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Gestational Trophoblastic Neoplasia-The Great Masquerader

KEYWORDS: Gestational trophoblastic neoplasia, metastasis, presentations, β hCG, FIGO

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ABSTRACT *Objective: To report 4 cases of gestational trophoblastic neoplasia (GTN) with varied interesting presentations who were admitted in our hospital between 2011 and 2014.*

Methodology: Medical records of these 4 patients with high risk GTN were examined. All 4 patients were treated with combination chemotherapy-EMACO.

Conclusion: GTN can have varied presentations depending upon the site of metastasis. A high index of suspicion and close follow up with serum β hCG is necessary for early diagnosis and treatment.

Introduction:
Most cases of Gestational trophoblastic neoplasia (GTN) are diagnosed with plateauing or rising serum β hCG levels following evacuation of hydatidiform mole. We report 4 interesting cases of GTN with varied presentations depending on the site of metastasis, months or even years after the causative pregnancy. Early diagnosis of gestational trophoblastic neoplasia increases the chances of cure with chemotherapy. Hence a high index of suspicion and close follow up with β hCG is necessary for early diagnosis and treatment.

Case 1: Haemothorax
A 24 year old multipara presented to emergency department with complaints of sudden onset left sided chest pain and breathing difficulty for a day, 2 months following term delivery.

Prior obstetric history-

Obstetric score: $P_2L_2VM_1$ ($Para_2$ $live_2$ vesicular $mole_1$)

1st pregnancy: She had lower segment caesarean section for non-reassuring fetal status and delivered a term baby girl 3.12 kg in June 2009.

2nd pregnancy: She was diagnosed to have partial mole when she presented with bleeding per vaginum at 18 weeks and 1 day of gestation in April 2011.Her serum β hCG pre evacuation was 10,000 mIU/ml. Suction evacuation was done, but she was lost for further follow up.

3rd pregnancy: She delivered a term baby boy by lower segment caesarean section done in August 2012.Serum β hCG was not checked at 6 weeks post-delivery.

Following 2 months of lactational amenorrhea, postpartum, she presented to our emergency department with chest pain and breathlessness. She was anaemic, tachycardic, tachypnoeic, and had decreased air entry on the left side of chest. Her Chest X-ray showed left sided pleural effusion .CT scan showed left pleural effusion with partial lung collapse and multiple lung nodules {Figure1}. Liver and brain imaging was normal. Her serum β hCG was found to be 156,400 mIU/ml. She was stabilised with blood transfusion followed by insertion of intercostal drainage tube and 1.5 litres of hemorrhagic pleural fluid was drained.

She was diagnosed as GTN Stage III: FIGO score 11 and was started on combination chemotherapy with EMACO (Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, Vincristine). She received 12 cycles of EMACO totally; the 11th cycle was delayed by 2 weeks as she developed neutropenia which responded to granulocyte colony stimulating factor. She received 2 cycles of chemotherapy after normalisation of serum β hCG and was on monthly follow up.

After the last cycle of EMACO, her 3 consecutive monthly β hCG reports were normal. In the fourth and fifth month after completion of chemotherapy, her β hCG values were 14 and 400 mIU/ml respectively. She was advised metastatic work up and the need for further chemotherapy, but she refused treatment.

Two months later, she presented to the emergency de-

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partment with complaints of severe holocranial headache associated with blurring of vision and projectile vomiting for 15 days. CT brain showed cerebellar metastasis with mass effect noted on 4th ventricle {Figure 2}. Her serum β hCG was 5844 mIU/ml. High dose chemotherapy was started with dosage of methotrexate increased to 1 gram from the usual 300 mg/m^2 given as an IV infusion over 12 hours in the EMACO regimen. As she was not responding to EMACO, she was started on salvage chemotherapy after 10 days with EP (Cisplatin 20 mg/m2/day as an intravenous infusion over 2 hrs from Days 1-5 and Etoposide 100 mg/m2/day intravenous infusion over 1 hour from Days 1-5). Inj. Pegfilgrastim 6 mg was given subcutaneously on Day 6 to compensate for bone marrow toxicity. Despite these measures, she developed febrile neutropenia (WBC count-400/mm^3), infection at chemoport insertion site and expired on 28th December 2012 of sepsis.

Case 2: Acute abdomen and Shock
A 25 year old lady presented to the emergency department with lower abdominal pain and giddiness for a day 2 months following evacuation for incomplete abortion.

Prior obstetric history:

Obstetric score: $P_1L_1A_1$ ($Para_1Live_1Abortion_1$)

1st pregnancy: She had a term normal delivery in 2010.

2nd pregnancy: She had an incomplete abortion 2 months prior to presentation for which evacuation was done .Products of conception were not sent for histopathologic examination . Two units of blood were transfused as she was anaemic.

On admission, she was tachycardic, hypotensing and the uterus was enlarged to 14 weeks size and tender.

Her haemoglobin was 3.3 g% and βhCG was 3,17,000 mIU/ml

Ultrasound scan abdomen showed cystic lesions filling uterine cavity with breach of posterior myometrium and free fluid in the peritoneal cavity {Figure 3}.

The clinical impression was perforating mole with haemoperitoneum and she was taken up for emergency laparotomy. Intraoperatively, there was 2 litres of haemoperitoneum and molar tissue was found perforating the fundus of the uterus {Figure 4}. Total abdominal hysterectomy and peritoneal lavage was done and 3 units of blood were transfused.

CT scan done as part of metastatic work up 5 days after surgery showed evidence of liver and lung involvement. Brain imaging was normal. She was diagnosed as GTN Stage IV: FIGO score 12. She received 7 cycles of EMACO, 3 cycles after normalisation of β hCG. Presently, she is on monthly follow up with serum βhCG for the last 6 months which are normal.

Case 3: Haematuria
Thirty four year old multipara presented to the outpatient department with history of lower abdominal pain and haemuturia for a month.

Prior obstetric history:

Obstetric score: $P_1L_1A_1$ ($Para_1Live_1Abortion_1$)

1st pregnancy: She had a term normal delivery in 2000.

2nd pregnancy: She had evacuation for complete molar pregnancy 6 months ago.

Six months following the molar evacuation, she was evaluated for abdominal pain and haematuria. The serum βhCG was > 10,000 mIU/ml and she received 1st cycle of EMA-CO from a hospital in her hometown. She was referred with chemotherapy induced neutropenia for further management.

On admission, she was febrile with a leucocyte count of 1000/mm^3.She had hepatosplenomegaly and uterus was enlarged to 14 weeks size. Her β hCG was 1,00,000 mIU/ml. CT scan showed enlarged uterus with lesion involving myometrium infiltrating the bladder. Liver {Figure 5}and lung metastasis were present. Brain imaging was normal.

She responded to granulocyte colony stimulating factor and antibiotics. She was diagnosed as GTN Stage IV: FIGO score 12. She received EMACO with 75% of the normal dosage of etoposide and methotrexate and her β hCG showed regression (167 mIU/ml). She wanted further follow up and EMACO cycles from her hometown and hence was discharged. She was lost to follow up after that.

Case 4: Haemoptysis
41 year old multiparous lady presented with complaints of cough with haemoptysis for two months.

Obstetric score: $P_{11}L_9VM_1D_2$ ($Para_{11}Live_9$Vesicular

$Mole_1Death_2$)

She had 11 normal deliveries with last child birth 16 years ago.

She gives history of a molar pregnancy in August 2010 for which she underwent suction evacuation twice. On follow up, her β hCG was persistently high and was started on single agent chemotherapy with Actinomycin-D for a total of 8 doses, last dose in August 2011.Her βhCG normalised and she stopped further follow up. In June 2014, she developed haemoptysis. Evaluation revealed lung metastasis and hence she was referred for further management.

Her β hCG was 5,81,940 mIU/ml and imaging revealed metastasis in lung, liver and kidneys. CT brain was normal. Hence she was diagnosed as GTN Stage 4: FIGO score 18 and was started on multiagent chemotherapy-EMACO. She was allergic to etoposide and hence received only MA-CO from third cycle. After the 6th cycle, the β hCG was found to rise from 103 mIU/ml to 151 mIU/ml and hence the dose of the methotrexate was increased to 400mg from 300 mg. In spite of that, the serum β hCG level increased to 287.8 mIU/ml and hence she is started on second line chemotherapy with VIP regimen (Vinblastine, Ifosphomide and cisplatin).

The details of the 4 patients are summarised in Table 1 and the β hCG regression curves are shown in the graph 1.

Discussion:
Gestational trophoblastic neoplasia is an umbrella term for the malignant lesions that arise from abnormal proliferation of placental trophoblasts that includes invasive mole, choriocarcinoma, placental site trophoblastic tumour and epitheloid trophoblastic tumour. It is an extremely curable

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malignancy even in the presence of widespread metastasis due to its remarkable sensitivity to chemotherapy. Hence it is aptly described as "God's first cancer and man's first cure" (1).

GTN develops in 15-20% following complete hydatidiform mole, 4% following partial mole and infrequently following abortions, ectopic pregnancies and even term deliveries. But GTN developing after nonmolar pregnancies are more likely to be metastatic. The relative incidence of GTN metastasis in various sites is 80% in lungs, 30% in vagina, 20% in pelvis, 10% in brain and liver and <5% in bowel, kidney, spleen and other organs (2).

The management of GTN is based on the FIGO staging and the modified WHO prognostic scoring system (3). Patients with Stage 1 or low risk [FIGO score ≤ 6] Stage 2 or 3 are treated with single agent chemotherapy (Methotrexate or Actinomycin D). Patients with high risk [FIGO score > 6] Stage 2 or 3 and those with Stage 4 are treated with multi-agent combination chemotherapy-EMACO (Etoposide, MTX, ACT-D, Cyclophosphamide, and Vincristine). After the normalization of βhCG, 2 to 4 additional courses of chemotherapy should be given to prevent relapse.The complete remission rate with EMACO is found to be 100% in high risk Stage 2 GTN, 97.3% in high risk Stage 3 GTN and 91% in Stage 4 GTN (4).Unnecessary dose reductions and treatment delays should be avoided as they cause treatment failure and resistance.

Metastatic GTN is prone for early vascular invasion and dissemination. These patients may report with seizures, acute focal neurological deficits, haemoptysis, acute abdomen, gastrointestinal haemorrhage etc depending upon the site of metastasis. Biopsy of the metastatic lesion should be avoided as they are highly vascular and causes exsanguinating haemorrhage. A simple serum βhCG test aids in early diagnosis.

In patients with EMACO resistance, 76% attained complete remission with EMA-EP, a regimen that uses cisplatin and etoposide instead of cyclophosphamide and vincristine on day 8 in the EMACO regimen. Some women may benefit from adjuvant surgical excision of the chemoresistant tumour. Clark et al reported complete remission in 76% of women with chemoresistant disease after hysterectomy (5). Surgery not only reduces the tumour burden, but also reduces the dose and length of chemotherapy.

In patients with brain metastasis, some modification in the current regimen is required to achieve complete remission. Increasing the dose of methotrexate in the EMACO regimen from 300 mg/m^2 to 1gm/m^2 in order to ensure adequate brain coverage is recommended (4). The use of concurrent brain irradiation [3,000 cGy in 200 cGy fractions], intra-thecal methotrexate, craniotomy and resection of chemoresistant tumour etc have been incorporated in the treatment protocols for brain metastasis.

GTN can have varied presentations depending on the site of metastasis. Clinicians in all fields of medicine who treat women of reproductive age group should be aware of the unusual presentations of GTN as early recognition increases the chances of cure with chemotherapy. Though GTN is a highly curable malignancy, some patients do succumb to it due to late presentation, delayed diagnosis of primary as well as recurrent disease and resistance to treatment. Hence educating primary care physicians and gynaecologists about the signs and symptoms of GTN, close follow up with βhCG and prompt treatment with chemotherapy will help to reduce adverse outcomes due to this disease. Psychological impact of the disease should not be neglected and the patient should be managed by a multidisciplinary team for optimal outcome.

Conflict of interest statement:
The authors declare that they have no conflict of interest. There is no funding source involved.

Figure 1. CT Thorax showing left pleural effusion with partial lung collapse and multiple lung nodules

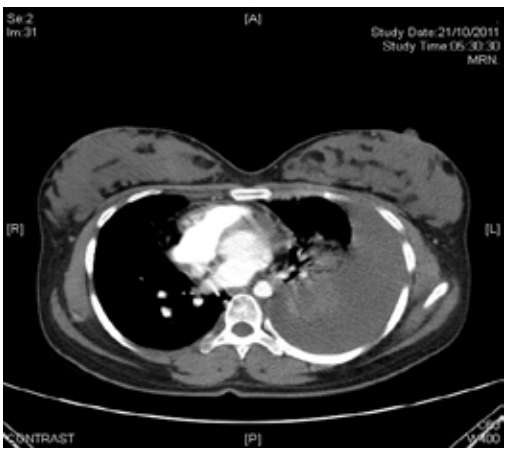
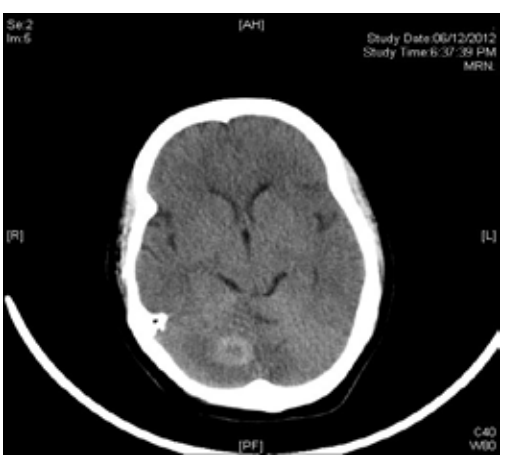


Figure 2. CT brain showing metastasis



3. USG abdomen and pelvis showing snow storm appearance inside uterine cavity with breach of posterior myometrium and free fluid in peritoneal cavity.

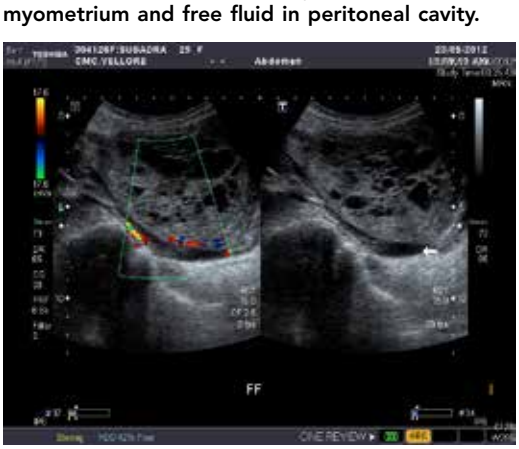


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Figure 4.Intraoperative finding showing molar tissue perforating through the fundus of uterus.

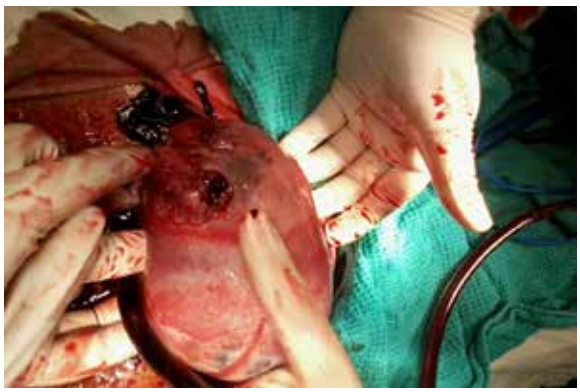
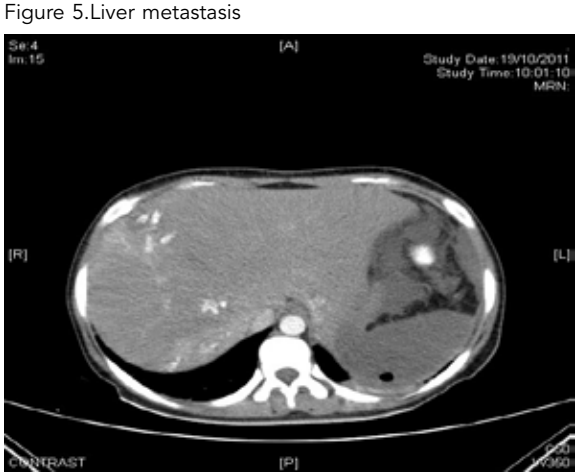


Figure 5.Liver metastasis



Graph 1: βhCG regression curves

Table 1: Case summary

Patient	Age	Antecedent pregnancy	Presentation	Stage	Treatment received	Present status
A	24	Term delivery	Haemothorax	IV:19	EMA-CO-12 cycles EP- 1 cycle	Expired
B	25	Abortion	Acute abdomen and shock	IV:12	Hysterectomy+ EMACO – 7 cycles	Remission
C	34	Molar pregnancy	Haematuria	IV:12	EMACO	Lost to follow up
D	41	Molar pregnancy	Haemoptysis	IV:18	EMACO-2 cycles MACO-4 cycles VIP- 2 cycles	On VIP regime

References:

1. Oster A. "God's first cancer and man's first cure":milestones in gestational trophoblastic disease. Anat Pathol 1996; 1:165-78
2. Ganjooei TA, Ghaemmaghami F. Patients presenting with unusual manifestations with gestational trophoblastic neoplasm: case series and review of literatures. Arch Gynecol Obstet 2008; 277: 465-70
3. Kohorn E I. Negotiating a staging and risk factor scoring system for gestational trophoblastic neoplasia: a progress report. J Reprod Med 2002; 47(6): 445-50
4. Taymaa May, Donald P. Goldstein, and Ross S. Berkowitz.Current Chemotherapeutic Management of Patients with Gestational Trophoblastic Neoplasia. Chemotherapy Research and Practice, vol. 2011, Article ID 806256, 12 pages. doi:10.1155/2011/806256
5. Clark RM, Nevadunsky NS, Ghosh S, Goldstein DP, Berkowitz RS. The evolving role of hysterectomy in gestational trophoblastic neoplasia at New England trophoblastic disease center. J Reprod Med 2010; 55(5-6): 194-98