Case report

Leptomeningeal spread of gestational trophoblastic neoplasia in a 19-year old woman

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ABSTRACT

Gestational trophoblastic neoplasia (GTN) with brain metastasis is usually seen in patients with advanced disease. Ten percent of metastatic gestational trophoblastic disease involves the brain and spinal cord, most often manifesting as an intracerebral mass or subdural hematoma, and are generally known to be a poor prognostic factor (Dadlani et al., 2010). Leptomeningeal metastases are tremendously rare and not well documented in the literature. A standardized treatment regimen for patients with brain metastases has not been established and is controversial due to a number of multimodal treatments that have been published in the literature without a prospective trial having been completed. We report a case of a patient with gestational trophoblastic disease that metastasized to the lung and leptomeninges, who after treatment with induction chemotherapy using etoposide (E) and cisplatin (P) followed by etoposide, methotrexate and dactinomycin (EMA) chemotherapy achieved a complete response without brain radiation (Han et al., 2012).

1. Case

A 19-year-old woman (gravida 2, para 0) initially presented to the emergency room complaining of vaginal bleeding and abdominal pain. β-Human Chorionic Gonadotropin (β-hcg) was initially 882 mlU/mL and transvaginal ultrasound (TVUS) at the time showed a normal uterus, an ovoid simple right ovarian cyst measuring 1.4×1.1 cm, and a small 6 mm vascular focus external the left inferior wall of the urinary bladder with indeterminate etiology. As the pregnancy was desired, a repeat β-hcg was 1168 mlU/mL 48 h later. She eventually had a termination of pregnancy at an outside facility and final pathology revealed fragments of disordered proliferative endometrium and few fragments of squamous epithelium with focal atypia. There was no evidence of gestational tissue identified. A repeat dilation and curettage at the same outside facility also showed similar pathology when slides were reviewed at our institution. β-hcg was now 2753 mlU/mL and a repeat TVUS was remarkable for an echogenic endometrium and small ovarian cysts but did not show an intrauterine pregnancy. The presumptive diagnosis of an ectopic pregnancy was made and she was treated with methotrexate at 50 mg/m^2, but her β-hcg levels did not fall appropriately. She re-presented on day 4 and day 7 with levels of 3154 mlU/mL and 3718 mlU/mL respectively. Repeat pelvic ultrasound did not show an intrauterine pregnancy, but the uterus was enlarged with bilateral ovarian cysts. She received a second dose of methotrexate on

day 7 and her β-hcg levels on days 11 and 14 were 3518 mlU/mL and 3091 mlU/mL respectively. One week later, she returned for follow-up. She remained without complaints and β-hcg was 3002 mlU/mL.

The patient re-presented two weeks later complaining of continued vaginal bleeding with cramping and a headache. Pelvic ultrasound was again unremarkable, but β-hCG at this time was 3893 mlU/mL. The concern for gestational trophoblastic disease was raised at this time. A chest radiograph and CT scan were remarkable for a 3 cm nodule/mass in the right midlung (Fig. 1). The uterus was noted to be heterogeneous in appearance. Head imaging showed multiple regions of linear and nodular enhancement within the supratentorial parenchyma. On brain CT and MRI, there was evidence of several foci of old hemorrhage and enhancing nodules in the extra-axial space indicating leptomeningeal spread of tumor (Fig. 2). Based on clinical findings and imaging, the diagnosis of gestational trophoblastic disease FIGO stage of IV with a WHO score of 9 (based on her antecedent pregnancy, interval months from index pregnancy, pre-treatment serum β-hcg, site of metastases, number of metastases and previous failed chemotherapy) was made, indicating high risk GTN (Berkowitz and Goldstein, 2009). The patient underwent multiple lumbar punctures with negative cytology. β-hcg from the cerebrospinal fluid was positive (Fig. 3). Angiography of the brain revealed end-artery intraluminal irregularities consistent with spasm and possibly mycotic aneurysms.

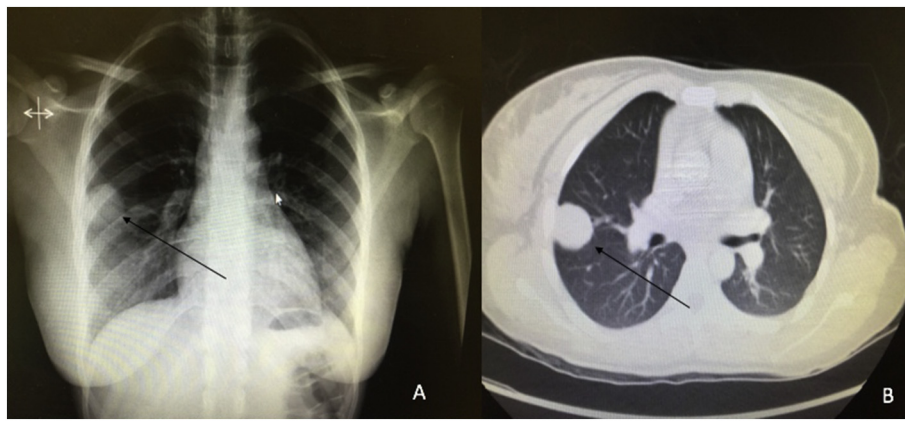She was initiated on induction chemotherapy with low dose EP for

Fig. 1. Radiography and CT scan of the chest demonstrating solitary lung module.
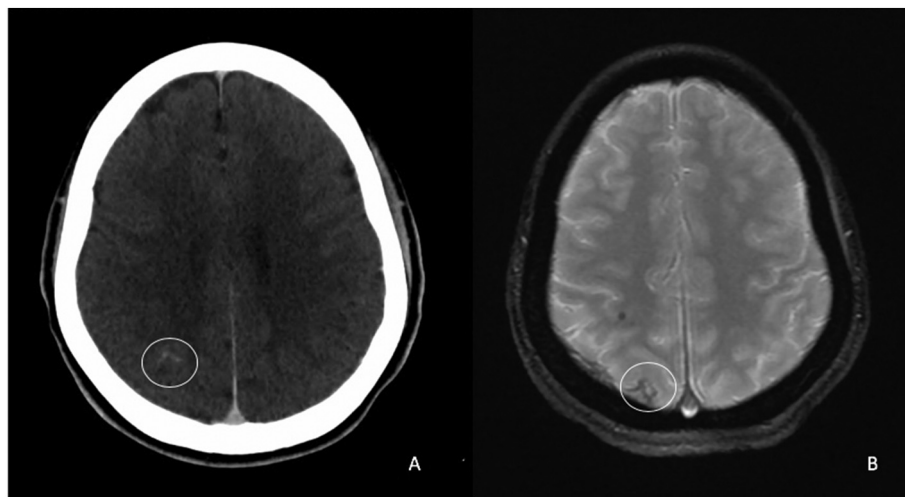

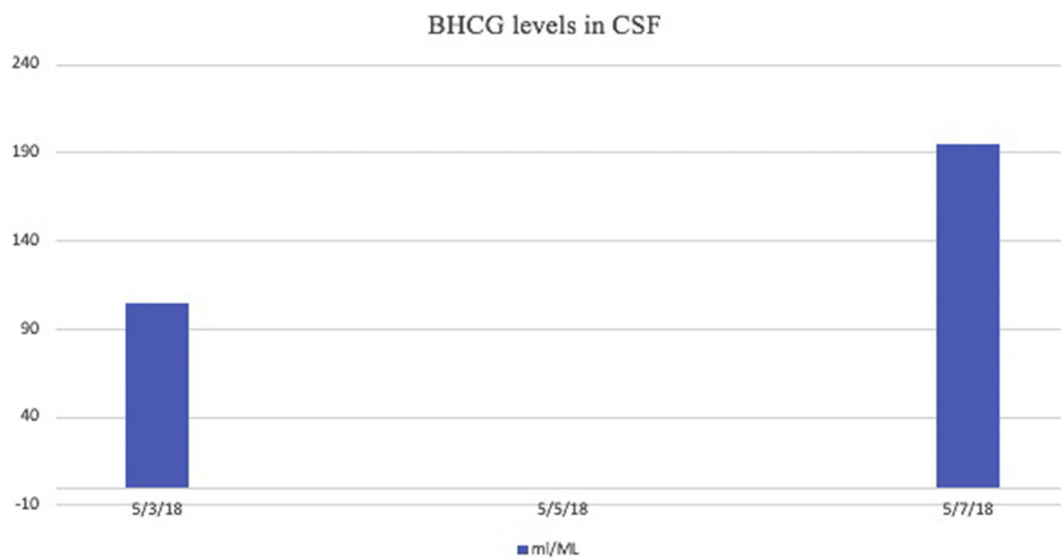Fig. 2. CT scan and MRI imaging demonstrating leptomeningeal spread of GTN.

Fig. 3. Graphical representation of β-HCG levels in CSF.

two cycles, then EMA/EP with high dose methotrexate after receiving leuprolide to preserve ovarian function (Table 1). Her β-hcg levels were normal after two cycles of EMA/EP, and she received an additional three cycles after which her β-hcg levels became undetectable (Table 2). She had a follow-up CT and MRI of the head three weeks after

chemotherapy initiation that showed resolution of the previously seen hyperattenuation or leptomeningeal disease (Fig. 4). The patient remains without neurologic symptoms. After she completed chemotherapy, the lung nodule remained but decreased in size to 2.1 cm. She underwent a wedge resection and mediastinal lymph node biopsy

Table 1

EP-EMA with high dose methotrexate regimen.

Time points[a]	Induction[b]	Day 1	Day 2
Chemotherapy agents	Etoposide 100 mg/m^2 IV infusion (60 mins) Cisplatin 20 mg/m^2 IV infusion (60 mins)	Etoposide 150 mg/m^2 IV infusion (90 mins) Methotrexate 1000 mg/m^2 IV infusion (24 h) Dactinomycin 0.5 mg IV bolus	Etoposide 150 mg/m^2 IV infusion (90 mins) Cisplatin 75 mg/m^2 IV infusion (60 mins) Leucovorin calcium 100 mg orally every 6 h for eight doses starting 32 h after start of methotrexate

IV = intravenous.
  [a] Schedule is based on fourteen-day cycles.
  [b] Schedule is based on seven-day cycles.

Table 2

β-HCG values over time with associated chemotherapy. MTX = Methotrexate. EP = Etoposide/Cisplatin. EMA = Etoposide/Methotrexate/Dactinomycin.

| Date	Chemotherapy	β-HCG CSF	Serum β-HCG
3/31/18	MTX		2753
4/7/18	MTX		3718
5/3/18		105.2	
5/7/18		193.5	
5/8/18	EP		3902
5/9/18	EP		
5/15/18	EP		4044
5/16/18	EP		
5/23/18	EMA		1473
5/31/18	EP		
6/6/18	EMA		135.4
6/21/18	EP		
6/30/18	EMA		3.2
7/9/18	EP		1.6
7/15/18	EMA		0.5
8/2/18	EP		< 0.1
8/9/18	EMA		< 0.1
8/24/18	EP		< 0.1

of the lung mass which showed it to be a necrotic nodule with no viable tumor. There was no evidence of nodal involvement, indicating a complete response to chemotherapy. The patient remains without any evidence of disease after completing chemotherapy and is followed with monthly β-hcg levels.

2. Discussion

The management of patients that have GTN with brain metastasis continues to be a challenge due to their high morbidity, long term sequelae, and the lack of consensus regarding optimal treatment. Xiao et al. (2015) reports that in patients with brain metastasis mortality reaches 30%, mostly linked to hemorrhage, compared to the overall death rate of 5% from GTN. Multi-agent chemotherapy for high risk patients is indicated. MAC chemotherapy (methotrexate, actinomycin D, and cyclophosphamide), CHAMOCA regimen (cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan, and vincristine) and EMA-CO/EMACE (cyclophosphamide vs cisplatin) chemotherapy have all been presented as viable regimens for patients with GTN, each with different cure rates (Han et al., 2012; Hiramatsu et al., 2005; Leslie et al., 1996). MAC therapy has been shown to have a cure rate of 30–51% and in contrast EMA-CO therapy has been shown to have an 88% survival rate in high risk patients (Hiramatsu et al., 2005). The National Comprehensive Cancer Network (NCCN) guidelines recommend EMA-CO for high risk GTN, but given the low β-hcg levels in our patient, the concern for placental site trophoblastic tumor was also raised, prompting the use of EMA/EP. Although EMA-CO is commonly a first line combination with a good overall survival rate, up to 30% of patients will need some form of salvage chemotherapy (Aminimoghaddam et al., 2018). EP-EMA has been suggested as an alternative first line therapy with results of some studies achieving complete remission in up to 89% of patients (Han et al., 2012). According to Alifrangis et al. approximately one-third of deaths in patients with high risk GTN occur within the first four weeks of treatment secondary to high tumor burden and subsequent hemorrhage due to rapid tumor destruction. The use of low dose EP induction chemotherapy has been utilized to reduce this risk (Alifrangis et al., 2013).

Treatment choice is determined by size of tumor, number of metastases, and clinical urgency of treatment (Frost et al., 2017). There are cases that have required whole brain radiation, stereotactic radiation and intrathecal chemotherapy in addition to excisional surgery (Leslie et al., 1996; Newlands et al., 2002; Soper et al., 2007). In patients with an intracerebral hemorrhage, emergency radiation therapy is indicated to prevent deterioration of neurologic function and herniation. Whole brain irradiation has been suggested in the treatment of brain
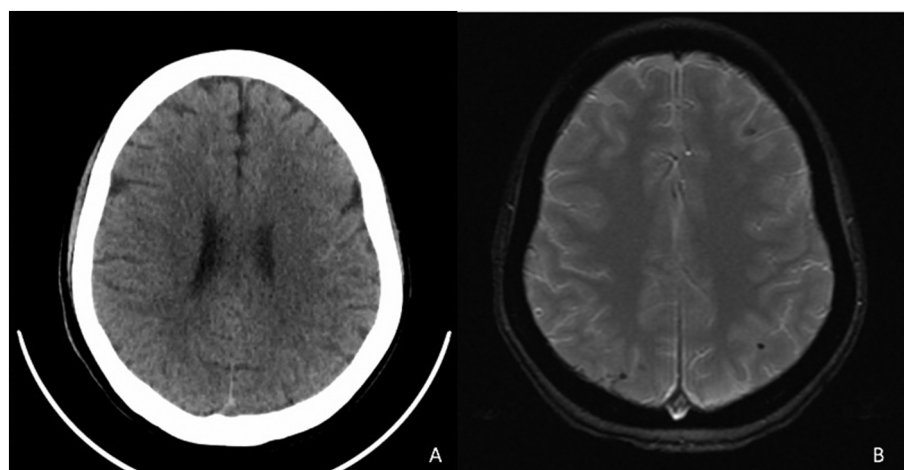
Fig. 4. CT and MRI imaging indicating resolution of leptomeningeal disease after chemotherapy.

metastasis with multiple nodules, however, high beam localized radiation has proven to be effective (Yordan Jr et al., 1987). Yordan et al. reported that deaths as a result of cerebral involvement occurred in 11 of 25 patients (44%) treated with chemotherapy alone, but there were no deaths in the 18 patients treated with brain irradiation and chemotherapy. Concurrent use of combination chemotherapy and brain irradiation could potentially lessen the risk of spontaneous cerebral hemorrhage. Though brain radiation reduces mortality, it can induce long term cognitive impairment including impaired cognitive function, dementia, gait ataxia and behavioral changes (Blay et al., 1998). In the United Kingdom, the Charing Cross group has reported cure rates up to 75% with early surgical resection in combination with EMA-CO chemotherapy including intrathecal methotrexate (Leslie et al., 1996). Soper et al. was successful in utilizing early craniotomy or stereotactic radiosurgery in addition to alternative regimens of systemic chemotherapy including etoposide, cisplatin and methotrexate.

Surgical intervention in the presence of brain metastasis of GTN has been shown to prevent hemorrhage and early mortality, and most solitary brain metastasis are amenable to surgical resection (Newlands et al., 2002). Our patient's only neurological symptom was a headache, and her brain imaging was consistent with focal hemorrhage likely related to suboptimal low dose methotrexate treatment in the setting of presumed ectopic pregnancy. The presence of β-hcg in the CSF suggests the presence of malignancy, however doesn't indicate presence of disease in the CSF. Older reports initially reported that measurements of β-hcg in CSF can be used to detect the presence of central nervous system (CNS) metastases from choriocarcinoma. However, measuring the CSF/serum β-hcg ratio in patients with brain metastases is not accurate enough to be included in the workup, management, or surveillance of gestational trophoblastic disease with brain metastases (Bakri et al., 2000).

The Charing Cross group initially recommended intrathecal methotrexate due to concerns for subtherapeutic CNS levels, however, therapeutic CSF methotrexate levels have been documented when > $600\,mg/m^2$ of high dose intravenous methotrexate was used (Tetef et al., 2000). Given the presence of leptomeningeal disease, our patient received $1000\,mg/m^2$ of high dose methotrexate instead of the usual dosing. The superiority of intrathecal versus intravenous high-dose methotrexate has not been established for patients with brain metastases from GTN. Intrathecal chemotherapy is more invasive compared to systemic chemotherapy and it can be associated with significant complications such as infection and catheter-related dysfunction.

Patient outcomes in cases of residual pulmonary lesions following successful chemotherapy for GTN with lung metastases is not well known (Powles et al., 2006). This has resulted in uncertainty regarding the management of these residual lesions, with some studies advocating surgical management (Jones et al., 1993). Powles et al. showed that residual lung abnormalities in women who are in marker remission following chemotherapy for malignant GTN does not appear to have an increased risk of relapse. They concluded that the observation of persistent radiological abnormalities at the end of the treatment has no bearing on the outcome for patients.

3. Conclusion

This is the first report to our knowledge of a patient with stage IV GTN having leptomeningeal involvement. It was surprising to see leptomeningeal spread considering our patient's low β-hcg levels. While many patients have lung metastases, our patient had a solitary nodule. While our patient experience is limited and does not establish a new standard of care for patients with GTN and brain metastases, it does present a different scenario in which the patient was partially treated with methotrexate in the setting of presumed ectopic pregnancy. This highlights the importance of maintaining a differential diagnosis when evaluating a pregnancy of unknown location. Our patient was presumed to have had an intrauterine pregnancy at the time of her termination,

but given the lack of gestational tissue on pathological evaluation and her ultrasound, GTN should have been considered earlier in the workup.

Regardless of the patient's misdiagnosis and protracted delay in proper diagnosis, she had a favorable outcome, even in the setting of leptomeningeal spread. We do not provide intrathecal chemotherapy at our institution. Whole brain radiation was deferred due to the long-term deficiencies associated with whole brain radiation considering our patient's age. In summary, chemotherapy alone can cure the majority of patients with GTN, but high dose methotrexate is required for patients with brain metastases. There is also no support for surgical management of residual pulmonary disease if β-hcg levels are negative. Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Author contribution

NG was primarily responsible for drafting the manuscript while the reviews were primarily handled by DG and LV. YE also helped with reviewing the report prior to its submission and it was her attention to detail and clinical judgement was what helped in making the diagnosis of gestational trophoblastic neoplasia.

Declaration of funding

Declaration of Competing Interest

The authors have no relevant conflict of interest to report.

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