Case report

Subarachnoid hemorrhage in a postpartum mother: A rare manifestation of an uncommon disease

Oraianthi Fiste a,*, 1, Evaggelos Mavrothalassitis a,*, 1, Christos Markellos a, Alexandros Rodolakis b, Flora Zagouri a, Meletios-Athanasios Dimopoulos a, Michalis Liontos a

a Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
b Division of Gynecologic Oncology, 1st Department of Obstetrics and Gynaecology, Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece

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ABSTRACT
Subarachnoid hemorrhage, a potentially lethal medical emergency, represents an atypical clinical manifestation of gestational choriocarcinoma. We present the uncommon case of a 31-year-old primigravid female who presented with cerebral onotic aneurysmal rupture, five weeks after vaginal delivery. Albeit the absence of neurological deficits after endovascular embolization, the patient was soon readmitted, complaining of fever, abdominal pain, and fetid lochia, all suggestive of puerperal endometritis. Upon a comprehensive diagnostic work-up, she was subsequently diagnosed with metastatic choriocarcinoma. Early initiation of multitagent chemotherapy, despite being in septic shock associated with Escherichia coli bacteremia, resulted in favorable prognosis.

1. Introduction

Nontraumatic subarachnoid hemorrhage (SAH) has a wide range of potential underlying etiologies including cerebral venous thrombosis, vascular malformations, vasculitides, arterial dissection, infections (myotic aneurysms), and malignancies (onotic aneurysms) (Cuvinciuc et al. (2010)). Intracranial hemorrhage associated with neoplasia, which is commonly attributed to tumor emboli on the peripheral branches of the blood vessel wall, (ii) aneurysmal changes, and (iii) rupture (Wang et al. (2013)), represents a rather rare entity. Indeed, relatively few cases have been previously reported in the literature. Cardiac myxoma and myxosarcoma, lung carcinoma, and choriocarcinoma are among the most prevalent causes of neoplastic aneurysms (Wang et al. (2013)).

Herein, we report the case of a young female who presented with spontaneous SAH during the subacute postpartum period and was eventually diagnosed with high risk, metastatic choriocarcinoma with cerebral, splenic, and pulmonary metastases. Furthermore, we discuss both the clinical course and outcome of her quite challenging disease, in parallel with a brief literature report.

2. Case presentation

A 31-year-old, non-smoking, Caucasian female, with no past medical history, experienced a sudden-onset severe headache accompanied with left arm numbness five weeks postpartum. The cranial computed tomography (CT) scan, performed in the emergency department of a regional rural hospital, was suggestive of grade 2 (Hunt and Hess scale) SAH. No prior history of head injury was elicited and the courses of both pregnancy and vaginal delivery were uncomplicated. She admitted to the neurosurgical ward and the subsequent digital subtraction angiography (DSA) revealed a ruptured right middle cerebral artery aneurysm, measuring 3.5 mm, which was successfully treated with perecutaneous endovascular coil embolization, without permanent neurological deficits.

Almost one month later, on postpartum day 61, the patient admitted once again at the same hospital with suspected postpartum endometritis, as she reported fever, chills, constant abdominal pain, and purulent uterine discharge, but denied urinary or respiratory symptoms. Samples for blood culture were obtained prior the initiation of empiric antibacterial therapy, consisting of piperacillin/tazobactam combined with

* Corresponding author at: Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

E-mail addresses: ofiste@med.uoa.gr (O. Fiste), krism@med.uoa.gr (C. Markellos), arrodolak@med.uoa.gr (A. Rodolakis), fzagouri@med.uoa.gr (F. Zagouri), me_dimop@med.uoa.gr (M.-A. Dimopoulos), mlionto@med.uoa.gr (M. Liontos).

1 O.F. and E.M. contributed equally to this work and both should be considered first author.

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vancomycin and azithromycin. However, within four days, the patient developed sepsis, which abruptly progressed to septic shock, thus she was transferred to the intensive care unit of our university hospital.

On admission, her body temperature was 38.3 °C, invasive blood pressure was 90/65 mmHg requiring crystalloid and vasopressor, heart rate was 135/min, and arterial oxygen saturation was 82 %. Physical examination revealed mild disorientation, slower capillary refill, and coarse rales especially over the lower lung zones. The sequential organ failure assessment (SOFA) score was 4 (15 points on the Glasgow Coma Scale, norepinephrine < 5 μg/kg/min, acute respiratory distress syndrome with PaO2/FiO2 < 400 mmHg, platelets 65 × 103 /μL, bilirubin 0.89 mg/dL, and creatinine 0.54 mg/dL). Several laboratory tests were abnormal including hemoglobin of 6.8 g/dL, u-dimers of 4.58 μg/mL (normal range < 0.5), C-reactive protein 322 mg/L, and fibrinogen concentration 6.4 mL, whilst blood culture showed E. coli sensitive to the administered treatment with piperacillin/tazobactam.

Also, chest radiography, performed upon admission, demonstrated several pulmonary nodules up to 40 mm, confirmed by the subsequent CT of the thorax. Given the recent delivery and the presence of metastatic lung nodules, further diagnostic work-up was performed with the suspicion of gestational trophoblastic neoplasia. The transvaginal ultrasound described an enlarged uterus with complete loss of zonal anatomy and the abdominal magnetic resonance imaging (MRI) confirmed not only the presence of an enlarged heterogeneous myometrial mass, but also the presence of a single splenic metastatic lesion. Serum β-human chorionic gonadotrophin (β-hCG) was 232,085 mIU/mL (normal range < 5 in non-pregnant patients) suggesting the possibility of a choriocarcinoma.

Suction evacuation and curettage was performed and pathology report confirmed choriocarcinoma diagnosis. According to the International Federation of Gynecology and Obstetrics (FIGO) modified WHO prognostic scoring system for gestational trophoblastic disease (GTD), our patient obtained a total score of 12 (31 years old, term pregnancy, <4 months interval from pregnancy to chemotherapy, β-hCG = 97,521 mIU/mL, one day after uterine evacuation, >8 metastatic lesions, including brain metastasis occurring as an oncotic aneurysm, largest tumor lesion within the lung of 40 mm, whereas she was chemonaïve).

Therefore, she was diagnosed with metastatic choriocarcinoma at high risk of developing resistance to single-drug chemotherapy with either methotrexate or actinomyacin D. Taking into consideration not only the high survival rates even in high risk GTN, but also the patient’s young age and advanced disease, it was more than necessary to initiate a multiagent chemotherapy regimen without the risk of early mortality. Thus, we commenced low-dose etoposide (100 mg/m²) in combination with cisplatin (20 mg/m²), on days 1–2, for one cycle, and upon her clinical improvement one week later, she immediately started EMA/CO regimen (etoposide, methotrexate, and actinomyacin D, alternating on a weekly basis with cyclophosphamide and vincristine), of which she completed six cycles before β-hCG levels plateaued above normal.

Hence, restaging with MRI of the brain and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan was conducted and indicated decreased, in size, pulmonary nodules and a uterine mass, grade 2 fatigue. Noteworthy, in order to prevent any unplanned pregnancy during antineoplastic treatment and the first year of follow-up, we recommended the use of male condoms, considering the lack of comprehensive guidance regarding contraceptive methods in this setting. Figs. 1 and 2 depict the treatment timeline and corresponding biomarker and imaging findings, respectively.

3. Discussion

Gestational trophoblastic disease (GTD), a pregnancy-related entity, encompasses a wide spectrum of benign to malignant tumors, including hydatidiform mole, either complete or partial, invasive mole, placental site trophoblastic tumor, epithelioid trophoblastic tumor, and choriocarcinoma (Seckl et al. (2010)). Apart from the history of a prior molar pregnancy, two distinct age groups, early adulthood and age older than 40 years in particular, are linked to higher risk of gestational trophoblastic neoplasia (GTN) (Goldfarb et al. (2020)). Despite representing the most malignant among GTNs, choriocarcinomas are curable even in advanced stage (Seckl et al., 2010). They are rare tumors usually following a complete molar pregnancy (hydatidiform mole), but also arising after ectopic pregnancy, spontaneous nonmolar abortion, or scarcely after a term pregnancy (Seckl et al., 2013). Indeed, post-term gestational choriocarcinomas occur in approximately 1 in 150,000–160,000 full-term pregnancies, have the propensity to present with extensive disease including cerebral and liver metastases, and are associated with poor outcome, given the lower response rates to chemotherapy compared with other GTNs (Ghaemmaghami and Karimi (2008)).

In regard to their clinical presentation, irregular vaginal bleeding, with or without pelvic or abdominal pain, is the most common symptom; yet menstrual abnormalities are not universal (Seckl et al., 2010). As highly vascular neoplasms, choriocarcinomas are characterized by their invasive nature and highly metastatic potential, thus can affect several organ systems presenting with varying symptoms and signs (Mangla et al. (2017)). In a systematic review of 121 cases with unusual presentation, 20.7 % displayed cardiopulmonary, 18.4 % gastrointestinal, and 17.8 % neurological manifestations (Mangla et al. (2017)). Such findings are in parallel with the published literature, as brain metastases are involved in 10–20 % of choriocarcinoma patients (Berkowitz et al. (2007)), who are automatically categorized by FIGO as stage IV (Seckl et al., 2013).

Intracranial hemorrhage, as a complication of ruptured neoplastic cerebral aneurysms, remains a rare, thus challenging from a differential diagnostic standpoint, neurological sequela of choriocarcinoma (Borella et al. (2022)). Since Vaughan and Howard reported the first case of oncocytic aneurysm related to metastatic choriocarcinoma, in 1962 (Vaughan and Howard, 1962), only 30 cases associated with GTN have been described (Borella et al., 2022). From pathogenesis to therapeutic approach, oncocytic aneurysms remain a source of controversy. Among several proposed mechanisms, vascular occlusion by tumor cell aggregates followed by penetration and destruction of vessel wall is commonly perceived to be the most important pathophysiological pathway in aneurysm formation (Sedat et al. (2007)).

Notwithstanding that <6 % of cerebral aneurysms arise from the distal middle cerebral arteries (Joo et al., 2007), neoplastic aneurysms are frequently located in their distal branches (Borella et al., 2022). Brain MRI remains the gold standard imaging modality for cerebral metastases assessment (Seckl et al., 2013), while DSA may be essential for the accurate detection and characterization of oncocytic aneurysms (Yoon et al. (2007)). Due to their rarity, treatment strategy has yet to be standardized. Endovascular coil embolization and occlusion, open surgery, chemotherapy with or without whole-brain radiotherapy (WBRT) have all been proposed (Zheng and Zhang (2015)).

Undoubtedly, early initiation of chemotherapy is of utmost
importance, taking into account not only the rapid hematogenous spread of choriocarcinomas but also their chemosensitivity (Wang et al., 2018). More specifically, EMA/CO multidrug regimen results in high complete remission rates conferring an overall survival rate of almost 90%, even if widespread metastatic disease is present (Dadlani et al., 2010). In the rather uncommon case of chemoresistance or relapse (~20%), other combinational chemotherapy could be considered; EP/EMA (etoposide and cisplatin alternated weekly with etoposide, methotrexate, and actinomycin D), TE/TP (paclitaxel and etoposide followed by paclitaxel and cisplatin), VIP (etoposide, ifosfamide, cisplatin), and BEP (bleomycin, etoposide, and cisplatin), whilst high-dose chemotherapy and stem cell transplant may be offered as a rescue therapy (Seckl et al., 2013). Over recent years immune checkpoint inhibition has emerged as a promising treatment option for refractory disease, given the intense programmed death-ligand 1 (PD-L1) immunoreactivity of choriocarcinomas (Seckl et al., 2013). Over recent years immune checkpoint inhibition has emerged as a promising treatment option for refractory disease, given the intense programmed death-ligand 1 (PD-L1) immunoreactivity of choriocarcinomas (Seckl et al., 2013). Over recent years immune checkpoint inhibition has emerged as a promising treatment option for refractory disease, given the intense programmed death-ligand 1 (PD-L1) immunoreactivity of choriocarcinomas (Seckl et al., 2013). Over recent years immune checkpoint inhibition has emerged as a promising treatment option for refractory disease, given the intense programmed death-ligand 1 (PD-L1) immunoreactivity of choriocarcinomas (Seckl et al., 2013).

4. Conclusion

In conclusion, our case presents a female young patient who was diagnosed with post-gestational metastatic choriocarcinoma after the occurrence of oncocytic aneurysmal SAH. Despite her rather complicated disease course, she remains alive 21 months post diagnosis. Choriocarcinoma should always be ruled out in any patient with unexplained hemorrhagic manifestations, especially those of reproductive age, as early diagnosis may lead to prompt curative treatment, thus optimal outcome.

Ethics

No ethical approval was required for this manuscript.

Patient consent for publication

Written informed consent has been obtained from the patient to publish this paper.

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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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