

## Case Series

# A spectrum of gestational trophoblastic neoplasia

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## Abstract

Gestational trophoblastic disease is a spectrum of diseases caused by overgrowth of chorionic villi of placenta. They range from most Benign to most Malignant. Those with local invasion or metastasis are labelled as Gestational trophoblastic Neoplasia (GTN). We have conducted a retrospective observational study of various Gestational trophoblastic neoplasias (GTN) at NRIGH for a period of 3 years, out of which, one example of each variety is being presented. All these varieties have been successfully treated and all the patients are under follow up.

## Key words

GTN (Gestational Trophoblastic Neoplasia), EMACO (Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, Oncovirin), ETT (Epitheloid Trophoblastic Tumor), PSTT (Placental Site Trophoblastic Tumor).

## Introduction

Gestational trophoblastic disease is spectrum of diseases caused by overgrowth of chorionic villi of placenta. They are classified into Benign and Malignant [1]. Benign disease includes Hydatidiform Mole which may be complete or partial. Local invasive and Malignant form is termed Gestational Trophoblastic Neoplasia (GTN). Of them 50% follow molar pregnancy,

25% follow miscarriage and 25% follow term or preterm delivery. There are four malignant forms of GTN 1) Invasive mole, 2) Gestational choriocarcinoma, 3) Placental site trophoblastic tumor (PSTT), 4) Epitheloid trophoblastic tumor (ETT). All these varieties of gestational trophoblastic neoplasias have been successfully treated in NRIGH, and all the patients are under follow up.

## Materials and methods

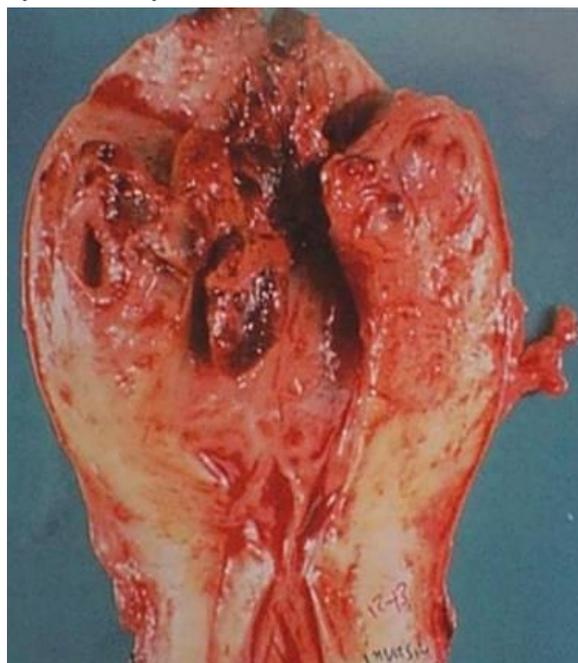
It was a retrospective observational study of 3 years duration of patients attending Department of Obstetrics and Gynecology, NRIGH.

### Case reports

#### Case - 1: Invasive Mole

A 22 year old P1L1, with history of evacuation for molar pregnancy elsewhere 2 months ago, was presented with heavy bleeding per vaginum to our hospital. On examination, she was found to be anemic and uterus enlarged to 12 weeks pregnancy size. On the day of admission patient had profuse bleeding per vaginum for which she had to be subjected for emergency hysterectomy even before detailed workup was done. She required multiple blood transfusions. Histopathology of the specimen revealed Invasive mole. GTN work up done. Initial  $\beta$ hCG was 33000 mIU/ml. She was then treated with single drug chemotherapy of Methotrexate alternating with folinic acid.  $\beta$ hCG became negative following one course. After three weekly consecutive negatives, two more courses of chemotherapy were given and patient was followed up for one year (**Figure – 1, 2**).

**Figure - 1:** Cut section of uterus, following hysterectomy in case of Invasive mole.



**Figure - 2:** Microscopic picture of Invasive mole with presence of villi along with trophoblasts, mild to moderate hydropic swelling of villi, variable degrees of trophoblastic proliferation with atypia.

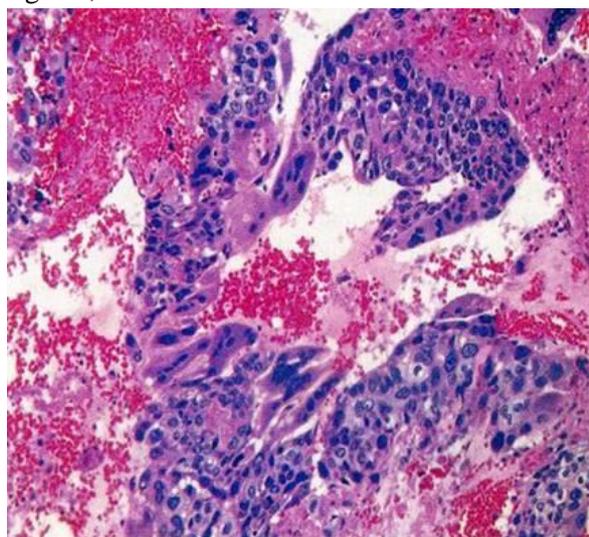


#### Case - 2: Choriocarcinoma

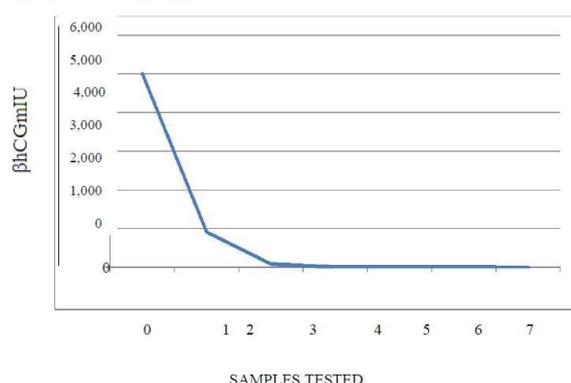
A 19 year old unmarried, with history of irregular bleeding for one and a half years duration for which patient was treated on and off with oral pills elsewhere. After admission to NRI hospital detailed physical examination and ultrasound abdomen and pelvis was done. Emergency evacuation done in view of heavy bleeding per vaginum and histopathology of endometrium showed proliferating trophoblastic tissue with both cytotrophoblast and syncytiotrophoblasts and bizarre looking mitotic figures and no villi suggestive of Choriocarcinoma. On enquiry, patient revealed a history of molar pregnancy one and half years back with no follow up after evacuation. Serum  $\beta$ hCG showed raised levels. GTN workup was done. Chest X-Ray showed 'cannon ball' metastasis and FIGO stage 4 with WHO score of 9. Subsequently patient got married following which she received multi drug chemotherapy with EMACO regimen. Patient needed 4 courses of chemotherapy before getting three consecutively negative  $\beta$ hCG. After negative  $\beta$ hCG, three more courses of EMACO regime were given. She had strict follow up with urinary

$\beta$ hCG every 6 months and was given oral contraceptive pills for two years. She subsequently conceived and had a vaginal delivery at term. Following the delivery, placenta was sent for histopathological examination, and patient had serum  $\beta$ hCG after 6 weeks followed by urinary hCG every 6 months (**Figure – 3, 4**).

**Figure - 3:** Sections studied show proliferating trophoblastic tissue with cyto and Syncytiotrophoblasts, with bizarre looking mitotic figures, no villi were seen.



**Figure - 4:**  $\beta$ hCG regression curve in Choriocarcinoma.

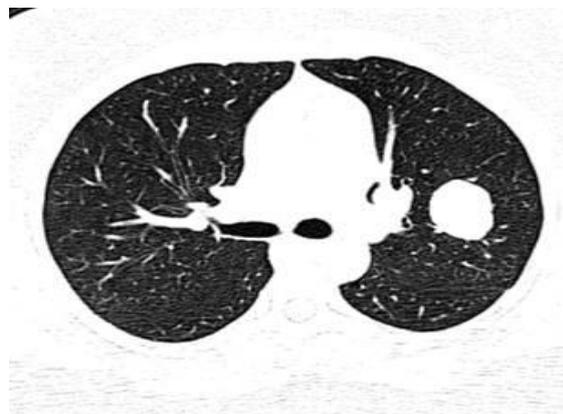


### Case - 3: Epitheloid trophoblastic tumor

A 26 year old P1L1A4 presented with persistent raised levels of  $\beta$ hCG following emergency hysterectomy and 3 courses of chemotherapy in a different hospital for Epitheloid trophoblastic tumor. Enquiry of past obstetric history revealed history of Molar pregnancy first time

followed by a term delivery by cesarean section and 3 abortions. Following last abortion she had complaints of persistent bleeding for which she was investigated elsewhere. Medical records revealed 12 weeks pregnancy sized uterus with different ultrasound scan reports of query fibroid/ adenomyosis of uterus/ invasive mole. Hysterectomy was done outside by a senior gynecologist on patients request in order to control a heavy bout of bleeding. Histopathology of the specimen revealed Epitheloid trophoblastic tumor. GTN workup was done. CT scan of brain revealed metastasis and was labelled as FIGO stage 4 and WHO score of 12. Patient was given 6 cycles of EMACO regimen. Patient had remission and relapses intermittently for which platinum based chemotherapy was also given. But still there was a slow raise of  $\beta$ hCG following remission for 1 year. Patient was admitted in NRIGH for the same reason. A total metastatic workup again was done except CT scan of Chest which showed solitary lung metastasis. Other sites were negative for metastasis. Patient was subjected to excision of the solitary metastasis with left lobectomy by the CT surgeon following which there was dramatic fall in  $\beta$ hCG. Patient has been on follow up for the last 2 years without any relapse or morbidity. From the time of diagnosis of Epitheloid trophoblastic tumor in the year 2010, even with remissions and relapses with EMACO and platinum based chemotherapy followed by lobectomy patient is doing well till date (**Figure – 5, 6, 7, 8**).

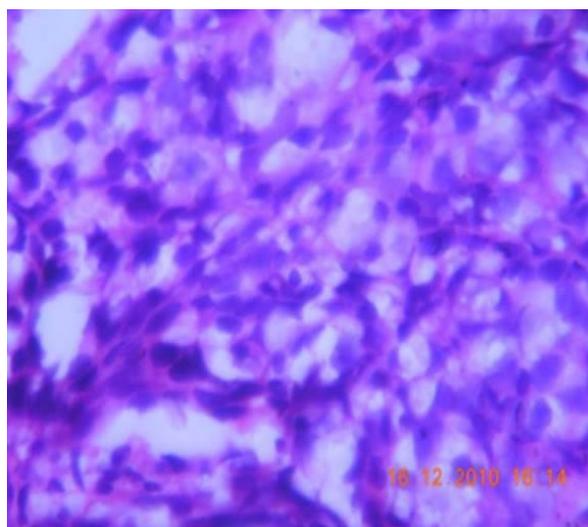
**Figure - 5:** CT image showing solitary lung metastasis.



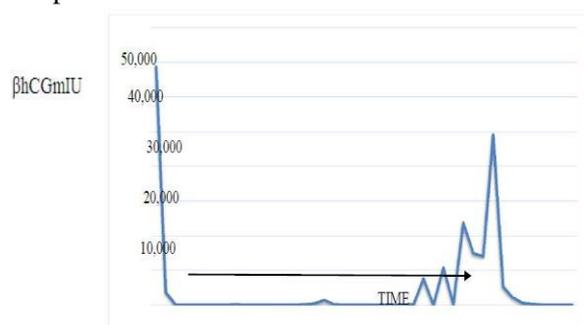
**Figure - 6:** Hysterectomy specimen of Epitheloid trophoblastic tumor.



**Figure -7:** Microscopic picture of epitheloid trophoblastic tumor showing uniform population of mononucleate trophoblastic cells arranged in nests and cords.



**Figure – 8:**  $\beta$ hCG regression curve in Epitheloid Trophoblastic tumor.



#### **Case - 4: Placental site Trophoblastic tumor**

A 20 year old G2 A1 presented with blighted ovum of 2 months amenorrhea with previous history of blighted ovum. Evacuation was done and products were sent for histopathology which revealed Placental Site trophoblastic tissue. Serum  $\beta$ hCG was normal two weeks after evacuation. However patient was advised follow up even though it was not exactly a Placental site trophoblastic tumor.

#### **Case - 5: Persistant GTN**

20 year old nulliparous woman came with past history of molar pregnancy (6 months ago) with persistent raised levels of serum  $\beta$ hCG. GTN work up was done and WHO score was 4. Patient was given two courses of single drug chemotherapy with methotrexate before her serum  $\beta$ hCG became negative. Following negative levels of serum  $\beta$ hCG, two more courses of chemotherapy were given and followed up for 1 year with contraceptive pills. Patient conceived subsequently and delivered a live baby by caesarean section at term. Placenta was sent for Histopathology, and patient was followed up after delivery.

#### **Discussion**

Gestational trophoblastic neoplasms are preceded by molar pregnancy in 50%, miscarriage in 25%, and term or preterm delivery in 25% of cases [1].

The Criteria for diagnosis of GTN [2] are:

- Serum  $\beta$ hCG > 20,000 mIU/mL 4 wks after S/E
- Plateauing of  $\beta$ hCG – 4 measurements over a period of 3 weeks - 1, 7, 14, 21 days
- Rise of  $\beta$ hCG — 3 measurements over a period of 2 weeks - 1, 7, 14 days
- Level of  $\beta$ hCG — Remain elevated 6 months after.
- Histological evidence of - Choriocarcinoma.

All the cases of GTN should be thoroughly evaluated before chemotherapy administration.

This includes physical examination, serum  $\beta$ hCG, complete blood count, hepatic, renal and thyroid function tests and metastatic work up which includes chest X -ray, ultrasound of abdomen and pelvis, CT abdomen and pelvis and sometimes CT brain if brain metastasis is suspected [3]. FIGO has given a simple staging for GTN. There are 4 stages of GTN according to FIGO [4]. WHO has given a risk scoring system based on various prognostic factors like age, antecedent pregnancy, interval between the pregnancy and tumor, serum beta hCG, site of metastasis, number of metastases etc. Based on this scoring system, GTN are categorized into low risk and high risk.

Low risk includes FIGO I, II, III with a risk score  $< \text{or} = 6$ .

High risk includes FIGO I, II, III with risk score  $\geq 7$  or FIGO stage IV.

Low risk is treated with single drug chemotherapy regimen with Methotrexate and folinic acid or Actinomycin-D.

Cure rate for both non metastatic and low risk metastatic GTN with single agent chemotherapy of Methotrexate / Actinomycin is 100% [5].

High risk GTN is treated with multidrug regimen with EMACO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Oncovirin).

When three consecutive weekly  $\beta$ hCG levels fall within normal range it is called as remission. After remission, chemotherapy should be given. Two additional cycles for a non-metastatic, low risk GTN, three additional cycles for high risk GTN [6]. Patient should be followed up with monthly  $\beta$ hCG levels for 1 year in low risk GTN and for 2 years in high risk GTN [7]. The total number of GTN's admitted in our hospital were 16 during the study period, of which 6 cases were Invasive moles, 4 cases were Choriocarcinomas, 5 were persistent GTNs, one case was Epitheloid trophoblastic tumor and one case of Placental site trophoblastic tumor. All GTNs are either referred or came with persistent bleeding preceded by history of molar pregnancy. On enquiry most of the patients were

not explained about the importance of follow up, therefore landed in severe GTN.

## Conclusion

Outcome of GTN depends on early detection of persistent disease by regular follow up after evacuation of molar pregnancy. In our case series, both choriocarcinoma and invasive mole had a history of molar pregnancy with a long duration of irregular bleeding per vaginum. All cases of persistent vaginal bleeding in reproductive age, even if unmarried, should be dealt with suspicion of GTN and  $\beta$ hCG should be estimated. All cases of molar pregnancies should be followed up with serum  $\beta$  hCG. The pregnancies following GTN, should be subjected to early ultrasonography for excluding recurrence. After delivery and abortion, the products have to be sent for histopathology. All High risk GTNs should be followed up life-long with every 6 monthly urinary hCG. Even though GTN is not preventable, since there is 15-20% incidence of developing GTN following molar pregnancy, early detection makes the staging of GTN less there by limiting the chemotherapy requirement to single drug, which has 100% cure rate along with fertility preservation. Every obstetrician should know molar pregnancy events, thereby can give good follow up, or if not available should refer to centre where facilities are available. GTN registry should be maintained and good counseling to patient's relatives need to be given.

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