Case Report

Cerebral Hemorrhage in Choriocarcinoma - A Case Report

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Abstract

Choriocarcinoma is a rare cause of cerebral hemorrhage. We herewith report a 19 year old female patient, who was treated earlier for choriocarcinoma with methotrexate, was readmitted with complaints of convulsions. She was diagnosed as cerebral hemorrhage due to choriocarcinoma. Measurement of Beta Human Chorionic Gonadotropin (HCG) in CSF and serum is necessary for the diagnosis and helps in effective management of the disease. After 3 cycles of chemotherapy with EMA-CO Regimen, patient improved, but did not turn up for further chemotherapy.

Key words

Cerebral Hemorrhage, Choriocarcinoma, Beta Human Chorionic Gonadotropin (HCG), EMA-CO Regimen.

Introduction

In 50% of patients, intracerebral hemorrhage is the first manifestation of tumor either primary or metastatic intracranial neoplasms [1]. Usually metastatic tumors bleed more often than primary CNS neoplasms. Choriocarcinoma, bronchial carcinoma, melanoma and renal cell carcinoma are more common metastatic tumors responsible for intracerebral hemorrhage, apart from lymphoreticular malignancy [2, 3, 4].

Gestational choriocarcinoma is a rare tumor in the Western countries, but its incidence is reported to be frequent in South East Asia. One report from India quotes the incidence of choriocarcinoma as 1 in 2958 pregnancies [5].

The diagnosis of this disease is more common in South East Asian countries, with an incidence rate of one per every 2,000 pregnancies. There were 150 cases of choriocarcinoma that showed brain and pulmonary metastasis [6-9].

Choriocarcinoma is known to spread by the vascular route and often metastasizes to the central nervous system (CNS). The incidence of CNS metastasis from gestational choriocarcinoma has been reported to range from 3% to 28% [10, 11, 12, 13, 14].

In spite of the significant improvement in the treatment of choriocarcinoma, mortality is still high; Brain metastasis being responsible for death in nearly 50% of cases. These tumors metastasize in the central nervous system and are known to produce hematoma and intracranial hemorrhages, causing the morbidity and mortality [15]. Trophoblastic disease is considered to be a condition that generally has a benign clinical outcome. Choriocarcinoma is part of this disease and acts as an aggressive tumor. It has the ability of local invasion in the uterus, and less frequently, at distance for blood spread to other organs. Consequently, the clinical signs can be very different, depending on the site of the lesions. It is characterized by causing autonomous secretion of human chorionic gonadotropin (HCG). The diagnosis can be complex, as the symptoms are varied. The treatment is mainly chemotherapy. The prognosis is usually favorable **[**16].

Case report

A 19 year old female patient presented with complaints of convulsions of one day duration with history of Nuchal pain+, No history of Syncopal attacks, No history of Blurring of vision, No history of trauma, No history of Palpitations or chest pain, No history of Orthopnea, Platypnea, No history of Limb Weakness, No history of Pregnancy.

Past history - No history of similar complaints in the past, No history of any drug allergies, No history of contact with TB, No history of Asthma, Epilepsy, CVA, MI, no history of bleeding diathesis, no history of head injury, No history of HTN, NIDDM, history of Hydatidform Mole ++, dd &c done, 1 year ago and treated with MTX. No history of any other surgery done.

On examination – Vitals - Temp – Normal, PR = 90/min with regular rhythm, BP = 120/80 mm of Hg, RR = 20/min.

General examination - Patient conscious, coherent, answering questions well, Moderately Built, Moderately Nourished, No Icterus, Cyanosis, Clubbing, Koilonychias, Lymphadenopathy, Pedal Edema, No Neuro Cutaneous Markers, no petechiae, no ecchymosis, no bruises, No peripheral nerve thickening, No trophic ulcers, Head and Spine = Normal. No Tenderness, Thyroid = Normal.

CNS examination – There was no neurological deficit, Neck Rigidity ++
Gynecological examination was normal.

Investigations - CBP – Hb - 10.4 gm%, TLC - 8000, Plt - 2,40,000, N - 74, L - 24, B - 0, E - 2, M - 0, ESR: 06 mm, Bleeding Time – 4 mts, Clotting Time – 6 mts, Prothrombin Time - 12 seconds, CUE –Urine Albumin - Nil, Sugar – Nil, HIV – Non reactive, HbsAg – Negative, HBC – Negative, USG abdomen – NAD, Lipid Profile – NAD, Bl Sugar – 114 mg/dl, Bl Urea – 24 mg/dl, S. Creatinine – 0.6 mg/dl, S. Electrolytes – Serum sodium – 128 mmol/L, serum potassium - 6.9 mmol/L, LFT - Normal, CSF analysis – Appearance - Hemorrhagic, Cells - Plenty of RBC's, Proteins - 200 Mg, Glucose - 60 Mg%, Globulin - Positive, Blood HCG levels - 12.1 mIU/ml, CSF HCG levels - 61 mIU/ml. Histopathology of D.D& C during earlier admission reviewed, and it revealed and it revealed features suggestive of Choriocarcinoma (**Figure - 1, 2**).

X – Ray Chest PA View - NAD (**Figure - 3**), ECG – WNL, CT Brain – Cerebral Hemorrhage in Right capsulo ganglionic region with perilesional oedema, with extension into lateral ventricle (**Figure - 4**).

A diagnosis of Cerebral Hemorrhage in Right capsulo ganglionic region with extension into lateral ventricle, secondary to Choriocarcinoma was made (Choriocarcinoma – Stage IV).

Figure – 1: Low power view of choriocarcinoma showing neoplastic cytotrophoblast and syncytioblast with areas of hemorrhage.

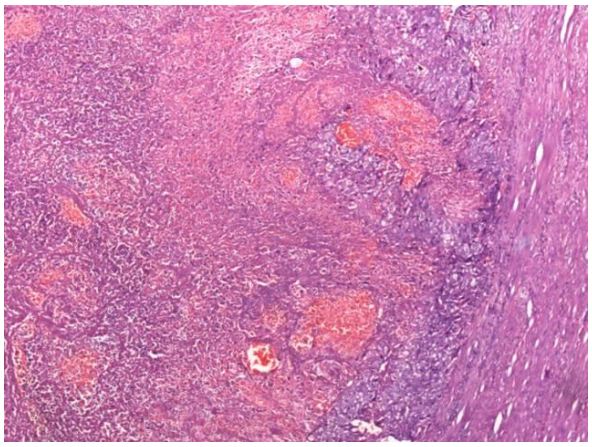


Figure – 2: High power view of choriocarcinoma showing mononuclear cells with pale staining cytoplasm with hyperchromatic nucleus - cytotrophoblast surrounded by syncytiotrophoblast showing giantcells with multiple hyperchromatic nuclei and abundant eosinophilic cytoplasm with areas of hemorrhage.

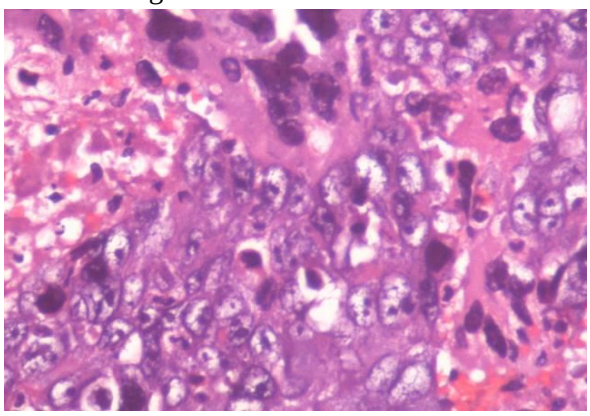


Figure – 3: X-Ray Chest PA View - Normal.

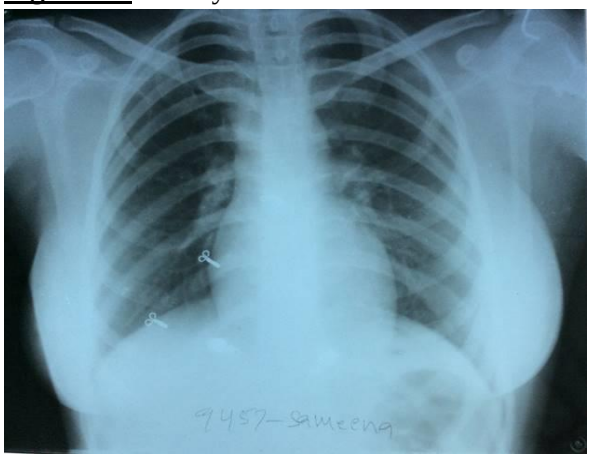
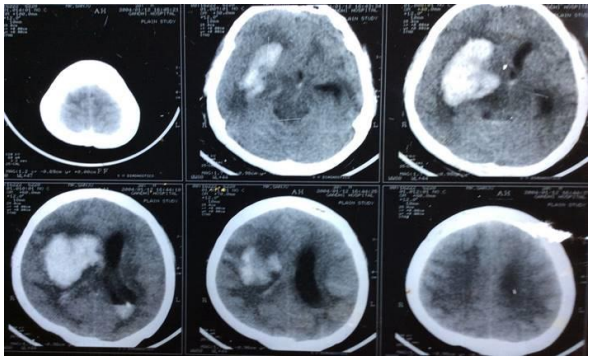


Figure – 4: CT Scan Brain Plain revealed Cerebral Hemorrhage in Right capsulo ganglionic region with perilesional edema, with extension into lateral ventricle.



Staging was done according to FIGO staging (**Table - 1**).

Table – 1: WHO Classification and FIGO staging.

WHO Classification

Molar lesions

Hydatiform mole

Complete

Partial

Invasive mole

Non-molar lesions

Choriocarcinoma

Trophoblastic tumor at the site of implantation

Other trophoblastic tumors

Exaggerated reaction at the site of implantation

Node at the site of placental implantation

FIGO staging

Stage Findings

I - Disease limited to the uterus.

II - Disease out of the uterus but limited to the female genital tract.

III - Metastasis in the lung with or without involvement of female genital tract.

IV - All metastasis at other locations.

* Stages I–IV are subdivided into A and B depending on the prognostic marker.

The classification is based on that adopted by FIGO in 1992, updated in the year 2001 [17, 18].

Treatment given

- Inj. Mannitol 10% 100ml IV TID
- Tab Nimodip 30 mg 2 TID
- Inj Ampicillin 500mg iv QID
- Inj Amikacin 500 mg iv BD
- Inj Metrogyl 500 mg iv TID
- Inj Optineuron 1 amp iv OD
- I.V. Fluids
- After stabilization we planned chemotherapy for Choriocarcinoma.

Chemotherapy planned

EMA-CO Regimen X 6 cycles (**Table – 2**).

Table – 2: EMA-CO Regimen [19].

EMA-CO regimen	Chemotherapeutic agent	Dosage and administration
Day 1		
EMA	Act-D Etoposide MTX	0.5 mg IVP 100 mg/m^2 IVPB 300 mg/m^2 IV continuous infusion over 12h
Day 2		
EMA	Act-D Etoposide Leucovorin	0.5 mg IVP 100 mg/m^2 IVPB 15 mg PO/IM q12h x 48h; initiate 24h after start of MTX
Day 8		
CO	Vincristine Cyclophosphamide	0.8 mg/m^2 IVP 600 mg/m^2 IVPB

The patient was lost to follow up after three cycles of chemotherapy. After three cycles of chemotherapy patient was clinically normal and her betaH C G were normal. But suddenly she appeared in the clinic, after a gap of two years, with full term pregnancy. She delivered a baby boy with cleft palate.

Discussion

Beta hCG level of less than 5 mIU/mL is considered negative for pregnancy, and anything above 25 mIU/mL is considered positive for pregnancy. Beta hCG level between 6 and 24 mIU/mL is considered a grey area, and one needs to retest to see if the levels rise to confirm a pregnancy.

When a woman is pregnant, she produces high levels of a hormone called beta human chorionic gonadotropin (HCG). But if there is no pregnancy, the elevated HCG levels can be a sign of a rare form of cancer called a gestational trophoblastic tumor. If untreated, it can metastasize rapidly and results in morbidity and mortality.

Standard hCG levels

Pregnancy week	Standard hCG range
9–12 weeks	25,700–288,000 mIU/mL
13–16 weeks	13,300–254,000 mIU/mL
17–24 weeks	4,060–165,400 mIU/mL
25–40 weeks	3,640–117,000 mIU/mL

Does Choriocarcinoma Cause C. Hemorrhage?

YES

How do you know whether it is due to routine hemorrhage or due to Choriocarcinoma?

Blood HCG levels were 12.1 mIU/ml, and CSF HCG levels were 61 mIU/ml, in this case.

HCG measurements play an important part in the diagnosis of Choriocarcinoma arising after term delivery or non-molar abortion. Such measurements are likely to be requested only on the basis of clinical suspicion**.** A diagnosis of Choreocarcinoma is untenable if HCG is not detectable by radioimmunoassay**.** Radioimmunoassay of beta human chorionic gonadotrophin (HCG) should be used to confirm the diagnosis. It is estimated that serum: CSF ratio of less than 60:1 is a sensitive indicator of metastasis in the brain [20].

The old idea that Choriocarcinoma produces very high levels of HCG dies hard. It is true only for advanced disease and since it is desirable to achieve early diagnosis it is necessary to emphasize that any level of HCG detected may indicate the presence of tumor [21].

Non-pregnant patients with no evidence of clinical disease who have been found for one reason or another to have positive tests have generally proved to have Choriocarcinoma. It has also been seen that patients with intracranial hemorrhage in the absence of overt disease in the uterus or lungs. The detection of HCG in body fluids indicates the presence of malignant trophoblast.

CSF HCG levels - HCG circulating in the blood does not readily enter the cerebrospinal fluid.

The concentration of HCG in the CSF in the absence of brain metastases is proportional to that in the serum. In the absence of brain metastases, Serum/CSF ratio is generally > 200: 1 and rarely < 60: 1, unless a precipitate fall in serum concentration is in progress when the sample is taken. When serum concentrations are low (< 60: 1) then absolute concentrations in the CSF are significant. In the presence of brain metastases CSF concentrations of HCG increases relative to that in the blood and the Serum/CSF ratio then falls below 60: 1. If the mass tumour within the CNS is high relative to that outside the CSF, the CSF concentration of HCG exceeds that of the plasma [21].

Approximately 30% of the patients with choriocarcinoma show metastasis on diagnosis. In our case, it had spread to the brain, which occurs 10% of the cases. Other less common locations are the lungs (50%) vagina (30%), liver and kidney [22].

In one series, it was preceded by a hydatiform mole in 60% of the cases, by previous miscarriages in 23%, primary in 5% and after full-term pregnancy in 10% of the cases. In the present case also it is preceded by hydatiform mole [23]. Beta-HCG is necessary for the diagnosis, and is also useful for the follow-up in the detection of recurrence and as prognostic marker. The FIGO classification and TNM classification of the AJCC are other valuable classification scales [17, 18].

CT scan showed hemorrhagic lesions with significant perilesional edema and mass effect in most of the cases. These imaging findings are often mistaken for primary intracerebral hemorrhage due to local causes, rather than tumor metastasis, particularly when there is no clue for a primary tumor in the patient. Chest X-ray done in the present case failed to reveal any metastatic deposit [24].

It is also reported, that pulmonary metastasis in 27 out of 28 patients with brain metastasis in patients with gestational choriocarcinoma. However, metastatic cerebral choriocarcinoma without pulmonary metastasis has been reported in literature [25, 26]. This illustrates the need to consider the diagnosis of metastatic cerebral choriocarcinoma even if pulmonary examination is negative.

The treatment of choriocarcinoma consists of chemotherapy, including regimens that have generally shown to be beneficial with acceptable cure rates and low recurrences. Treatment with the EMACO regimen (etoposide, methotrexate, actinomycin/ cisplatin-vincristin) in a study performed by Bolis, et al. showed a 32-month survival of 88%, in patients at a high risk [27]. We also gave EMA-CO regimen in the present case. Swisher et al reported 28% complete remissions in their study [28]. The EMA-CE regimen is more potent than the abovementioned, and is considered to be a better option in case of disease with metastasis or recurrences [29, 30].

Other options are BEP regimens and VIP (vimblastin, iphosphamide, cisplatin) that are considered as second-line options in cases of recurrence of disease progression [31].

The case of adjuvant radiation therapy is still controversial [32, 33]. Surgery is considered a second option in patients with local, chemotherapy-resistant metastasis and in recurrences [33]. Surgical treatment is the method of choice for brain metastasis in patients displaying rapidly deteriorating signs. A better prognosis will be achieved by a combination of surgical removal, chemotherapy and irradiation [34].

Conclusion

Choriocarcinoma is a malignant tumor of cytotrophoblasts and syncytiotrophoblasts, which can arise in any type of gestation and the types of preceding pregnancy includes most often hydatiform mole followed by normal pregnancy, spontaneous abortion or ectopic pregnancy [35]. It is very challenging to diagnose choriocarcinoma presenting with intra cerebral hemorrhages. A circumscribed hemorrhagic lesion with perilesional edema in young women should raise the suspicion of metastatic choriocarcinoma. Measurement of HCG in CSF and serum helps to confirm the diagnosis. It helps in initiating early therapy and effective management of these patients.

Despite the fact that prognosis of primary disease has improved greatly with effective chemotherapeutic agents, presence of metastasis in the CNS is considered an adverse prognostic factor [10]. The incidence of CNS metastasis from gestational choriocarcinoma has been reported to range from 3% to 28% [10, 11, 12, 13, 14]. The prognosis is usually favorable [16].

Pregnancy outcomes and fertility - The rates of fetal wastage, malformations, twin pregnancies, and neonatal and infantile deaths did not deviate from the normal. The published data indicate that treatment of malignant trophoblastic neoplasms with chemotherapy alone is compatible with the preservation of fertility in most women [36].

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