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Role of Uterine Artery Ligation and Chemotherapy in Atypical Cases of Gestational Trophoblastic Disease: A Case Report of Atypical GTD Diagnosis & Management

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Introduction

Gestational trophoblastic disease[1[i]] is a rare developmental form of proliferative trophoblastic tissue in women of reproductive age that involves both benign and malignant entities that include hydatidiform mole (complete or partial), choriocarcinoma, invasive mole, epithelioid trophoblastic tumor (ETT), and placental site trophoblastic tumor (PSTT). Four of these known as *gestational trophoblastic neoplasia* [2[ii]], and hydatidiform is most common type of GTD. Gestational trophoblastic neoplasia (GTN) is a type of gestational trophoblastic disease that is almost always malignant, and can metastasize and be fatal if not treated. The ultimate treatment for GTD includes surgery (evacuation of the proliferative trophoblastic tissue, hysterectomy), chemotherapy regimens, radiotherapy and emerging targeted therapies. It is one of the most chemotherapy responsive and highly curable cancer. In most instances, it is cured by surgical evacuation of the uterus. If persistent, it is treated with chemotherapy which provides response in >90% of the cases. In the unresponsive persistent cases and if the women has completed her child bearing, hysterectomy is generally recommended. Here, we report a case of atypical GTD {uncommon, that is not fitting a single diagnosis} treated by chemotherapy and bilateral uterine artery ligation.

Case

In our institution in JAN2022, A 34-Year-old woman, G5P1L1A2, presented with a history of recurrent miscarriage in past for which 3-4 curettage was done in a row. Due to this, She developed Asherman Syndrome and distortion of endometrial-myometrium junction which latter led to development of "Atypical GTD". *Diagnosis*[3[iii]] was by clinical, radiological

[ultrasound pelvis, MRI pelvis and PET CT scan] and blood chemistry studies but she was not fitting into a single diagnosis. She was presented with the option of undergoing a hysterectomy but she chose to have other options instead. So, She was managed[4] by chemotherapy using single anticancer drugs followed by bilateral uterine artery ligation to cease profuse bleeding.

Keywords: gestational trophoblastic neoplasia, gestational trophoblastic disease, human chorionic gonadotropin, hydatidiform mole, drug therapy, chemotherapy, uterine artery ligation, evacuation.

Objective

- Implement appropriate screening measures, such as evaluating persistent or rising human chorionic gonadotropin levels and identifying clinical signs and symptoms suggestive of gestational trophoblastic disease.
- Differentiate the pathophysiology and distinguishing features of various GTD subtypes, including invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.
- To access the age or previous history of molar pregnancy as it affects risk of GTD.
- Assess the current evidence-based treatment strategies for managing GTD, including medical management, chemotherapy, radiotherapy, surgical interventions or targeted therapies.

Case Presentation

A pregnant 34 year old female with G5P1L1A2 with previous LSCS visited in Gynae Obs dept. Patient had history of several dilatation and curettage procedures in 2019 & 2020, after which adhesions were formed inside uterine cavity which was diagnosed as Asherman syndrome(Jan,2021). Further she had a period of amenorrhoea for 8-9 months with thin endometrium, for which she was administered with estrogen and progesterone therapy resulting in conception in Dec, 2021. Screening showed missed abortion of 6 weeks with irregular g-sac shape due to synechiae which might be a consequence of previous adhesions inside cavity. This was removed by dilatation and curettage in January/2022. The patient sought medical attention in our dept. as she had continuous bleeding p/v followed curettage for 20 days with profuse bleeding in between accompanied by pain in pelvis & vomiting. The outpatient records indicated that the patient`s serum beta human chorionic gonadotropin was 1364mIU/L. After that, an ultrasound was done [27/01/2022] showed thin endometrium(2.1mm) with regional endometrial-myometrial interface is not well seen and contents appear to be infiltrating into myometrium, [In our opinion, distortion of endometrial-myometrial junction had led to infiltration of Rpoc's into the myometrium]. Regional vascularity is increased [as shown in figure 1] gestational trophoblastic disease to be ruled out. We went ahead with MRI pelvis[30/01/2022], which showed a focal lesion of heterogeneous signal characteristics with

myometrium epicentre in the right lateral myometrium of uterus at fundus with associated extensive disorganized tumoral hyper vascularity in the adjoining myometrium with disruption of adjacent junctional zone as described- suggesting possibility of invasive gestational trophoblastic disease{ figure 2}. In view of GTD, PET CT[8,02,2022] conducted (to look for metastases) that reveals uterus is enlarged in size with mildly FDG avid enhancing lesion in right half of the uterus{ figure 3 }.

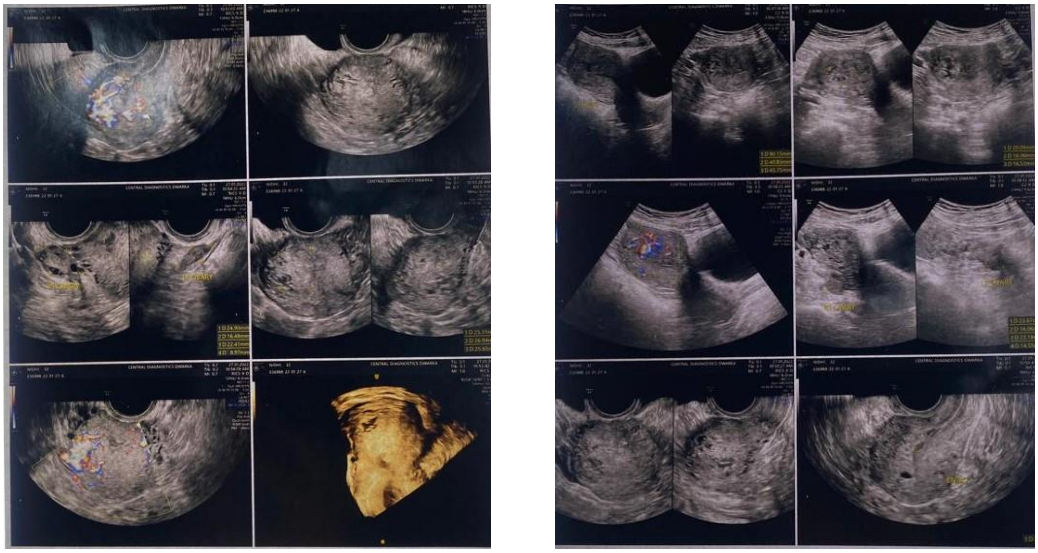


Figure 1[USG]

The contents appear to be infiltrating the right fundo-anterior myometrium with size of lesion 25.3x26.9x25.6mm. Regional vascularity is increased.

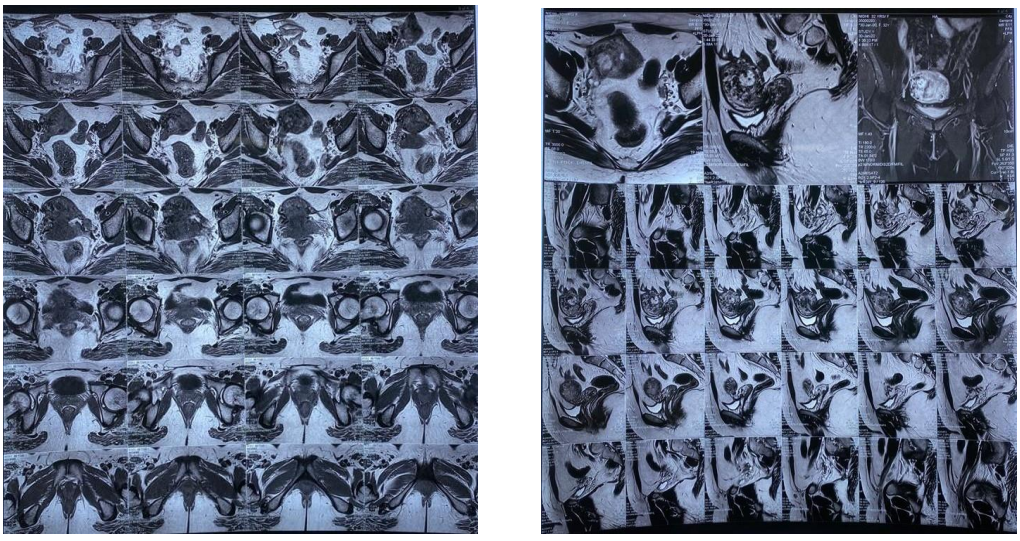


Figure 2[MRI]

A focal mass lesion of heterogeneous signal characteristics with myometrial epicentre in the right Lateral myometrium of uterus at fundus which measures approximately 30x23x25mm. Lesion shows Heterogeneously signal intensity in both T1 & T2W images. Increased perivascularity seen.

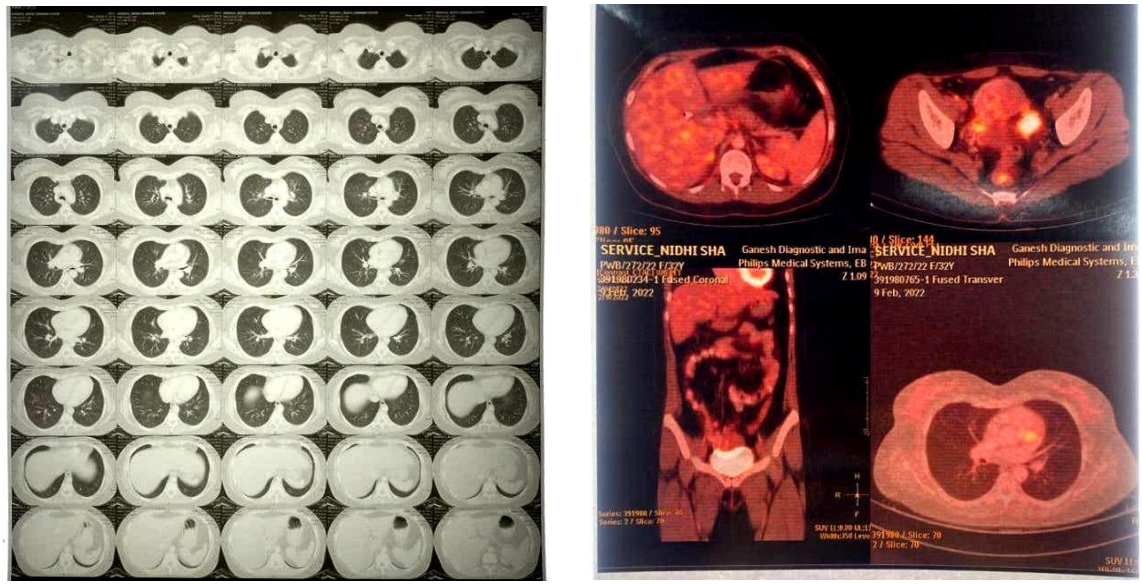


Figure 3[PET scan]

Mildly FDG avid enhancing lesion in the right half of the uterus (3.9x3.6 cm, SUV max 5.8)

She was given an option to undergo hysterectomy but she refused and chose to have other options instead. So, she was referred to oncology department and the HCG test was done again. The result of test was 202mIU/L.

Even though β HCG levels were not too high (202mIU/L) but after considering clinical features and above investigations, patient was not fitting into a single diagnosis and titled as "Atypical GTD" and was administered with single drug systemic chemotherapy from feb,2022 with Intravenous methotrexate along with drug calcium leucovorin (folic acid analog). This treatment showed significant fall in β HCG levels but patient still complaint of profuse bleeding in between changing 6-7 pads per day. A Repeat ultrasound performed in April/2022 (after 2 months of chemotherapy) following the complaints, suggestive of focal poorly margined heterogeneous area (approx. 39x28x30) in right upper endometrial cavity. The area shows a bunch of tortuous vascular channels showing a high degree of internal vascularity consisting of arterial vessels (PSV of up to 116cm/sec, similar to that in right uterine artery) [as shown in figure 4] and accompanying dilated draining veins with high flows. Bilateral parametrial and paracervical vessels are dilated. Bilateral uterine arteries are dilated and show low resistance high velocity flows.

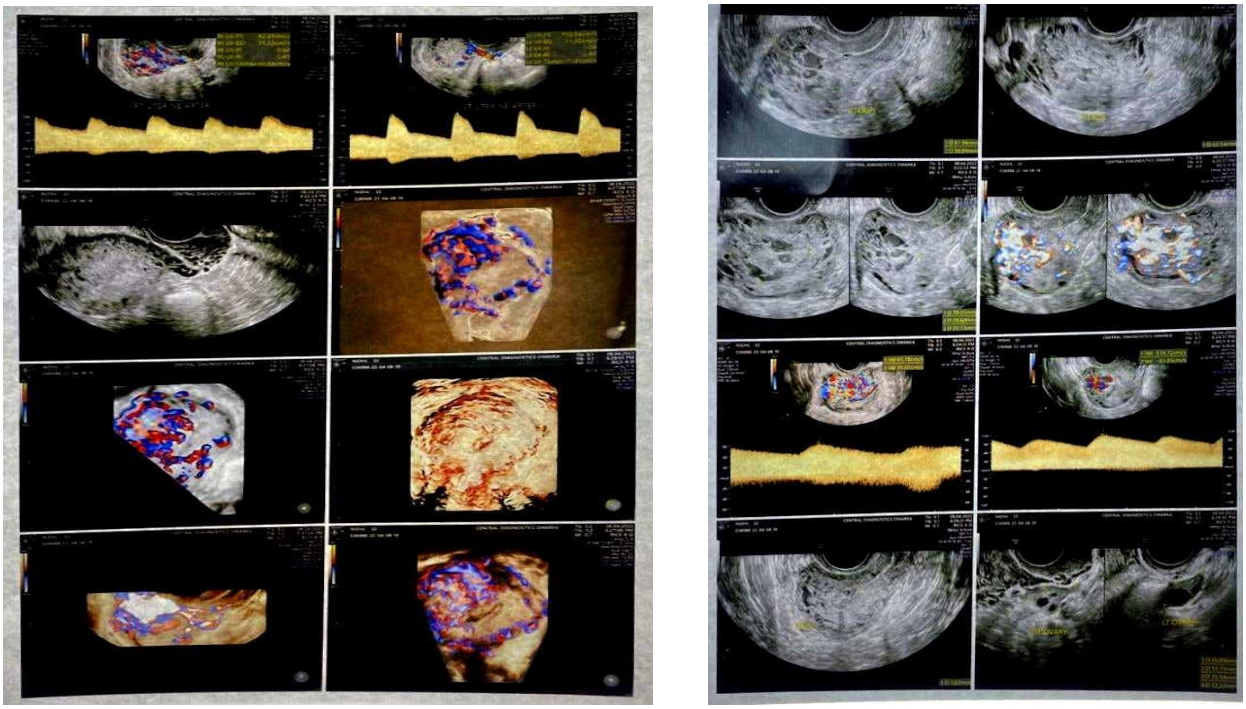


Figure 4

The area shows a bunch of tortuous vascular channels showing a high degree of internal vascularity consisting of arterial vessels (PSV of up to 116cm/sec, similar to that in right uterine artery)

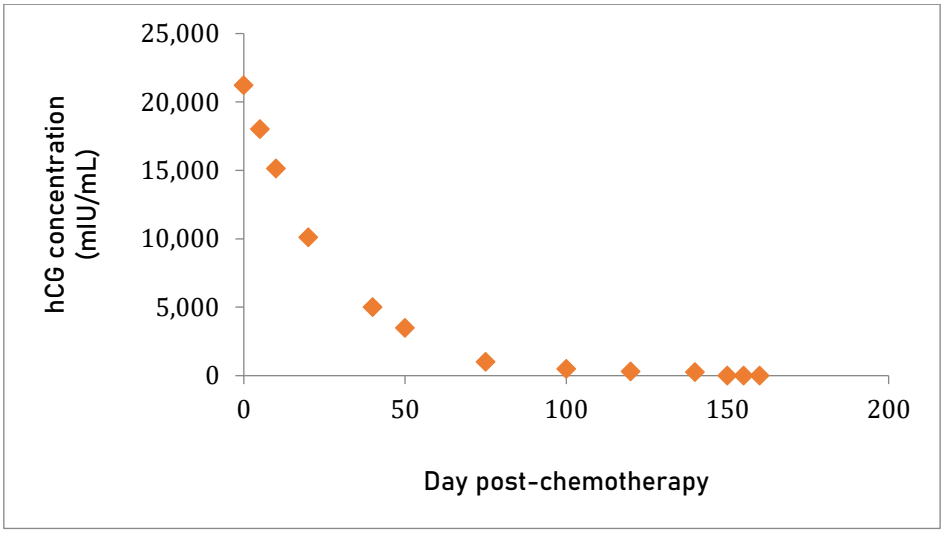
As there was a high degree of internal vascularity in ultrasound along with dilatation of bilateral uterine arteries and high velocity flows, so in order to control bleeding patient underwent laparoscopic bilateral uterine artery ligation and chemotherapy was continued.

During surgery, her vital status showed moderate pallor, tachycardia (120/min), tachypnoea (32 breaths/min), and B.P of 90/60 mmHg. Her respiratory and cardiovascular examinations revealed no abnormality. On abdominal palpation, abdomen was soft, non-tender and there was no organomegaly. Her baseline investigation showed Hb- 9.2 gm%, TLC- 22,000/mm^3, LDH 191.81, and Sr. TSH 1.87, renal and liver function tests were all within normal limit.

5 months of chemotherapy with surgical management resulted in falling levels of beta HCG followed by normal β HCG levels for 3 consecutive readings [0.17, 0.14 & 0.10](as shown in

Figure **4**) and symptomatic normalcy [as shown in Graph 1]

Sometimes 1 to 2 cycles of maintenance chemotherapy is advised after first normal βHCG.



GRAPH 1 Patient's serum HCG response to chemotherapy over time

DATES	10/02	21/02	28/02	14/03	30/03	12/04	25/04	07/05	02/06	21/06	12/07	04/08
βHCG	202	57.18	41.05	20.73	11.16	6.32	2.67	1.31	0.26	0.17	0.14	0.10

Figure 4: Falling levels of beta HCG on chemotherapy treatments

As methotrexate infusion can cause hepatotoxicity, renal impairment, pulmonary damage, repeated CBC, LFT, KFT, βHCG performed [LFT/KFT-normal].

On follow-up, βHCG monitoring had done every month for at least 12 months. Reliable contraception must be used throughout this period. After 3 months, repeat USG showed no abnormality and patient was asymptomatic. Now, patient is pregnant with 13weeks 4 days pregnancy post 18 months of chemotherapy treatment proving that an adequate collateral blood supply develop to support pregnancy.

Result

In our case, clinical diagnosis is made after implementing all screening measures such as physical examination, human chorionic gonadotropin levels, identifying all clinical signs and symptoms, differentiating pathophysiology and GTD subtypes with all diagnostic investigations and serum tumour marker test, patient is diagnosed with "Atypical GTD". Patient is managed by single drug systemic chemotherapy followed by laparoscopic bilateral uterine artery ligation to cease bleeding. Chemotherapy continued until the beta human chorionic

gonadotropin levels were normal for at least 3 weeks after treatment ends.

12 months follow up done & patient is presently free of symptoms and pregnant with 13weeks 4days pregnancy post 18months of chemotherapy treatment.

Discussion

GTD comprises a spectrum of premalignant and malignant diseases, including hydatidiform mole (complete or partial), placental site trophoblastic tumour, choriocarcinoma and gestational trophoblastic neoplasia (low risk or high risk). Hydatidiform mole (also known as molar pregnancy) is the most common form of these. Each of these conditions can perforate the uterine wall, metastasize and lead to death if left untreated.

GTD classically presents with a combination of symptoms such as uterine enlargement greater than gestational dates, vaginal bleeding, pain and pressure in the pelvis, hyperemesis, pregnancy-induced hypertension with swelling of feet and hands and sometimes overactive thyroid(hyperthyroidism) that can cause fast or irregular heartbeat, sweating, frequent bowel movements, trouble sleeping, feeling anxious or irritable or weight loss. Clinical diagnosis is based on history, physical examination, pelvic ultrasound and high serum β-HCG quantification and after assessing whether the tumour has spread to the uterus, lymph nodes or distant parts of the body. Treatment is to choose standard treatment for patient with different types of gestational trophoblastic disease like urgent surgical evacuation and curettage/hysterectomy or chemo or radio therapy. Some treatment are being tested in clinical trials.

In North America, there is a 0.1% incidence of molar pregnancy in all pregnancies; in Asia, it is up to three times higher. It is even rare to encounter advanced GTD in the modern era, due to earlier diagnosis by serum β-HCG quantification and pelvic ultrasound, as well as effective means of uterine evacuation.

In 2002, FIGO [4[iv]] adopted a combined anatomic staging and modified WHO risk-factor scoring system for GTN. Patients with non-metastatic disease (Stage I) and low-risk metastatic GTN (Stages II and III, score <7) can be treated initially with single-agent chemotherapy with either methotrexate or actinomycin D[5[v]] with cure rates approaching 80-90%. Low risk patients are usually treated with single agent chemotherapy. Single agent actinomycin-D or methotrexate with or without folinic acid is the primary management [6[vi]]. With appropriate initial classification [7[vii]] and proper treatment, cure rate approaches 100%. Careful monitoring for evidence of drug resistance (plateau or ↑ β-HCG and/or devolvement of new metastasis) as 30-50% develops resistance to the first line chemotherapy agent and 5-15% may require multi-agent chemotherapy and/or other modalities. DuBeshter *et al*. treated 48 patient between 1965 - 1990 with low risk metastatic GTN with single agent MTX or actinomycin D and noted all patients achieved sustained remission, although

51% required 2nd single-agent regimen and 14% need multi-agent chemotherapy, and 12% underwent resection of resistant tumour foci.

In our case, the patient was diagnosed by imaging[8[viii]] like USG, MRI pelvis and whole body PET scan. Her beta HCG level was not too high, still on basis of all investigations patient was not fitting into a single diagnosis and treated as "Atypical GTD". She underwent single drug chemotherapy but to cease bleeding laparoscopic bilateral uterine artery ligation done. The patient showed improvement with fall in beta HCG levels. The treatment continued for 5 months and on follow up there is no rise in beta HCG levels for 12 months.

As patient encouraged for contraception during the entire interval of monitoring. The risk of abnormal pregnancy (spontaneous abortion, still birth, repeat mole) is greater during the first six months following treatment (for low risk or high risk GTN) than after a year following treatment; therefore, patients are normally advised to avoid pregnancy for the first year following treatment. First trimester ultrasound and serum βHCG testing is indicated for women who become pregnant for the first time after treatment for GTD. β HCG testing at 6-8 weeks after delivery to assure it has normalized and placenta should be sent for histopathology.

Conclusion

Patient with GTD in this study diagnosed when there is clinical, radiology [9[ix]], pathological or hormonal evidence of gestational trophoblastic disease not fitting into a single diagnosis. Due to recurrent miscarriage in past, patient developed Asherman Syndrome and distortion of endometrial-myometrium junction which led to infiltration of RPOC'S into myometrium. For further evaluation, MRI pelvis shows Gestational Trophoblastic Disease and PET scan shows mildly FDG avid enhancing lesion in right half of uterus. Though β HCG was not too high, but considering all investigations and symptoms, she falls into category of "Atypical GTD". Patient was given an option to undergo hysterectomy, but she chose other options and opted for chemotherapy. Though chemotherapy showed good results in our patient still in view of high degree of internal vascularity and dilatation of bilateral uterine arteries in later ultrasound with profuse bleeding, she went for laparoscopic ligation of bilateral uterine arteries. This proves that early adequate treatment ensures an excellent prognosis. Early diagnosis and management[10[x]] along with regular follow up is the key in GTD. One should emphasize on persual of different treatment modalities to reduce the suffering and better outcomes for the patients.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Patient Consent

Written informed consent was obtained from the patient for the publication of this case report.

Biography

Dr Poonam Chandora

Obtained her MBBS from University of Rajasthan and her post-graduation MD in obstetrics and gynaecology from University of Delhi. Her field of specialisation includes laparoscopic surgeries, obstetrics, ultrasound, infertility and has 10+ years of experience in them. She is working as department head obstetrics and gynaecology at Mata Roop Rani Maggo hospital, Delhi for last 15years.

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