

# Gestational Trophoblastic Neoplasia with Brain Metastasis Presented with Initial Presentation of Dyspnea: A Case Report

Haleh Ayatollahi<sup>\*</sup> , Samira Jahangard 

Department of Obstetrics and Gynecology, School of Medicine, Solid Tumor Research Center, Research Institute on Cellular and Molecular Medicine, Shahid Motahari Hospital, Urmia University of Medical Sciences, Urmia, Iran



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## Corresponding Information:

**Haleh Ayatollahi,**

Department of Obstetrics and Gynecology, School of Medicine, Solid Tumor Research Center, Research Institute on Cellular and Molecular Medicine, Shahid Motahari Hospital, Urmia University of Medical Sciences, Urmia, Iran

**Email:** [hayatollahi@yahoo.com](mailto:hayatollahi@yahoo.com)

## ABSTRACT

**Background:** Choriocarcinoma is the most aggressive kind of gestational trophoblastic neoplasia (GTN). Although the risk of brain metastasis in GTN is rare, in patients with choriocarcinoma, the incidence of brain metastasis is 11%. In this paper, we reported a case of choriocarcinoma with brain metastasis, which was successfully treated with an etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO) regimen.

**Case presentation:** A 34-year-old woman was presented with vaginal bleeding, dyspnea, and moderate abdominal pain. She had a menstrual delay of about two weeks. She had a primary  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) of 132600 mIU/mL. On lung computed tomography (CT) scan images, a metastatic lesion with a size of 68×50 mm was observed in the lower lobe of the left lung. The patient underwent dilation and curettage (D&C) that revealed choriocarcinoma. Brain magnetic resonance imaging (MRI) also showed a small metastatic mass with a size of 7 mm at the right occipital lobe. The patient was started on chemotherapy with an EMACO regimen. The patient's  $\beta$ -hCG decreased continuously, and it was negative after the fourth cycle and six sessions of radiotherapy. It also remained negative six months after chemotherapy. The final examinations of the patient had no abnormal findings.

**Conclusion:** Brain metastasis may be relatively asymptomatic in patients with choriocarcinoma, and it should be considered by physicians, even when there are no neurological symptoms. Also, the EMACO regimen seems to be an appropriate regimen for the treatment of metastatic choriocarcinoma.

**Keywords:** Gestational trophoblastic neoplasm, Metastasis, Pleural effusion, Dyspnea



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## Introduction

Gestational trophoblastic disease (GTD) refers to a group of malignant or benign conditions (1). Gestational trophoblastic neoplasia (GTN) is a term for malignant tumors that consist of invasive moles, choriocarcinoma, placental site trophoblastic tumors (PSTTs), and epithelioid trophoblastic tumors (ETT) (1). Choriocarcinoma is the most aggressive malignant tumor with an incidence of 0.18 per 100000 women and 1 to 9 in 40000 pregnancies between the ages of 15 and 49 years in the United States (2, 3).

Although the risk of brain metastasis in GTN is rare, and it is approximately 2-3 cases per million pregnancies, in patients with choriocarcinoma, the incidence of brain metastasis is 11% (3, 4). Based on the International Federation of Gynecology and

Obstetrics (FIGO) anatomic staging, patients with brain metastasis are classified at disease stage IV (2). According to this staging system, FIGO stages II-III (score >7) and stage IV are considered as high-risk GTN and treated with multiple chemotherapy regimens (5).

The etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO) regimen is used as the most common option for the treatment of metastatic choriocarcinoma. In brain metastasis cases, an increase in intravenous methotrexate to 1 mg/m<sup>2</sup> will help better drug permeation into the blood-brain barrier (6, 7). In this case report, we aimed to present a case of choriocarcinoma with brain metastasis and

unusual initial presentation of dyspnea, which was successfully treated with an EMACO regimen.

## Case Presentation

A 34-year-old (gravida 5, para 3, abortion 2) woman was referred to the Gynecological Emergency Department of Motahari Hospital, Urmia, Iran, with vaginal bleeding, dyspnea, and moderate abdominal pain. She had a menstrual delay of about two weeks. The patient's blood pressure was 90/60 mm Hg, and pulse and respiratory rates were 120 and 26 per minute, respectively. The fundal height was about eight weeks. Primary laboratory data showed a  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) of 132600 mIU/mL and hemoglobin (Hb) of 5 g/dL.

The patient underwent abdominal and pelvic ultrasonography, which showed the uterus larger than normal with completely heterogeneous myometrium and several hypo- and hyperechoic regions, which was consistent with molar pregnancy. The endometrium thickness was 4 mm, and there was no free fluid in the pelvis. The ultrasonography of the abdomen and ovaries was normal. The patient also underwent chest radiography, which showed a pleural effusion in the left hemithorax (Figure 1). Three units of packed cells were given, and a chest tube was inserted in the left hemithorax.  $\beta$ -HCG of pleural fluid was 64000 mIU/mL. Then, the patient underwent a dilation and curettage (D&C).

The final pathology of D&C revealed choriocarcinoma. So, the patient was transferred to the Gynecology-Oncology Department for further oncological management. The patient also underwent spiral computed tomography (CT) scan of the lungs and peritoneum with and without contrast, which demonstrated a moderate pleural effusion in the left hemithorax. Also, the collapse of the left lung in the inferior regions was seen. There was no abnormality in the right lung, heart, and large vessels of the mediastinum. Finally, a round lesion with a size of 68×50 mm was observed in the inferior lobe of the left lung, which was consistent with metastasis due to the patient's history of choriocarcinoma (Figure 2).

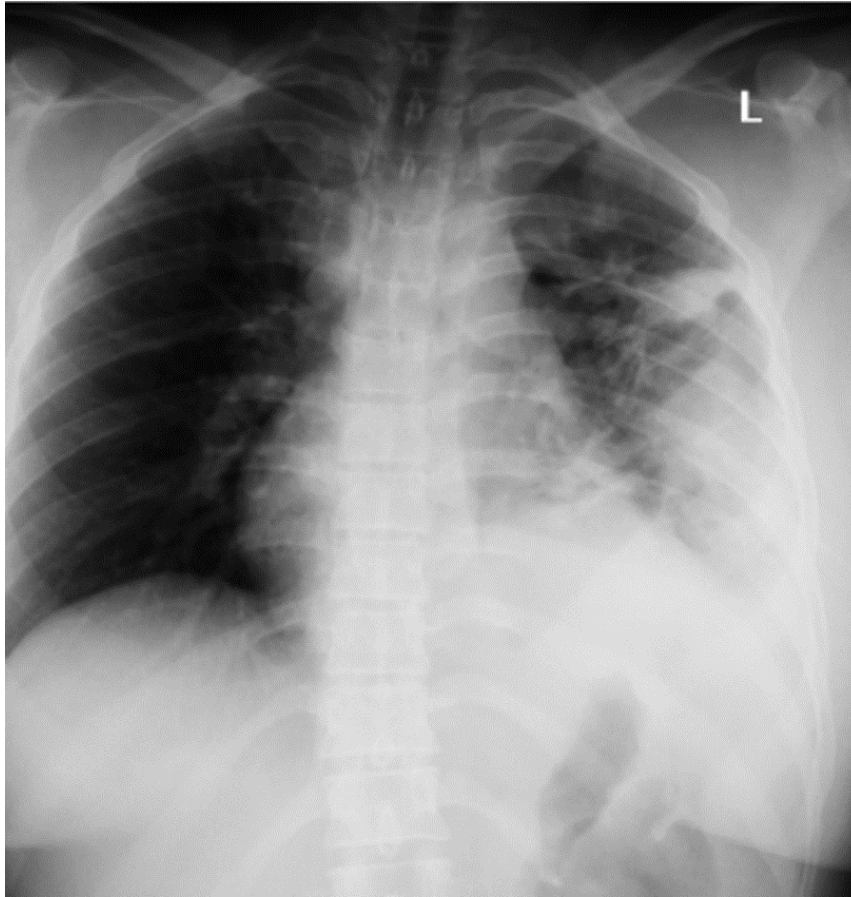
The patient's respiratory symptoms were mostly resolved after chest tube insertion, and she underwent further chest radiography (Figure 3) and spiral CT scan of the lungs and mediastinum (Figure 4), which showed a very mild pneumothorax near the tip of the chest tube in the posteroinferior region of the left hemithorax in the shape of a 60×60 mm loculation with an air-fluid level. Collapse consolidation was also seen in the base of the left lower lobe. Three days later, the

patient became disoriented, and a neurology consultation was requested. Consequently, the patient underwent a brain CT scan that showed no abnormality, but brain magnetic resonance imaging (MRI) was recommended for further assessment. She underwent brain MRI that showed a small mass with a size of 7 mm at the right occipital lobe with several vasogenic edema, which was consistent with brain metastasis.

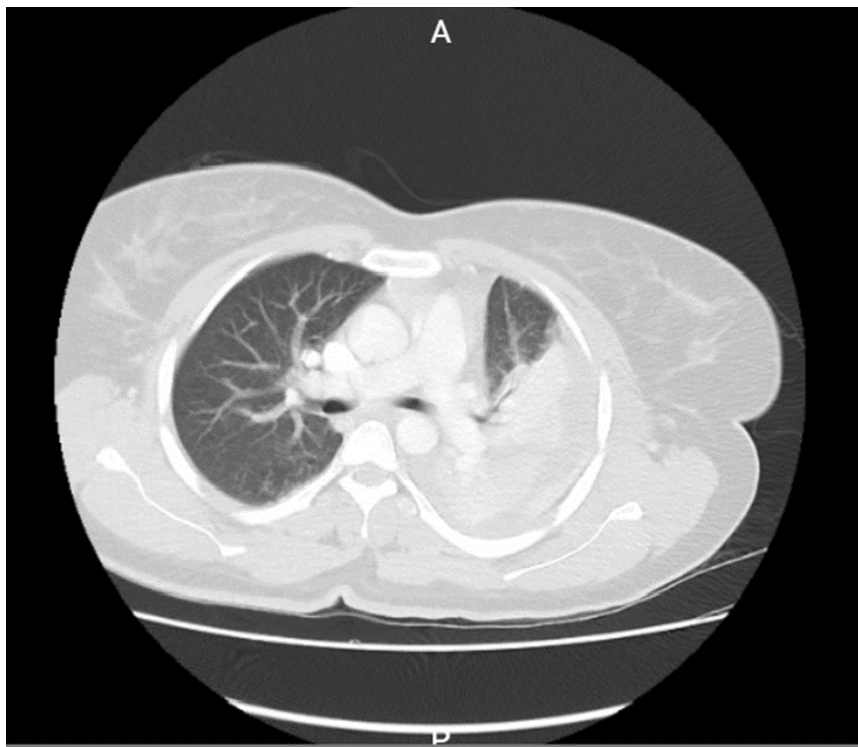
The patient was started on chemotherapy with an etoposide, methotrexate (EBETREX 1000 MG/10 CC, EBEWE PHARMA, Austria), actinomycin D, cyclophosphamide (T Cyclophosphamide, ip.ctx-gls200, Telangana state, India), and vincristine (EMACO, usp, ACTIZA, India) regimen" (8). It included actinomycin D 0.5 mg IV bolus, etoposide 100 mg/m<sup>2</sup> IV infusion (30 minutes), and methotrexate 1000 mg/m<sup>2</sup> IV infusion (24 hours) for the first day. It also included actinomycin D 0.5 mg IV bolus, etoposide 100 mg/m<sup>2</sup> IV infusion (30 minutes), and leucovorin calcium 15 mg orally every eight hours for nine doses, starting 32 hours after the start of methotrexate for the second day. Finally, the eighth day consisted of vincristine 1.0 mg/m<sup>2</sup> IV bolus and cyclophosphamide 600 mg/m<sup>2</sup> IV infusion.

She underwent a total of four cycles; during each cycle, two vials of Granulocyte colony-stimulating factor (G-CSF) were given every other day. Only during one of the cycles, the patient did not receive G-CSF due to fever (body temperature of 38.2°C, axillary), empyema, and white blood cell (WBC) count of 30 000/mm<sup>3</sup>. In that period of time, the patient underwent thoracoscopy, and adhesion was observed in the left pleural cavity, which was resolved during thoracoscopy. It might have been the cause of incomplete drainage of pleural effusion after chest tube insertion.

The cytological study of pleural effusion showed reactive mesothelial cells, red blood cells, and hemosiderin-laden macrophages. We also administered two grams of intravenous ceftriaxone every 12 hours and 900 mg of clindamycin every eight hours for two weeks. The patient's symptoms recovered after thoracoscopy and antibiotic administration, and the WBC count was within the normal range. During the chemotherapy course, the patient's  $\beta$ -hCG decreased continuously, and it was negative ( $\beta$ -hCG=4 mIU/mL) after the fourth cycle. It also remained negative six months after chemotherapy. The final examinations of the patient had no abnormal findings. After treatment, the patient underwent brain MRI, and it was negative for lesions; the final chest radiography was also normal.

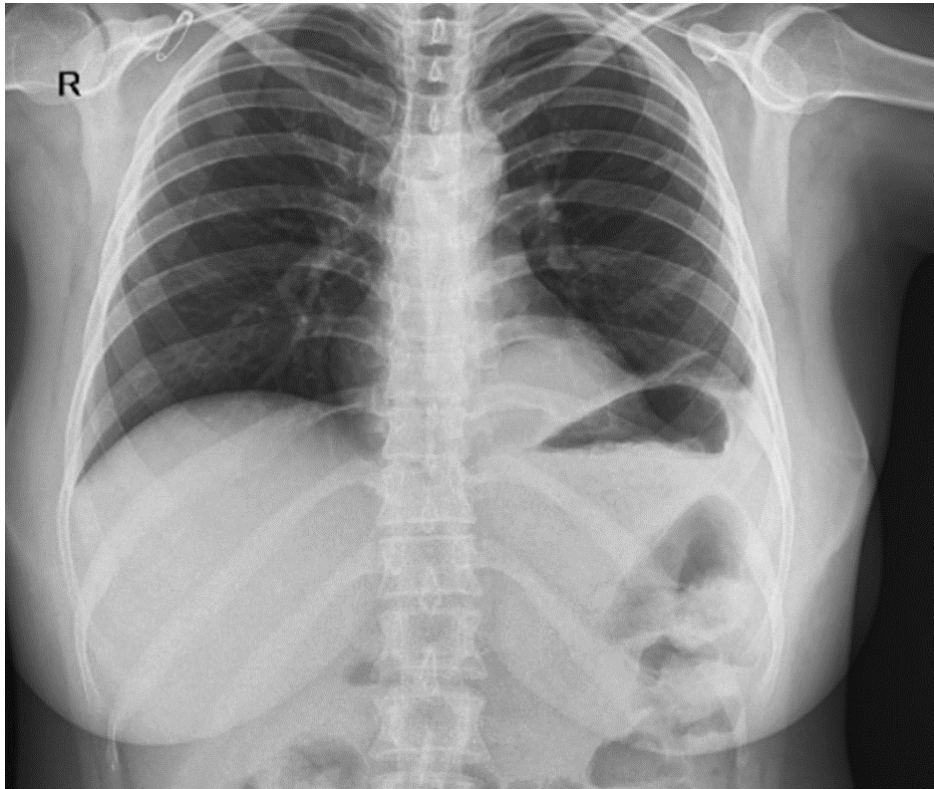


**Figure 1.** Primary chest radiography of the patient presented with dyspnea, spotting, abdominal pain and menstrual delay (pleural effusion in the left hemithorax)

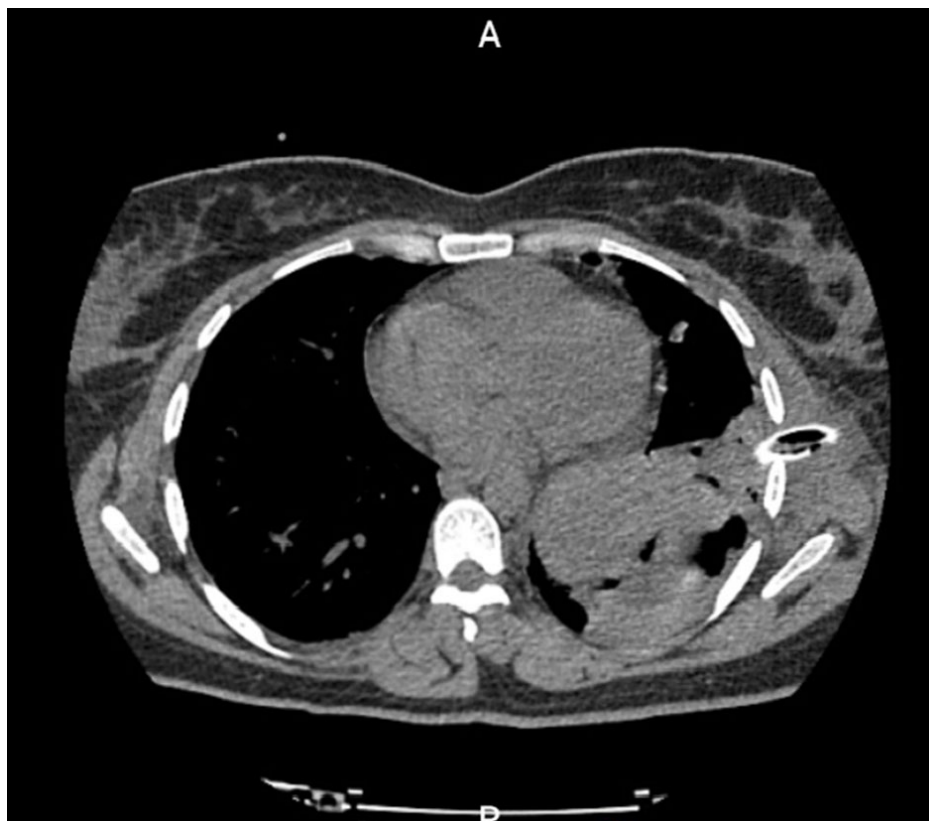


**Figure 2.** Primary lung and mediastinum CT scan of the patient (moderate pleural effusion in the left hemithorax, collapse of left lung in the inferior regions, and a round lesion with a size of 68×50 mm in the inferior lobe of the left lung)





**Figure 3.** Chest radiography of patient after chest tube insertion (a very mild pneumothorax)



**Figure 4.** Lung and mediastinum CT scan of patient after chest tube insertion (a very mild pneumothorax in the posteroinferior region of left hemithorax in the shape of a 60×60 mm loculation with air-fluid level and collapse consolidation in the base of left lower lobe)

## Discussion

Choriocarcinoma is a highly malignant tumor that responds well to chemotherapy. The clinical presentation of choriocarcinoma is so atypical and varied in the majority of cases, making it difficult to diagnose at an earlier stage. Thus, patients usually present in an advanced clinical stage (9).

One of the most common presentations of choriocarcinoma is abnormal uterine bleeding following ectopic or normal pregnancies and spontaneous/therapeutic abortions or a hydatidiform mole (10). Frequent metastasis sites of choriocarcinoma are lung (80%), vagina (30%), and liver and brain (10%). The gastrointestinal tract can also be affected (11-13). Brain metastasis has various symptoms. It is presented in the form of an intra- or extra-axial hemorrhage (14) due to intracranial aneurysm rupture (15), as well as in the form of a subdural hematoma and infarction (16).

Daniel *et al.* (17) reported a case of choriocarcinoma in the form of a stroke with right upper limb hemiparesis and right-sided facial nerve palsy (17). Symptoms of increased intracranial pressure, such as headache, vomiting, personality change, and sometimes loss of consciousness, have been the only presenting symptom in some cases (12).

In this case, the patient first presented with symptoms of vaginal bleeding, dyspnea, and moderate abdominal pain secondary to metastatic lesions, even though the primary site was the uterus. Our case was unique because the patient's dominant symptoms were neither vaginal nor neurologic symptoms, but dyspnea. Thus, it can be concluded that brain metastases may not be symptomatic in patients with choriocarcinoma. Due to the relatively high incidence of brain metastases in choriocarcinoma, it is recommended to always consider brain metastases in each patient presented with symptoms of GTN. The reason is that the mortality rate in patients with choriocarcinoma with brain metastasis is relatively high.

Xiao *et al.* (18) reported a mortality rate for choriocarcinoma with brain metastasis as 29.7%, while the overall mortality from GTN is estimated to be only 5%. It shows the significant difference in mortality caused by brain metastasis, which accentuates the importance of early diagnosis of brain metastasis in patients presented with GTN symptoms.

For patients with high-risk metastatic choriocarcinoma, several multi-agent chemotherapy regimens have been introduced. These regimens include methotrexate, actinomycin D, and cyclophosphamide (MAC) chemotherapy; cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan, and vincristine (CHAMOCA) regimen; and EMACO/EMACE (cyclophosphamide vs cisplatin). In patients treated with MAC therapy, a cure rate of 30%-51% has been

observed, while in EMACO therapy, the survival rate has been estimated as about 88%.

Also, it has been observed that in 75% of high-risk patients with metastatic choriocarcinoma, there was no evidence of disease after EMACO therapy (19, 20). As in cases of choriocarcinoma with brain metastasis, it is required to use high-dose methotrexate, we used high doses of methotrexate for the treatment of the patient. Frost *et al.* (20) also used the same regimen for their patient with brain, lung, and vaginal metastases. Their patient was successfully treated without brain radiation or intrathecal chemotherapy. In their case, the patient underwent craniotomy with complete excision due to significant focal neurological deficits and concerns for bleeding secondary to hemorrhagic mass. In our case, we did not perform surgery because there were no focal neurologic deficits, and the patient only had disorientation.

Moreover, the neurological symptoms of our patient were completely cured after using the EMACO regimen without performing surgery. Thus, in cases with focal neurological deficits, craniotomy is recommended, while in patients without these kinds of deficits, we recommend immediate start of a chemotherapy regimen.

We can conclude that brain metastasis may be relatively asymptomatic in patients with choriocarcinoma, and it should be considered by physicians, even when there are no neurological symptoms. Also, the EMACO regimen seems to be an appropriate regimen for the treatment of metastatic choriocarcinoma.

## Conclusion

## Acknowledgments

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## Conflict of Interest

Authors declared no conflict of interests.

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