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RESEARCH ARTICLE

EARLY PRESENTATION OF GESTATIONAL TROPHOBLASTIC NEOPLASIA AFTER TERM DELIVERY

Dr. Roshni[1], Dr. Prashant Kharde[2] and Dr. V.B. Bangal[3]

1. Final Year Resident, MS (Obstetrics and Gynaecology), DBVP Rural Medical College, Loni.
2. Professor, Department of OBGY, DBVP Rural Medical College, Loni.
3. Professor and Head, Department of OBGY, DBVP Rural Medical College, Loni.

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Abstract

Introduction:-

The term Gestational Trophoblastic Disease (GTD) encompasses a spectrum of tumours with a wide range of biologic behavior and potential for distant metastases. GTD refers to both the benign and malignant entities in the spectrum and includes Hydatidiform Mole (complete and partial), Invasive mole, Choriocarcinoma, Placental Site Trophoblastic Tumor (PSTT), Epithelioid Trobhoblastic Tumor (ETT).[1]The last 4 are referred to as Gestational Trophoblastic Neoplasm (GTN)- all may metastasize and are potentially fatal if left untreated. The incidence of Postpartum GTN is 1 in 1,50,000 pregnancies.[2]

Case Report:

A 28 year old female Gravida 2 Para 1 Living1 with previous LSCS with 34 weeks of gestational age went to private hospital with complaints of pain abdomen and absent fetal movements; diagnosed Intrauterine fetal death on Sonography. Patient underwent hysterotomy for the same. Patient was discharged on Post-Operative Day 4. Patient started complaining of on & off pervaginal bleeding after 2 weeks and she was treated symptomatically. She felt better for 1 week and again started having similar complaints. She went to a private hospital where Pelvic Ultrasound imaging was done which reported around 60-70 cc of retained products of conception. Patient underwent Dilatation and Evacuation under general anesthesia. Patient was stable and was discharged after the procedure. After 2 weeks, Patient presented again with similar complaints, USG revealed 60cc of Intrauterine collection and Beta HCG of 20000 mIU/ml. Patient's Hb was 4g/dl, hence 2 PCV were transfused and was referred to our tertiary care setting for further management. On Admission, Patient was vitally stable. On routine investigations, patient was found to have severe anaemia with Hb 5.5 gm/dl. USG was done which reported approx. 36*23*21 mm (Volume 15cc) of echogenic area in Endometrial cavity showing peripheral vascularity on color Doppler likely possibility of retained Placenta. Beta HCG levels were 15,000 mIU/ml. MRI Contrast was done which reported 3.9*3.3*2.1 cm lobulated area suggestive of Retained Succenturiate lobe of Placenta in Endometrial cavity, uterus measured 10.2*8.5*7.2 cms. Patient underwent USG guided Dilatation and Evacuation and products were sent for Histopathological analysis. HP report – Gross: multiple dark brown tissue pieces aggregate measuring 7*1 cm, no fetal parts or vesicular structures identified. Microscopy: Sections showed blood clots, fibrin and clusters of trophoblasticcells with hyperchromatic nuclei and eosinophilic cytoplasm; focally the trophoblastic tissue appear infiltrating into myometrium, Chorionic villi not seen and at places multinucleated trophoblast seen. Beta HCG levels after 1 week were 37468 mIU/ml, repeated after 2 days – 64000 mIU/ml. USG repeated at this stage revealed 7*28*9.6mm (vol 20cc) sized heterogeneously hyperechoic areain posterior Right lateral and fundic wall of Uterus

Corresponding Author:- Dr. Roshni
Address:- Final Year Resident, MS (Obstetrics and Gynaecology), DBVP Rural Medical College, Loni.

in Endometrial &Myometrial junction suggestive of GTD. After 2 days, her Beta HCG peaked to 257710mIU/ml. Review USG was done which revealed 41*42*30 mm (33-35cc vol) area showing internal vascularity on color Doppler involving 60-70% of posterior myometrial wall.
MRI contrast was repeated which showed an ill-defined lobulated heterogeneously enhancing lesion suggestive of Placental site aggressive lesion. Chest X-ray and CT Brain were done to rule out metastasis. Scoring for GTN was done (FIGO anatomical staging and WHO risk assessment score) classified patient as Stage I:9, High risk GTN. Medical Oncologist opinion was obtained and she was started on Multidrug Chemotherapy -EMACO regimen. Patient received 5 cycles of EMACO regimen at 2 weeks interval.

Day 1 – Inj Methotrexate 300mg/m^2IV infusion for 12 hours
Tab Leucovorin (folinic acid) 15mg 24 hours after methotrexate – 4 doses each every 12 hours apart
Day 1 &2:
InjEtoposide 100mg/m^2 IV in 500ml DNS over 3 hours
InjDactinomycin 0.5mg IV push in running 5% dextrose over 5 minutes
Day 8:
Inj Cyclophosphamide 600mg/m^2 in 500 ml NS IV over 2 hours
Inj Vincristine 0.8 mg/m^2 IV push in 100ml NSover 10 minutes

Since the first cycle, patient had severe nausea and vomiting. Patient underwent 2 cycles, and then she was diagnosed to have Herpes Labialis. Even though precautionary antibiotics were given, Chemotherapy causes leukopenia (neutropenia) and hence the body becomes susceptible to infections. Chemotherapy was put on hold and Herpes labialis was treated with Acyclovir. Monitoring of Beta HCG levels and USG were done in every cycle. Serum Methotrexate levels were monitored to check for toxicity. After second cycle, Patient's serum Beta HCG levels dropped to 2252 mIU/ml. After third cycle, they fell to 5.45 mIU/ml. She underwent fourth and fifth cycle successfully and Beta HCG levels were 2.4 mIU/ml. Other than Nausea and vomiting, alopecia was only prominent side effect noted. Patient was discharged after counselling regarding the importance of follow up for regular Beta HCG levels monitoring and to strictly use contraception for next 2 years.

Discussion:-

Epidemiology:
A wide global variation in the prevalence of molar pregnancy has been reported, ranging from0.5 – 1 per 1000 pregnancies in North America to 12 per 1000 pregnancies in Asian countries including India. Likewise, the reported prevalence of choriocarcinoma varies widely worldwide, from a low 2 per 100000 pregnancies in USA to 202 per 100000 pregnancies in China.[3]

Pathophysiology:
Trophoblast cells are the first to differentiate from the fertilized ovum: they form the outer layer of blastocyst, providing nutrients to the embryo and ultimately forming the fetal portion of the placenta. Normal trophoblasts are composed of the cytotrophoblasts, syncytiotrophoblasts and intermediate trophoblasts. Hydatidiform mole and choriocarcinoma arise from cytotrophoblast&syncytiotrophoblast, whereas PSTTs and ETTs arise from intermediate trophoblasts.[4] Invasive mole and Choriocarcinoma follows Complete H-Mole, in 15-20% of cases and Partial mole in less than 5% cases.

Choriocarcinoma is a rare type of GTN and may manifest after hydatidiform mole (most common precursors -50%), normal pregnancy or an abortion. It is a malignant Beta-HCG producing epithelial tumor with abnormal cytotrophoblasts and syncytiotrophoblast that lack chorionic villi. It has potential to invade pelvic structures and metastasize to distant sites. PSTTs and ETTs arise from neoplastic proliferation of intermediate trophoblasts at placental implantation site. They typically occur after non molar gestation, grow slowly tend to spread locally to uterus, and have a propensity for lymphatic metastases. The GTD spectrum has been recently expanded to include Atypical Placental Site Nodule (ASPN).

Diagnosis and Staging:
The most common Clinical finding in GTN is Irregular PV bleeding associated with uterine sub involution. The bleeding maybe continuous, intermittent or sudden and massive. Myometrial invasion from trophoblastic growth can cause intraperitoneal hemorrhage. Lower genital tract metastasis and distant metastases have to be screened. Consideration for the possibility of GTN is the most important factor in its recognition. Unusually persistent

bleeding after any pregnancy should prompt serum Beta HCG level measurement.Once the diagnosis is verified, baseline serum Beta HCG levels and routine investigations should be done. Metastases to lung, liver and brain must be checked by Chest X-ray, USG/ CT/ MRI (Abdomen) and CT / MRI Brain respectively. Patient is classified using FIG0 2000 Staging system comprises of WHO prognostic scoring system. WHO score of 6 and below is low risk GTN and is treated with Single drug Chemotherapy mostly Methotrexate. Score of 7 and above is high risk GTN and is treated using multidrug chemotherapy regimen (EMACO/EMAEP protocols).

Stage	Description
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	GTN extends to the lungs with or without known genital metastases
IV	All other metastases

WHO score	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4 to <7	7 to <13	≥13
Pretreatment serum hCG (IU/mL)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$\geq 10^5$
Largest tumor size (including uterus)	<3 cm	3 to <5 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	–	1 to 4	5 to 8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

WHO adopted FIGO 2000 Diagnostic & Scoring system

Dobsan[5] et al studied clinical manifestations of 9 patients with postpartum choriocarcinoma; noted that all 9 patients presented with abnormal uterine bleeding. In 4 cases, it was persistent from the time of delivery and in other 5 patients bleeding commenced from the median of 5 weeks after delivery. In our patient it was early presentation of abnormal bleed 2 weeks after delivery. The WHO risk assessment scoring categorized our patient in high risk GTN, hence hysterectomy was not indicated and Multidrug Chemotherapy was given. In study by Dobson[4]all 9 patients received Chemotherapy with median 8 cycles, whereas our patient received 5 cycles and responded well to Chemotherapy. With only one living child and hysterectomy not done, fertility was preserved. Had Hysterectomy been done in our patient, probably we could have come to a more appropriate diagnosis of PSTT. In both low and high risk GTN, once Serum Beta HCG levels become undetectable, Serosurveillance is continued for1 year. During this period, patients are advised to use contraception so as to prevent teratogenic effects of chemotherapy to fetus and also to avoid confusion of rising HCG levels caused by superimposed pregnancy.

Conclusion:-

GTD is a complex spectrum of related disorders originating from placenta. The morbidity and mortality from GTD were substantial before the advent of sensitive assays for Beta HCG. However, the vast majority of women currently afflicted with GTD have favorable outcomes, largely due to improved diagnostic and surveillance techniquesand state-of-the-art chemotherapeutic regimens. Early diagnosis and treatment reduces the mortality and morbidity of GTD.

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3. Residents – Dept of OBGY, Radiology, Pathology and Radiooncology.

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