Case report

Pulmonary arterial venous malformations as primary manifestation of gestational trophoblastic neoplasia

Abigail Cain*, Edward Kost, Kevin Hall, Keeley Bell, Erin Mankus, Amanda Murray, Georgia McCann

University of Texas at San Antonio Health Science Center Long School of Medicine. 7703 Floyd Curl Drive, San Antonio, TX 78229, United States

1. Introduction

Gestational trophoblastic disease (GTD) includes a spectrum of tumors, both benign and malignant, with various biologic behaviors and different potentials for metastases. GTD encompasses complete and partial hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). The last four are persistent forms of GTD that are referred to as gestational trophoblastic neoplasia (GTN) and have the potential to metastasize.

GTN occurs more frequently after complete and partial molar pregnancies at rates of 15–20% and < 5%, respectively (Lurain, 2010). However, only 50% of GTN cases follow molar pregnancies, the remainder occurring after spontaneous abortion, ectopic pregnancies, or even term pregnancies (Ngan et al., 2018). Most patients with GTN present with abnormal vaginal bleeding but they can also present with bleeding from metastatic sites.

Arteriovenous malformations (AVMs) are abnormal connections between the arteries and veins that bypass the capillary system. AVMs in the uterus have been noted in patients with GTN and can be a possible cause of life-threatening hemorrhage. One explanation for the relationship between AVMs and GTN is by a disorganized trophoblastic proliferation and increased angiogenesis caused by high levels of human chorionic gonadotropin (Touhami et al., 2014).

GTN has been associated with uterine AVMs and with pulmonary AVMs in other case reports. However, to our knowledge, hepatic and brain AVMs have not been described in association with GTN.

2. Case

This is the case of 33-year-old Caucasian female, G4P3013. She was initially diagnosed with pregnancy of unknown location at an outside facility. She was treated with two doses of methotrexate in April 2018 by different providers. Her HCG levels were slow to decrease but ultimately normalized without additional treatment.

She was referred to our hospital for a pulmonary AVM in June 2018. The gynecology team was consulted for elevated HCG levels. Her HCG at the time of this admission was 66 mlU/mL, then spontaneously decreased to 31 mlU/mL with onset of vaginal bleeding consistent with menses. During this admission, the pulmonary team embolized the pulmonary AVMs and the patient was discharged home. She was then followed with weekly quantitative HCG levels until July 2018 when they were noted to be 3 mlU/mL (considered to be negative for our lab). The patient was advised to get monthly HCGs thereafter but was lost to follow up shown in Fig. 1.

In October 2018 she presented to our gynecology emergency room with right shoulder pain, abdominal pain and shortness of breath. She was noted to have abdominal tenderness with rebound on exam. Quantitative beta HCG level was 1011 mlU/mL and transvaginal ultrasound demonstrated free fluid in her pelvis. Her labs at the time were also notable for transaminitis (AST 193 U/L and ALT 270 U/L). The patient was taken to the operating room emergently for diagnostic laparotomy due to concern for ruptured ectopic pregnancy. Intraoperatively there was 650 cc hemoperitoneum, however the fallopian tubes were normal without any evidence of ectopic pregnancy. The liver was the source of hemoperitoneum, and general surgery was consulted intra-operatively for ruptured hepatic subcapsular

---

* Corresponding author at: 4123 Legend Bend Drive, San Antonio, TX 78230, United States.
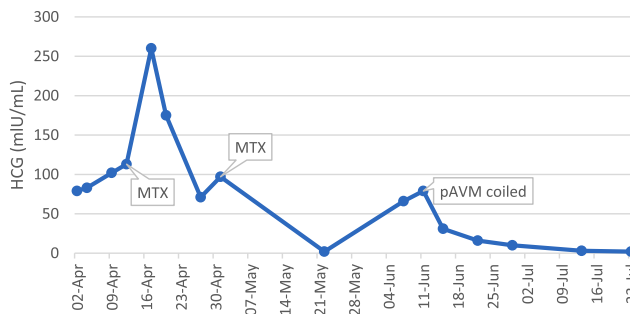*E-mail address:* caina3@uthscsa.edu (A. Cain).

Fig. 1. This shows our patient's HCG levels overtime during her first presentation. Her first and second dose of methotrexate (MTX) have been note. The date of coiling of her pulmonary arterior venous malformaiton (pAVM) is also noted.

Fig. 2. This shows our patient's HCG levels overtime during second presentation. The date of her dilation and curretage is marked. The two rounds of induction chemotherpay are marked as EC#1 and EC#2. The first round of EMACO is also marked.

hematoma. There was no active bleeding at that time. Post-operative CT scan noted several foci of active extravasation in both hepatic lobes concerning hepatic AVMs. Computer tomography angiogram (CTA) of the head was significant for a left parietal sub arachnoid hemorrhage. Cerebral angiography noted a left parietal micro AVM. During this evaluation her quantitative HCG levels were trended daily (1011 > 748 > 861 > 1185 mlU/mL). There was extensive multi-disciplinary discussion regarding differential diagnosis. The transplant team was concerned for and tested her for hereditary hemorrhagic telangiectasia (HHT). All imaging was reviewed with radiology, who felt that the radiologic findings were most consistent with HHT and not GTN. Patient then underwent dilation and curettage due to abnormally rising HCG. The endometrium was benign in appearance and surgical pathology was secretory endometrium. HCG on post-operative day #1 was 2186 mlU/mL and continued to rise thereafter. Gynecologic Oncology felt strongly that above constellation of findings was consistent with GTN and planned to treat accordingly. WHO score was calculated at 8.

Given the multiple AVMs and previous spontaneous hemorrhage, the patient was felt to be at high risk of hemorrhage from treatment. For this reason, she was received two cycles of induction chemotherapy with cisplatin (20 mg/m^2) and etoposide (100 mg/m^2) (EP) regimen. She remained in the intensive care unit for the first cycle of induction chemotherapy to monitor bleeding. She was then transferred out of the ICU and remained inpatient for the subsequent cycle of induction chemotherapy. We assumed the left parietal AVM was GTN and high-dose methotrexate infusion (1000 mg/m^2) was given as part of the etoposide (100 mg/m^2), methotrexate, actinomycin D (0.5 mg), cyclophosphamide (600 mg/m^2), vincristine (1 mg/m^2) (EMA-CO) regimen. She received a total of nine cycles of EMA-CO between October 2018 and February 2019. She had a single one-week delay in treatment secondary to fever in January 2019. She completed one year of surveillance HCGs which all were < 2 mlU/mL between 10/2018 and 2/2019. A trend of her HCG levels upon this presentation and throughout treatment until they normalized is available in Fig. 2.

3. Discussion

Approximately 1 in 40,000 pregnancies undergo malignant transformation to become choriocarcinoma or a placental site tumor requiring further treatment (Ngan et al., 2018). Chemotherapy is an effective treatment for GTN and has allowed complete remission in greater than 95% of patients with gestational trophoblastic tumors, even when there is evidence of metastatic disease (Ngan et al., 2018). Chemotherapy has been shown to decrease mortality in these patients. However, their prognosis can be compromised due to complications associated with hemorrhage from these vascular sites. In this case we have an example of a patient with severe life-threatening bleeding from a hepatic AVM.
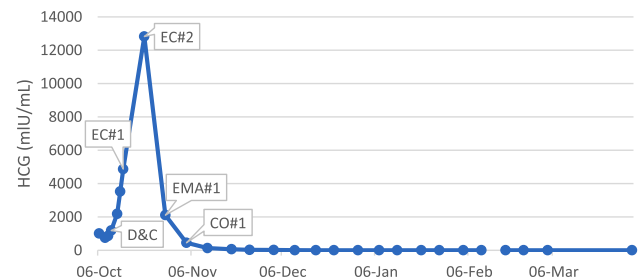
The effect of tumor-derived HCG on angiogenesis is well documented (Berndt et al., 2006). Uterine AVMs are relatively common and often managed with uterine artery embolization in cases of heavy bleeding. GTN metastases at other anatomical sites may also be highly vascular and have the potential to form AVMs that can lead to life-threatening bleeding (Choi et al., 2003; Green et al., 1973). In this current case a patient developed severe bleeding from a ruptured subcapsular hematoma due to hepatic AVMs. This developed after initial normalization of HCG. However, the patient was lost to follow-up thereafter making interpretation of HCG difficult for this time period.

Most pulmonary AVMs occur in patients with hereditary hemorrhagic telangiectasia in whom there are usually multiple. HHT is an autosomal dominant disease that usually presents with recurrent epistaxis in up to 90% of cases and 80% of patients will have telangiectasias on buccal surface and on fingertips resembling petechiae. HHT's initial presentation is typically in childhood with recurrent epistaxis. The presence of pulmonary, hepatic, and cerebral AVMs in HHT is less common, occurring in 50%, 30%, and 10% respectively (Govani and Shovlin, 2009). A clinical diagnosis of HHT can be made using the Curacao criteria that consist of 4 signs: 1. Recurrent, spontaneous epistaxis, 2. Visceral AVM that can be pulmonary, hepatic, or cerebral, 3. Mucocutaneous telangiectasias at characteristic sites including the nose, fingers, and oral cavity, and 4. First-degree relative with HHT (Dupuis et al., 2020). In contrast, GTN usually presents following a pregnancy with abnormal vaginal bleeding and a plateau or rise of HCG levels. The most common site of metastatic disease is the lungs, but in advanced disease patients can have hepatic and brain metastasis. Also, rarely GTN can cause uterine AVMs.

In our case the patient presented with AVMs in multiple sites (pulmonary, hepatic, and brain). However, she lacked significant family history, had no reported history of spontaneous epistaxis and lacked mucocutaneous telangiectasias. In fact, she only met criteria number two (visceral AVMs) of the Curacao criteria. However, her history of a spontaneous abortion followed by abnormal vaginal bleeding and persistently elevated HCG levels lead to the diagnosis of GTN.

Pulmonary AVMs due to GTN are a rare occurrence with only two case reports identified and only one of which was available in English. Our patient's HCG normalized in July 2018, three weeks after her pulmonary AVM had been coiled. It is possible that coiling of her pulmonary AVM resulted in trophoblastic cell death and resulted in temporary normalization of HCG levels.

We decided to proceed with induction low-dose EP per National Comprehensive Cancer Network (NCCN) guidelines due to her extensive metastatic disease and risk of hemorrhage. Patients with extensive metastatic disease are at risk of sudden tumor collapse and severe bleeding when initially treated with multi-agent chemotherapy (Ngan et al., 2018). Initial management with induction low-dose EP significantly decreases risk of early deaths in patients with widely metastatic disease (Alifrangis et al., 2013). Furthermore, we considered whole brain radiation for treatment of the cerebral AVM. However, the

patient needed to start therapy emergently because of hemorrhage risk and she had small volume cerebral disease. We did give this patient EMA-CO with high dose methotrexate as this facilitates the drug's ability to cross the blood–brain barrier and treat brain metastasis (Ngan et al., 2018).

In patients with abnormal HCG levels and a pulmonary AVM without meeting any other clinical criteria for HHT there should be heightened concern for GTN as the diagnosis. Unfortunately, in our case the patient was lost to follow up after her pulmonary AVM was coiled and re-presented after the disease had spread. However, she had an excellent response to induction chemotherapy followed by EMA-CO.

Author contributions

Abigail Cain

Drafting and editing case report, provided oncologic care to patient.

Georgia McCann

Drafting, review, and edited case report provided oncologic care to patient.

Edward Kost

Review of case report and provided oncologic care to patient.

Hall Kevin

Review of case report and provided oncologic care to patient.

Keeley Bell

Review of case report and provided oncologic care to patient.

Amanda Murray

Review of case report and provided care to patient.

Erin Mankus

Review of case report and provided care to patient.

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.

References

Alifrangis, C., Agarwal, R., Short, D., et al., 2013. EMA/CO for high-risk gestational trophoblastic neoplasia: Good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J. Clin. Oncol. 31, 280–286.
Berndt, S., Perrier D'Hauterive, S., Blacher, S., et al., 2006. Angiogenic activity of human chorionic gonadotropin through LH receptor activation on endothelial and epithelial cells of the endometrium. FASEB J. 20, 2630–2632.
Choi, S.H.G.J., Kim, H.C., Im, J.G., 2003. Pulmonary arteriovenous fistulas developed after chemotherapy of metastatic choriocarcinoma. Am. J. Roentgenol. 181, 1544–1546.
Dupuis, O., Delagrange, L., Dupuis-Girod, S., 2020. Hereditary haemorrhagic telangiectasia and pregnancy: a review of the literature. Orphanet J. Rare Dis. 15.
Govani, F.S., Shovlin, C.L., 2009. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. Eur. J. Hum. Genet. 17, 860–871.
Green, J.D.C.T., Hammond, C.B., Johnsrude, I.S., 1973. Angiographic demonstration of arteriovenous shunts in pumlonary metasttic choriocarcinoma. Radiology 108, 67–70.
Lurain, J.R., 2010. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am. J. Obstet. Gynecol. 203, 531–539.
Ngan, H.Y.S., Seckl, M.J., Berkowitz, R.S., et al., 2018. Update on the diagnosis and management of gestational trophoblastic disease. Int. J. Gynecol. Obstetr. 143, 79–85.
Touhami, O., Gregoire, J., Noel, P., Trinh, X.B., Plante, M., 2014. Uterine arteriovenous malformations following gestational trophoblastic neoplasia: a systematic review. Eur. J. Obstetr. Gynecol. Reprod. Biol. 181, 54–59.