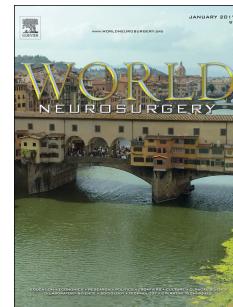


Accepted Manuscript

Recurrent Cerebral Hemorrhages In Normal Pregnancy Secondary to Mycotic Pseudoaneurysms Related to Choriocarcinoma

Crystal Jing Jing Yeo, MB BChir (Cambridge) PhD (Cambridge) MRCP(UK), Gavin W. Britz, MD, MBA, MPH, Suzanne Z. Powell, MD, R. Glenn Smith, MD PhD, Yi J. Zhang, MD



PII: S1878-8750(17)31703-5

DOI: [10.1016/j.wneu.2017.09.187](https://doi.org/10.1016/j.wneu.2017.09.187)

Reference: WNEU 6631

To appear in: *World Neurosurgery*

Received Date: 2 September 2017

Revised Date: 25 September 2017

Accepted Date: 26 September 2017

Please cite this article as: Yeo CJJ, Britz GW, Powell SZ, Smith RG, Zhang YJ, Recurrent Cerebral Hemorrhages In Normal Pregnancy Secondary to Mycotic Pseudoaneurysms Related to Choriocarcinoma, *World Neurosurgery* (2017), doi: 10.1016/j.wneu.2017.09.187.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: Recurrent Cerebral Hemorrhages In Normal Pregnancy Secondary to Mycotic Pseudoaneurysms Related to Choriocarcinoma

Authors:

Crystal Jing Jing Yeo, MB BChir (Cambridge) PhD (Cambridge) MRCP(UK)

Gavin W. Britz, MD, MBA, MPH

Suzanne Z. Powell, MD

R. Glenn Smith, MD PhD

Yi J. Zhang, MD

Affiliations:

Yeo, Britz, Powell, Smith and Zhang are affiliated with the Houston Methodist Neurological Institute, Texas Medical Center

Corresponding Author:

Crystal Jing Jing Yeo

Phone: 2818328970

Email: crystaljjyeo@cantab.net

The manuscript has not been previously published in whole or in part or submitted elsewhere for review.

Key Words: choriocarcinoma, mycotic aneurysms, cerebral angiogram, cerebral hemorrhages

Abstract 247 words

Abstract

Background: Choriocarcinoma coexisting with or after normal pregnancy is extremely rare. To our knowledge, our case report is the first time cerebral mycotic pseudoaneurysms from choriocarcinoma have been proven angiographically.

Case Description: A 38-week pregnant 26-year old woman presented with an acute left frontal hemorrhage. She underwent emergency Caesarian, followed by hematoma evacuation and resection of what grossly appeared to be a medium-sized arteriovenous malformation at the time of surgery. Angiogram before and after resection showed no obvious vascular pathology. One month later, she returned with status epilepticus and an acute parenchymal hematoma posterior to the surgical resection cavity was identified. Angiography showed a multilobulated pseudoaneurysm along the left middle cerebral artery. This was resected and found on histopathology to have choriocarcinoma within and around the blood vessels. Serum HCG levels increased daily. Pan CT showed a left lung lobular mass. The diagnosis was stage 4 WHO score 9 high risk metastatic choriocarcinoma requiring radiation followed by multi-agent chemotherapy. 2 weeks later, she had another seizure. Angiogram showed an unruptured pseudoaneurysm along the right posterior cerebral artery, which was embolized.

Conclusions: Metastatic choriocarcinoma is rarely considered during a viable pregnancy, but is almost always fatal if unrecognized. Early recognition enhances the chances of cure with chemotherapy. Arteriovenous malformations are typically considered in young women with intracerebral hemorrhages and have higher risk of rupture in pregnant women, but physicians should also be aware of metastatic choriocarcinoma and the development of mycotic aneurysms in peripartum women with intracerebral hemorrhages.

Introduction

Intracranial hemorrhage is a rare and devastating event in pregnancy, with significant risk of mortality and morbidity to both the mother and the child. The risk of hemorrhage is greatest during the third trimester and has been attributed to physiological changes in cerebral vasculature and autoregulation. Common causes of intracranial hemorrhage in pregnancy include arteriovenous malformation, aneurysms, pre-eclampsia, eclampsia, and cerebral venous thrombosis⁵. Of these, arteriovenous malformations are the most common⁸ and oncologic causes are among the rarest⁵.

Gestational choriocarcinoma arises from molar pregnancy in 57% of cases, normal pregnancy in 26%, and spontaneous or induced abortion in 17%⁷. Metastasis is widespread, with lungs, vagina, brain, kidney and ovaries being the most frequent sites. Cerebral metastases from choriocarcinoma have been rarely detected during the course of viable pregnancies, with only 4 cases reported in the literature^{2,4,6,9}. However, intracerebral metastases are the leading cause of death in metastatic choriocarcinoma. The malignant trophoblasts seed and invade the cerebral vessels and cause partial or total disruption of the vessel wall, causing pseudoaneurysm formation and subsequent hemorrhage⁷. While there are reports of metastatic choriocarcinoma with single cerebral neoplastic aneurysms or pseudoaneurysms in the literature, reports of multiple cerebral pseudoaneurysms resulting from metastatic choriocarcinoma confirmed by angiogram are rare^{3,7}.

We report a case of a pregnant woman who presented in her third trimester with recurrent intracerebral hemorrhages, which were confirmed on cerebral angiogram and pathology due to the formation of mycotic pseudoaneurysms from metastatic choriocarcinoma.

Case Report

Presentation and Examination

A 38-week pregnant G5P4003 26-year old woman presented with acute right hemiparesis, right homonymous hemianopia and aphasia. CT brain showed an acute left frontal hemorrhage with vasogenic edema and midline shift (Figure 1a). CT angiogram and Digital Subtraction Angiogram (DSA) of the anterior and posterior cerebral circulation before and after resection showed no obvious vascular pathology. She underwent an emergency Caesarian, followed by evacuation of hematoma and resection of what morphologically appeared to be a medium-sized arteriovenous malformation. Histopathology of the resected specimen showed hemorrhage with macrophage infiltration (Figure 2).

4 weeks later, she returned with status epilepticus and an acute parenchymal hematoma posterior to the surgical resection cavity. MRI showed enhancement of the lesion (Figure 1b). DSA of the anterior and posterior cerebral circulation

showed a multilobulated pseudoaneurysm along the distal middle cerebral artery (Figure 3a-c). This was completely resected and found on histopathology to have choriocarcinoma within and around the blood vessels (Figure 4). Serum Beta Human Chorionic Gonadotrophin (HCG) was elevated, consistent with choriocarcinoma. Pan-CT of the thorax, abdomen and pelvis detected a lobular mass in the left lung consistent with choriocarcinoma metastasis. Placental histopathology was negative for choriocarcinoma. The patient was diagnosed with Stage 4 WHO Score 9 high risk metastatic choriocarcinoma. She underwent elective hysterectomy and brain radiation followed by multi-agent chemotherapy including etoposide, vincristine and cyclophosphamide.

After another 2 weeks, she was re-admitted after another seizure. MRI brain showed another nodular area of enhancement in the right parietal-occipital area (Figure 1d and 1e). DSA of the anterior and posterior cerebral circulation now showed a 6.3mm fusiform pseudoaneurysm involving the bifurcation of the calcarine branch of the posterior cerebral artery (Figure 3d and 3e).

Embolization

Under roadmap guidance, a headway dual microcatheter was used to super-selectively catheterize the basilar artery and subsequently the distal right posterior cerebral artery calcarine branch carrying the pseudoaneurysm. Once the micro-catheter reached the segment immediately proximal to the aneurysm, micro-catheter angiograms confirmed the position. Through this system, Onyx®-34 liquid embolic material was carefully and precisely infused into the pseudoaneurysm lumen and achieved total occlusion (Figure 3f). Subsequent DSA showed no evidence of pseudoaneurysms in the left middle cerebral artery or the right posterior cerebral artery (Figure 5).

Histologic Examination

Histological examination of the initial resected left intracerebral hematoma specimen showed only brain tissue with hemorrhage and macrophage infiltration, with no histopathological evidence of choriocarcinoma (Figure 2).

Histological examination of the second specimen, from the resected left middle cerebral artery pseudoaneurysm showed atypical cells with mitotic figures and prominent nucleoli consistent with choriocarcinoma. Immunohistochemical staining was positive for beta-HCG, pan-cytokeratin, and GATA-3 in the choriocarcinoma cells (Figure 4).

Post-operative Course

The patient did not experience new symptoms after the embolization. After 1 year, the patient remains under oncologic follow up and continues to undergo multi-agent chemotherapy for a persistently elevated beta-HCG, despite no further evidence of new lesions. Her right hemiparesis, right homonymous hemianopia and aphasia have remained stable. Her recurrent seizures are being

controlled with multiple anti-epileptic medications including lacosamide, levetiracetam and clobazam.

Discussion

Cerebral metastases occur in 10–20% of patients with choriocarcinoma and are the major cause of death in these patients¹. Because the trophoblastic cells have an innate capacity to invade and erode vessels, patients with brain metastases can develop sudden neurological involvement due to mycotic pseudoaneurysms and intracerebral hemorrhages. These patients may present with headache, vomiting, hemiparesis, aphasia, seizures, or loss of consciousness.

Consistent with the finding of a solitary pulmonary nodule in this patient, pulmonary metastases are presumed to be the source of cerebral metastases, as pulmonary disease is present in almost all patients with cerebral metastases but only 55-70% of those without⁷. Metastatic choriocarcinoma without evidence of pelvic cavity lesions have been reported in the literature, suggesting that pelvic choriocarcinoma may regress after metastasis.

While choriocarcinoma is rare, it is important to consider it in the differential diagnosis of intracerebral hemorrhage in a pregnant woman, peripartum woman or a woman of child-bearing age. This is particularly true if a cerebral aneurysm or pseudoaneurysm is seen on angiogram. Cerebral angiograms and beta-HCG levels should be obtained in a pregnant or peripartum woman with intracerebral hemorrhage. Early diagnosis of choriocarcinoma can lead to early treatment with radiation therapy and multi-agent chemotherapy, which can be extremely effective and curative. Patients who undergo radiation and chemotherapy may have long-term survival rates as high as 80 percent¹. On the other hand, undetected and untreated cerebral metastasis from choriocarcinoma are fatal¹.

Conclusion

Physicians should be aware of metastatic choriocarcinoma and mycotic aneurysms in peripartum women with intracerebral hemorrhages. MRI, CT, DSA, histopathological studies, and serum beta-HCG levels should be considered for early diagnosis. While extremely rare, early diagnosis of choriocarcinoma can lead to early curative treatment.

References

1. Athanassiou A, Begent RH, Newlands ES, Parker D, Rustin GJ, Bagshawe KD : Central nervous system metastases of choriocarcinoma. 23 years' experience at Charing Cross Hospital. *Cancer* 52:1728–1735, 1983
2. Brudie LA, Ahmad S, Radi MJ, Finkler, NJ : Metastatic choriocarcinoma in a viable intrauterine pregnancy treated with EMA-CO in the third trimester. A case report. *J Reprod Med* 56: 359–363, 2011
3. Chang IB, Cho BM, Park SH, Yoon DY, Oh SM: Metastatic choriocarcinoma with multiple neoplastic intracranial microaneurysms. *J Neurosurg*, 108: 1014-1017, 2008
4. Dana A, Saldanha GJ, Doshi R, Rustin GJ: Metastatic cerebral choriocarcinoma coexistent with a viable pregnancy. *Gynecol Oncol*. Apr;61(1):147-9, 1996
5. Fairhall, JM, & Stoodley, MA: Intracranial haemorrhage in pregnancy. *Obstetric Medicine*, 2(4), 142–148, 2003
6. Greene JB, McCue SA: Choriocarcinoma with cerebral metastases coexistent with a first pregnancy. *Am J Obstet Gynecol*. Jun 1;131(3):253-4, 1978.
7. Kalafut M, Vinuela F , Saver JL , Martin N , Vespa P, Verity MA : Multiple Cerebral Pseudoaneurysms and Hemorrhages: The Expanding Spectrum of Metastatic Cerebral Choriocarcinoma, *Journal of Neuroimaging*, 8, 1998.
8. Liang CC, Chang SD, Lai SL, Hsieh CC, Chueh HY, Lee TH: Stroke complicating pregnancy and the puerperium. *Eur J Neurol* 13:1256–60. 2006
9. Mamelek AN, Withers GJ, Wang X:Choriocarcinoma brain metastasis in a patient with viable intrauterine pregnancy. Case report. *J Neurosurg*. Aug;97(2):477-81, 2002

Disclosures:
None

ACCEPTED MANUSCRIPT

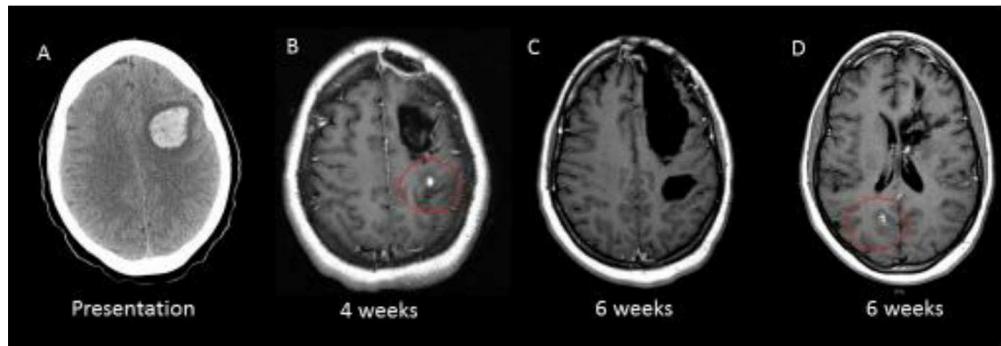


Figure 1:

(A) Non-contrast axial CT showed left frontal hemorrhage at presentation, which was emergently resected.

(B) MRI with contrast showed a small enhancing lesion in the left fronto-parietal area (circled) and post-operative changes in the left frontal resected area, 4 weeks after the initial presentation when the patient was re-admitted with status epilepticus.

(C) MRI with contrast showing no enhancement around the left fronto-parietal resection cavities, 6 weeks after the initial presentation. This was done after another seizure.

(D) MRI with contrast showed nodular area of enhancement in the right parietal-occipital area (circled), 6 weeks after initial presentation.

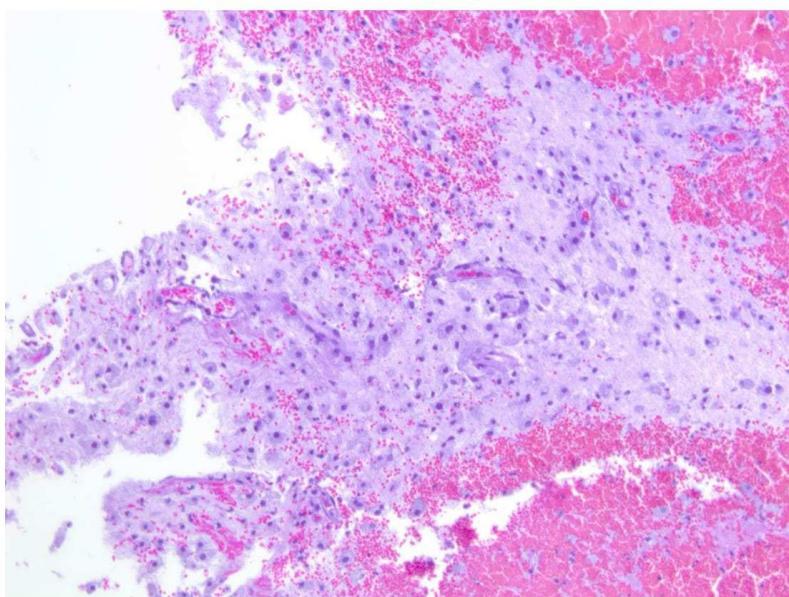


Figure 2:
Hemorrhage with macrophage infiltrate in brain. No histopathological evidence of choriocarcinoma at initial presentation.

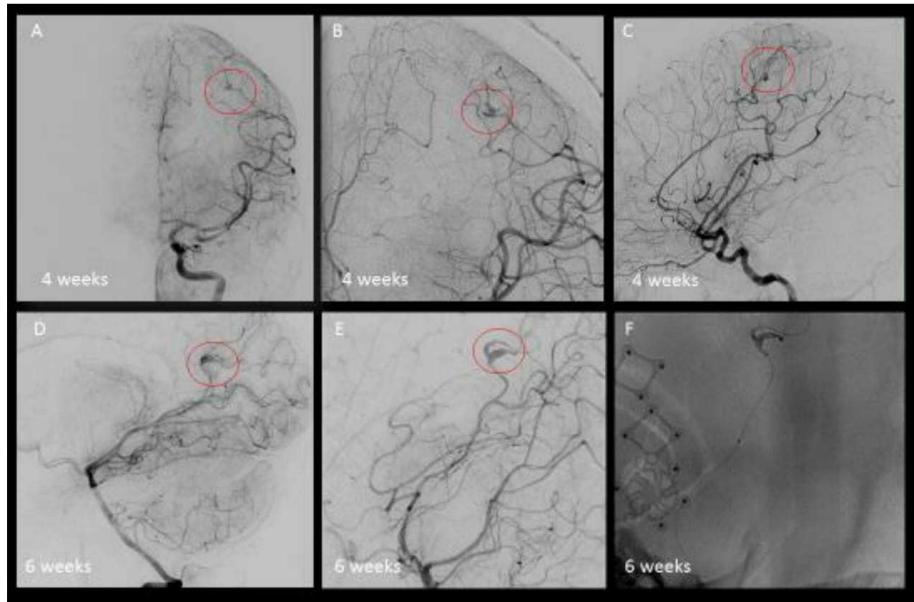


Figure 3

- (A) 4 weeks after initial left frontal cerebral hemorrhage and resection, left common carotid artery catheterization showed highly dysplastic and multilobulated distal left middle cerebral artery pseudoaneurysm, which was resected.
- (B) Dyna CT magnified view of (A)
- (C) Lateral view of (A)
- (D) 6 weeks after initial left frontal cerebral hemorrhage and resection, and 2 weeks after resection of the left middle cerebral artery pseudoaneurysm seen in (A), right vertebral artery catheterization showed interval development of 6.3mm fusiform pseudoaneurysm involving the bifurcation of the calcarine branch of the right posterior cerebral artery
- (E) Right vertebral artery catheterization showing magnified view of (D)
- (F) 6 weeks after initial left frontal cerebral hemorrhage, transarterial Onyx® embolization of the distal right posterior cerebral artery mycotic pseudoaneurysm.

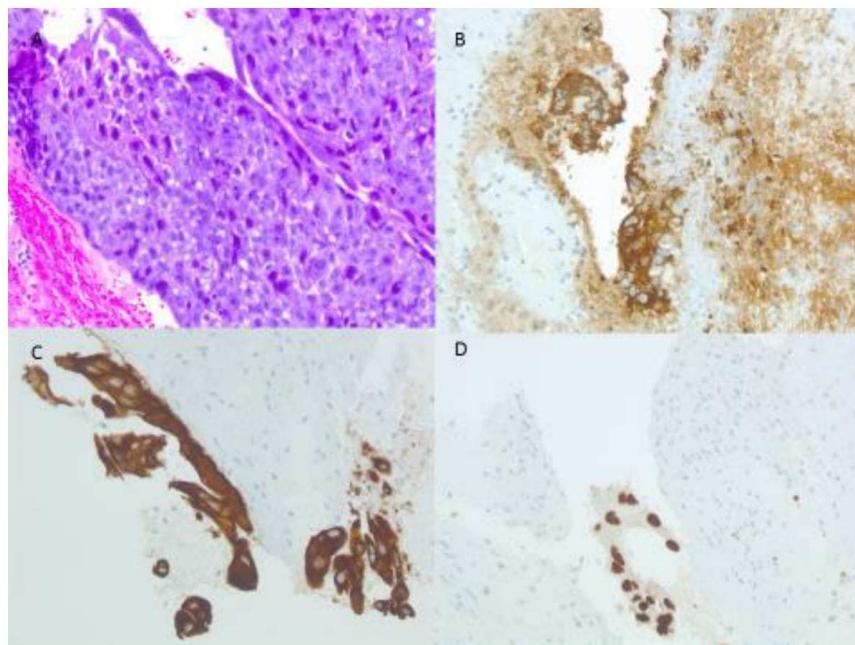


Figure 4: Histopathology of resected left middle cerebral artery pseudoaneurysm
(A) H and E stain showing atypical cells with mitotic figures and prominent nucleoli consistent with choreocarcinoma
(B) HCG immunostaining showing hormone secretion by tumor cells
(C) Pan-cytokeratin immunostaining showing epithelial origin
(D) GATA-3 transcription factor immunostaining consistent with choreocarcinoma

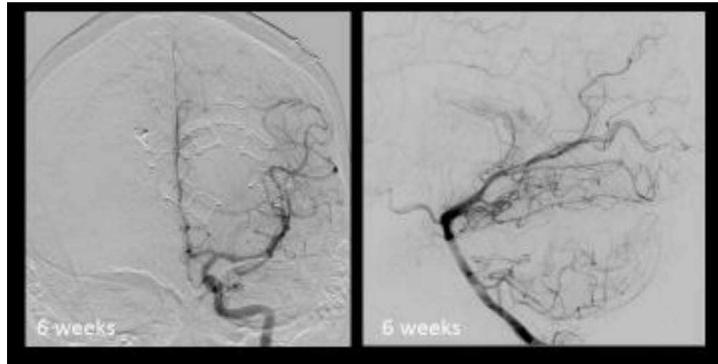


Figure 5: Angiogram after embolization of the distal right posterior cerebral artery pseudoaneurysm, 6 weeks after initial left frontal cerebral hemorrhage
(A) Left common carotid artery catheterization showed resolution of the distal left middle cerebral artery pseudoaneurysm after resection
(B) Right vertebral artery catheterization showed resolution of fusiform pseudoaneurysm involving the bifurcation of the calcarine branch of the posterior cerebral artery after Onyx® embolization

Highlights

- Choriocarcinoma is rarely seen in viable pregnancies
- Cerebral hemorrhages occur through erosion of cerebral vessels and formation of cerebral mycotic pseudoaneurysms, which, from our knowledge, our case report is the first to clearly demonstrate angiographically
- Cerebral metastases from choriocarcinoma are extremely responsive to treatment, and fatal if undiagnosed
- It is important to consider choriocarcinoma in peri-partum women with cerebral hemorrhages and screen for cerebral mycotic pseudoaneurysms using cerebral angiography.