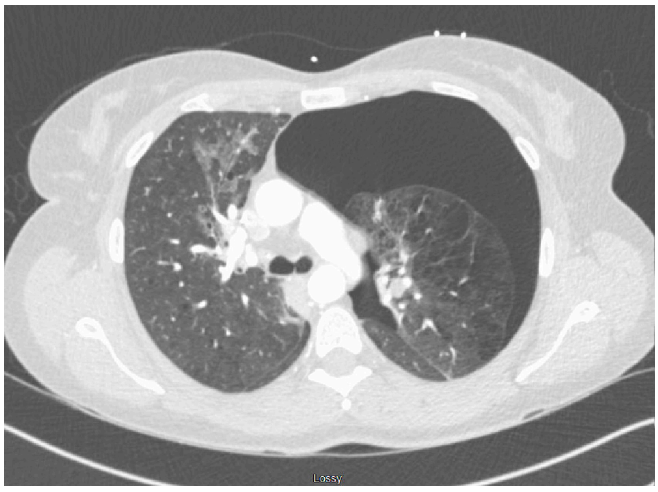

Fig. 1B. This CT pulmonary angiography demonstrates a large left-sided tension pneumothorax with mediastinal shift.

2.2. Case 2

A 26 year-old G1P1001 female presented with abnormal uterine bleeding 11 months after her term vaginal delivery. She had a positive pregnancy test, with a β-HCG level of 605 mIU/mL. A repeat β-HCG level in 48 h was 694 mIU/mL. A TVUS showed no evidence of an intrauterine pregnancy. She was treated with methotrexate for possible ectopic pregnancy. Her β-HCG level plateaued in the 500 s-600 s mIU/mL and a second dose of methotrexate was administered. Again, her β-HCG level did not fall appropriately. A chest X-ray (CXR) was then performed noting a 4.6 cm mass in the left lower lobe with scattered bilateral pulmonary nodules. She underwent a dilation and curettage with benign pathology noted. Staging CT scans showed brain and pulmonary metastases, along with several PAPs, the largest of which measured up to 4 cm (Fig. 2A). She was admitted to the hospital due to her significant risk for spontaneous rupture and subsequent rapid exsanguination. Interventional Radiology (IR) was consulted and recommended emergent embolization, given the size of the pseudoaneurysms and the high risk of rupture. However, given the patient's Stage IV GTN and WHO score of 13, the risk of complications during and following the embolization procedure delaying initiation of mortality-reducing chemotherapy was balanced against the risk of rupture and catastrophic bleeding. The decision was made to proceed with low-dose induction chemotherapy with EP, during which the patient remained hospitalized and was closely monitored by a multidisciplinary team including Gynecologic Oncology,

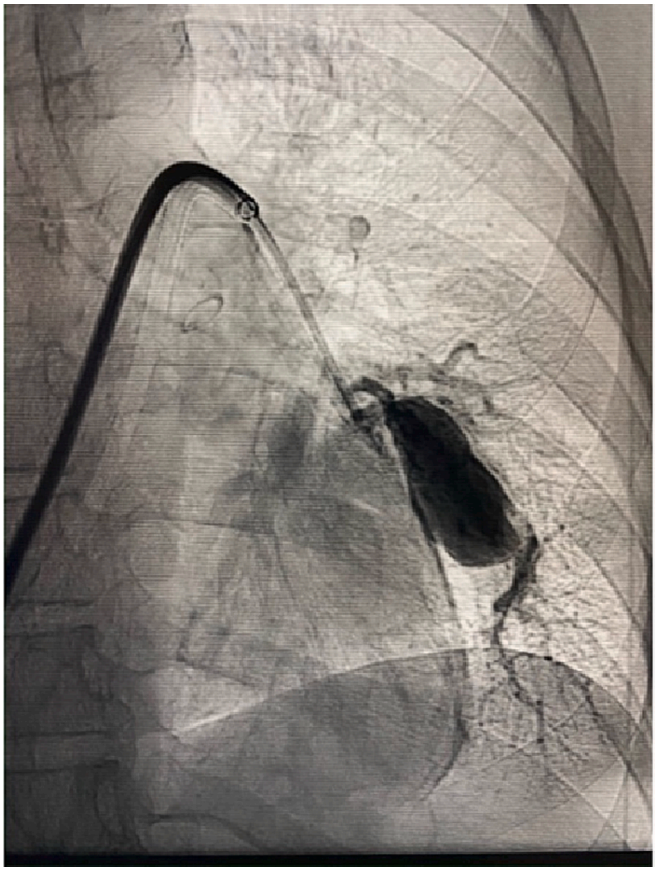

Fig. 2A. This illustrates the 4 cm pseudoaneurysm present prior to embolization at risk of spontaneous rupture and rapid exsanguination.

IR, and Thoracic Surgery. She successfully completed 2 cycles of EP and underwent IR pulmonary arteriogram with left lower lobe pseudoaneurysm embolization (Fig. 2B). She tolerated the procedure well and proceeded to full-dose chemotherapy with EMA-CO. She underwent a second embolization procedure for her left pulmonary vein pseudoaneurysm. After 8 cycles of EMA-CO, her β-HCG level decreased to 14 mIU/mL. She subsequently had a slowed drop in her β-HCG levels with cycles 9–12. Thus, she underwent 3 additional cycles of EMA alone. Her β-HCG nadired at 3 mIU/mL after cycle 15. Her β-HCG one month after completion of treatment was 2 mIU/mL, and 6 months later was 2 mIU/mL, indicating continued remission.

3. Discussion

Oncology patients are susceptible to numerous pulmonary complications as a result of not only their underlying cancer, but also from the antineoplastic therapies they receive. High-risk GTN, corresponding to a WHO score of ≥ 7, is treated with EMA-CO (Deng et al., 2013). These agents have known adverse pulmonary consequences. The incidence of pulmonary toxicity is estimated at $< 1\%$ with cyclophosphamide (Twohig and Matthay, 1990) and at about 8% with methotrexate (Courtney Broaddus et al., 2021). Lung toxicity is rarely reported with actinomycin D and etoposide, other than in the context of hypersensitivity reactions. However, rare reports of etoposide-induced pneumonitis have postulated that the pulmonary injury observed occurs from concurrent use with other agents, such as methotrexate or cyclophosphamide (Zimmerman et al., 1984), as etoposide has been shown to increase intracellular levels of methotrexate. Drug-induced lung injury has been well described with paclitaxel, the most common manifestation being interstitial pneumonitis (Bielopolski et al., 2017), with an incidence rate ranging from 0.73% to as high as 13% (Vahid and Marik, 2008).

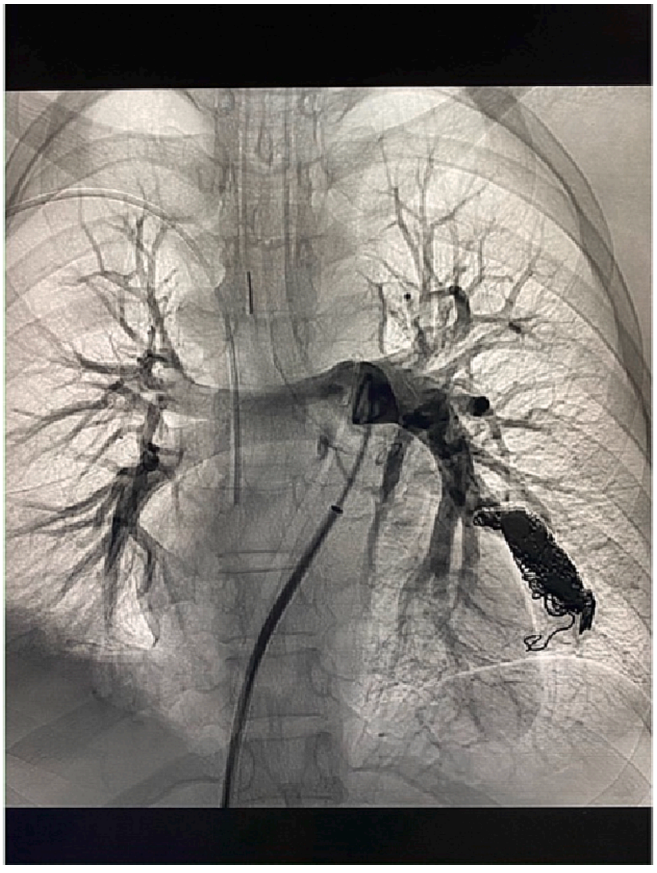

Fig. 2B. This illustrates the management of the pseudoaneurysm following interventional embolization.

In addition to pulmonary toxicity from the chemotherapeutic agents themselves, GTN can present with extensive pulmonary disease burden, which can lead to complications like massive hemorrhage, PTX, and respiratory failure. In the literature, a handful of reports of these rare pulmonary complications have been described. A case of bullae-forming choriocarcinoma with PTX formation was reported in South Korea (Hyun et al., 2015). A case of intermediate trophoblastic disease presenting as PTX was reported in 2015 (Multani et al., 2015). Choriocarcinoma as an etiology for PAP was reported in Singapore (Wee et al., 2017). A case of PAVM in the setting of GTN presenting with PTX was reported in 2022 (Chinthareddy et al., 2022). Rarer still, however, are reports on acute pulmonary events that occur in the setting of chemotherapy initiation. In 1992, Biran et al reported spontaneous PTX in a woman with GTN during induction of chemotherapy (Biran et al., 1992). A case of pulmonary arteriovenous fistula found after completion of chemotherapy for choriocarcinoma was reported in 2003 (Choi et al., 2003). Two cases of PAVM that developed after chemotherapy for non-thoracic malignancies with pulmonary metastases were reported in 2007, though these were not in the setting of GTN (Bruzzi et al., 2007).

In Case 1, our patient had lung metastases, underlying COPD, and accumulated pulmonary toxicity from chemotherapy that resulted in multiple hospitalizations for pulmonary emergencies. In her first hospitalization, pulmonary scarring and associated lung stiffness resulting from antineoplastic agents likely led to bleb formation and PTX. Alternatively, as previously described by Biran et al, chemotherapy-induced tumor lysis led to bleb formation then PTX (Biran et al., 1992). In her subsequent hospitalization, chronic chemotoxicity and her pre-existing pulmonary disease, likely led to mucus plugging with associated inflammation, emphysema, and lung collapse, ultimately leading to acute respiratory failure requiring intubation. During her last hospitalization, chemotherapeutic myelosuppression in combination with hypothesized immune-mediated thrombocytopenia led to bronchoalveolar hemorrhage, then intracerebral hemorrhage, which ultimately resulted in death. Throughout her course, the decision to continue chemotherapy was weighed against her risk of continued pulmonary injury.

In Case 2, our patient was found to have extensive lung metastases with PAP formation noted on CT. This could perhaps have occurred as a sequela of the hematogenous spread observed in GTN. It has been reported that pulmonary metastases of GTN are supplied by the pulmonary artery (Green et al., 1973). Increased volume or turbulence through the artery and its branches could cause increased arterial wall pressure and aneurysm or pseudoaneurysm formation. Additionally, hematogenous invasion and spread through angiogenesis and the formation of arteriovenous fistulas creating aberrant and weakened arterial walls, as described in previous reports, could have contributed to PAP formation (Wee et al., 2017); (Choi et al., 2003). She was immediately attended to by a multidisciplinary team, and the decision to proceed with chemotherapy was weighed against her high risk of catastrophic rupture and rapid exsanguination.

In these two cases, we identified the following key steps that we believe were critical in the management of these patients. First, we recommend rapid work-up and staging of GTN once metastases is suspected on exam or imaging. In Case 2, our patient was treated with methotrexate a second time for what was presumed to be an ectopic pregnancy before a CXR was considered and obtained. This perhaps could have delayed her diagnosis. Delay in staging and scoring can further delay life-saving chemotherapy, an urgent necessity for these patients. Second, we recommend consideration of inpatient administration of chemotherapy in patients with high WHO scores, particularly with pulmonary disease or solid organ involvement, at least initially. We further recommend considering low-dose induction EP prior to EMA-CO in patients with significant lung and brain disease burden as it has been shown to decrease the risk of early death by tempering the effect of tumor lysis and hemorrhage (Alifrangis et al., 2013). Conservative measures proved to be the mainstay of our strategies. Examples include,

holding antineoplastic agents when the etiology of the pulmonary issues are possibly chemotherapy related, judicious use of corticosteroids to reduce inflammation and pneumonitis, and utilizing bronchodilators and respiratory therapy interventions. Other key steps included early transfer to an intensive care unit if indicated, early intubation when a significant oxygen requirement develops, and involvement of multidisciplinary teams when needed. Flexibility in altering regimens to reduce pulmonary injury, once it was deemed safe to resume chemotherapy, also proved important.

Sequalae of pulmonary injury secondary to anti-neoplastic agents can present in a similar and nonspecific fashion to those secondary to the presence of pulmonary metastases. It is often thought of as a diagnosis of exclusion, though consistent criteria for chemotherapy-induced lung disease has not been established (Vahid and Marik, 2008). Therefore, the true incidence of lung injury that is directly related to chemotherapy versus a consequence of disease cannot always be clearly elicited. Subsequently, the clinician will often have to take symptom-management approaches rather than being able to identify the true etiology of the event. Another limiting factor is the lack of centralized care for a rare disease such as GTN. A paucity of GTN centers with regional differences in incidence can lead to inconsistent treatment decisions and the need to make ad-hoc management choices as these encounters are rare. Thus, it remains important to illuminate rarely seen complications and their management in the hopes of providing guidance to clinicians and in managing GTN pulmonary sequelae.

Consent

Informed consent was obtained from the patients described herein.

Author contribution

The authors confirm contribution to the case series as follows: case series conception, analysis, and drafting: H. Khadraoui; drafting of case series and revising it critically for important intellectual content, approved the version to be published: C. Billingsley; revision for critically important intellectual content and approved the version to be published: TJ. Herzog; revision for critically important intellectual content and approved the version to be published: A. Jackson. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest statement

The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript EXCEPT as outlined in the above conflict of interest forms.

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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