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Original Research Article.

Histomorphologic Interpretation of Gestational Trophoblastic Diseases: An Analytic Approach to Diagnosis

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ABSTRACT

Introduction: Gestational trophoblastic diseases (GTD) comprise a group of rare lesions that take origin from cells which would normally develop into the placenta during pregnancy. They include neoplastic lesions like choriocarcinoma, placental site trophoblastic tumour, epithelioid trophoblastic tumor and non-neoplastic lesions like hydatidiform mole, invasive mole, exaggerated placental site and placental site nodule. The interpretation is very important as the therapeutic approach and prognosis is dependent on diagnosis. There are several problematic areas in morphologic interpretation of these various GTD lesions which must be addressed to ease the categorisation.

Material and Methods: All the cases histopathologically diagnosed as gestational trophoblastic diseases in Department of Pathology, SCB Medical College, Cuttack were included in the study over a period of three years from February 2015 till January 2017. The age, clinical details, USG findings, serum β hCG level, gross features and histpathologic findings were analysed.

Results: Out of 77 cases of gestational trophoblastic diseases 70.6 % were hydatidiform mole, 06 % invasive mole and 14.4% choriocarcinoma, one case of metastatic choriocarcinoma and single case of placental site trophoblastic tumor and an interestingly rare association of a case of complete hydatidiform mole with invasive mole and placental site reaction. The serum β hCG level was highest in metastatic choriocarcinoma and > 1,00,000 mIU/ml in 10 cases of choriocarcinoma, 3 cases of invasive mole and one case of complete hydatidiform mole.

Conclusion: All the histopathologists have lot of scope to examine the products of conception. A thorough knowledge of different categories can make one aware of the occurrence of gestational trophoblastic disease. Histopathology is the gold standard in diagnosis of GTD. Therefore the diagnosis of GTD can be comfortably made from simply H&E stained tissue with the clinical details, investigation findings like USG and serum β hCG titer. This study will be a guideline for the pathologists to categorise the GTD lesions.

Key Words: Choriocarcinoma, Gestational Trophoblastic Diseases, Hydatidiform Mole, Histopathology, β hCG Titer.

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INTRODUCTION

Gestational trophoblastic disease (GTD) defines a heterogenous group of interrelated lesions arising from the trophoblastic epithelium of the placenta.[1] The incidence of various forms of GTD in United States is approximately 1 in 600 therapeutic abortions and 1 in 1,500 pregnancies.[2] The international rate of choriocarcinoma has been reported to be as high as 1 in 500-600 pregnancies in India to 1 in 50,000 pregnancies in Mexico, Paraguay, and Sweden.[3-5] GTD is among the rare human tumors that can be cured even in the presence of widespread dissemination.[6] The various forms of GTD can be defined and related to discrete pathologic aberrations occurring at different trophoblastic subpopulations and stages of trophoblastic differentiation during placentation.[7] The morphology in different forms of GTD are generally related to (1) trophoblastic proliferation with degree of pleomorphism, (2) presence / absence of chorionic villi and (3) hemorrhage and or necrosis. One has to be thorough with different types of trophoblasts and their presentation in different forms of GTD. Hence, the diagnosis can

be challenging histopathologically. Therefore, we undertook this prospective study with emphasis on diagnostic approach and morphologic pitfalls in histopathologic evaluation.

MATERIALS AND METHODS

The present study was carried out over a period of three years from February 2015 to January 2017 in the Department of pathology, S. C. B. Medical College, Cuttack. Cases diagnosed as any form of gestational trophoblastic disease after histopathological examination were included in the study. Histopathological diagnosis of different gestational trophoblastic diseases was given by taking into account of the diagnostic criteria of individual diseases. Age, clinical symptoms, USG findings, serum β hCG level and provisional diagnosis were recorded. The recognition and separation of the individual categories of gestational trophoblastic diseases are carried out according to the modified world health organisation classification system.[8]

Table 1: Specimen types showing GTD. (n=77)

Type of specimen	No.of cases (n)	HM	IM	CC	PSST	EPS	PSN	HM+ IM+ EPS
Curettings	59	52	-	-	-	03	04	-
Hysterectomy	17	-	05	09	01	-	01	01
Metastatic nodule	01	-	-	01	-	-	-	-
Total	77	52	05	10	01	03	05	01

HM: Hydatidiform mole; IM: Invasive mole; PSTT: Placental site trophoblastic tumor; EPS: Exagerated placental site; PSN: Placental site nodule; CC: Choriocarcinoma

Table 2: Agewise distribution of GTD. (n=77)

Histopathological diagnosis	No.of cases (n)	21-30	31-40	41-50
CHM	32	20	10	02
PHM	20	14	03	03
Invasive mole	05	-	02	03
Choriocarcinoma	10	-	07	03
PSTT	01	-	-	01
EPS	03	02	01	00
PSN	05	01	03	01
CHM+EPS+IM	01	-	01	-
Total	77	37	27	13

CHM: Complete hydatidiform mole, PHM: Partial hydatidiform mole,
PSTT: Placental site trophoblastic tumor, EPS: Exagerated placental site, PSN: Placental site nodule.

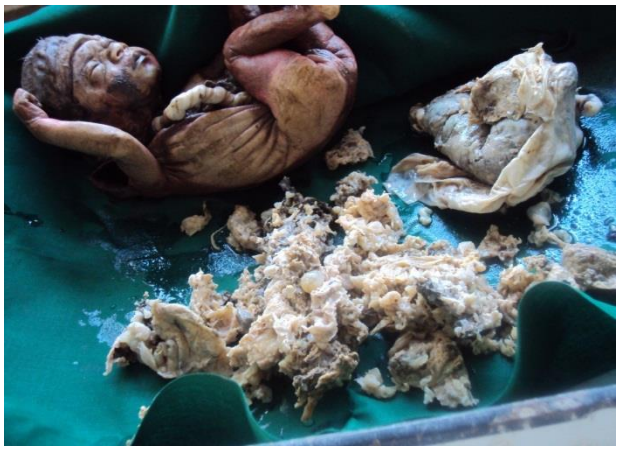

Fig 1: Twin pregnancy comprising of partial hydatidiform mole with a dead fetus in whom autopsy was done.

RESULTS

The study included 77 specimens of gestational trophoblastic diseases. The percentage of GTD in our study is 06.66% out of uterine curettings and hysterectomy specimens. Gross specimens showing features of GTD included 59 uterine curettings, 17 hysterectomy specimens and one metastatic nodule in lower female genital tract. Out of all hysterectomy specimens, the majority (9 cases or 56.25%) were choriocarcinoma (Table 1).

Most common type of GTD was hydatidiform mole (52 cases or 68.4%). Complete moles are relatively more common (32 cases or 42.0%) than the partial moles (20 cases or 26.49%). The ultrasonographic findings were absence of foetal parts with increased uterine size as per gestational age and a snowstorm or speckled pattern. The patients presented predominantly in the 2nd to 3rd decade (37 cases or 48.68 %) (Table 2). One rare case presented as a twin pregnancy with a term fetus with partial hydatidiform mole (Fig.1). The mother was 30 years old, G2P2L1 and had dichorionic, diamniotic twin pregnancy. Her serum β hCG level was 32,000 mIU/ml. After delivery it came down to 832 mIU/ml and reached normal value after 3 months.

Invasive moles (5 cases or 6.57%) were present in 5 hysterectomy specimens with clinical diagnosis of persistent gestational trophoblastic disease. Grossly small foci of invasion were seen in the myometrium. Histopathologically, there was presence of edematous chorionic villi with trophoblastic proliferation, which invade directly into the myometrium (Fig.3). An unusual case of 40 year female with bleeding per vaginum after 3 months of amenorrhoea diagnosed in hysterectomy with

complete hydatidifom moles in uterine cavity, myometrial exaggerated placental site reaction and invasive mole (Fig.4). Choriocarcinoma was detected in 10 cases (13.15%) in present study. An interesting case of choriocarcinoma with metastatic vaginal nodule was detected in a 35 years old female, who presented with bleeding per vaginum off and on for last 15 days. She had undergone suction and evacuation 2 months back following spontaneous abortion of 3 months of gestation. She was P4L4A2, all were vaginal deliveries. Her last child birth was 11 months back. There was a suburethral nodule of 2.5x2.0 cm on left vaginal wall. Fine needle aspiration (FNA) smears were paucicellular mostly showing haemorrhage. However extensive search revealed biphasic pattern constituting predominantly of cytotrophoblasts. Because of the presence of appropriate history, a provisional diagnosis of choriocarcinoma was given. Histopathologically, biphasic pattern of cytotrophoblast and syncytiotrophoblast were seen along with extensive areas of hemorrhage and necrosis (Fig.6). Her serum β hCG level was very high (1,20,080mIU/m). Another rare case of pure ovarian choriocarcinoma in ovary following ectopic pregnancy was encountered in our series. Other cases of choriocarcinoma were detected in hysterectomy specimens mostly showing diffuse involvement of endometrial cavity by friable mass constituting of hemorrhage and necrosis. (Fig.5)

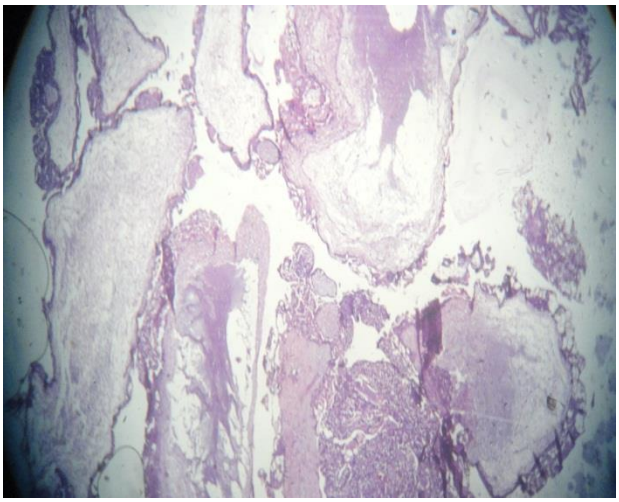

Fig 2: Large dilated hydropic avascular villi in complete hydatidiform mole. H&E x100

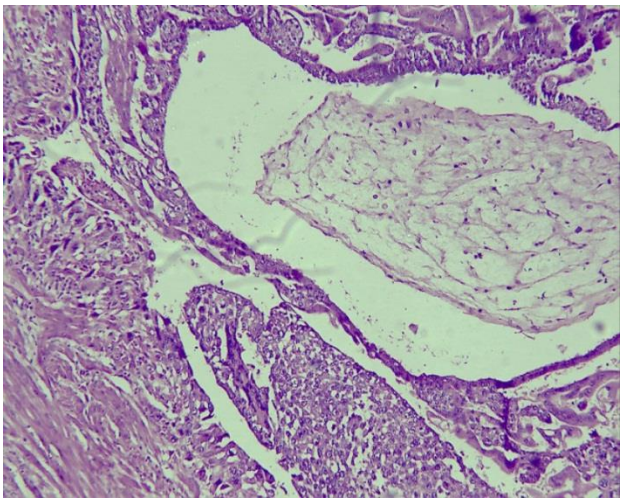

Fig 3: Photomicrograph of invasive mole with presence of hydropic dilated villi and trophoblast in myometrium,H&Ex100

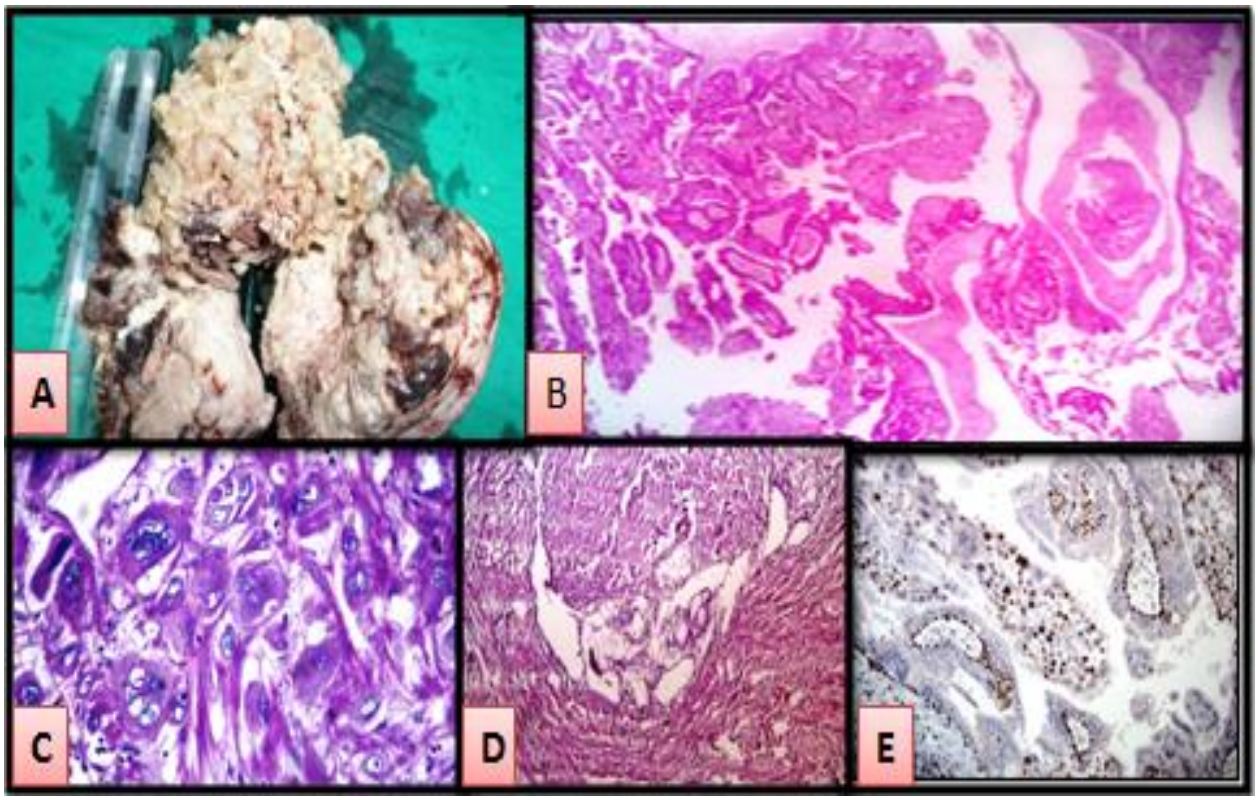

Fig 4: [A] Hysterectomy specimen with large volumes of moles, myometrial penetration [B] Complete hydatidiform mole. [C] Infiltrating pleomorphic Intermediate trophoblasts separating myometrial fibres in exagerrated placental site. [D] Invasive mole. [E] Ki67(MIB-1index) significantly high in Cyto- and Intermediate trophoblasts in the invasive mole components..

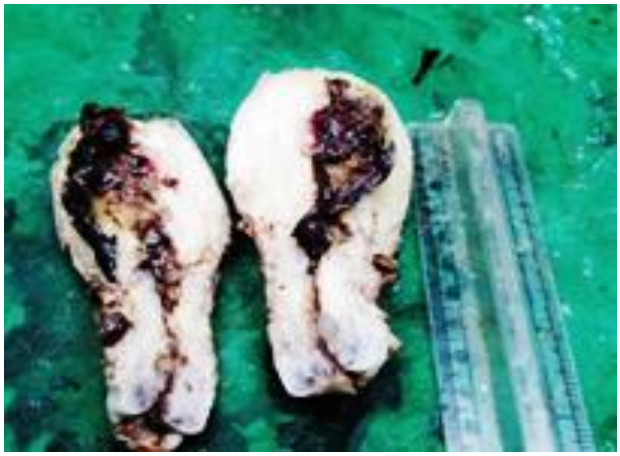

Fig 5: Gross: Diffuse haemorrhagic friable mass of choriocarcinoma in uterine cavity.

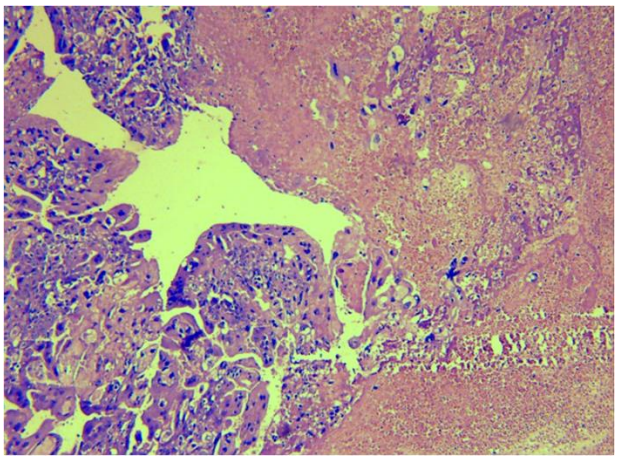

Fig.6: Photomicrograph of choriocarcinoma revealing trophoblasts with necrosis & hemorrhage, H&Ex100

We had one case of placental site trophoblastic tumor (PSTT) in our series. There was a circumscribed lesion in hysterectomy specimen measuring 2 cms in largest dimension. The histopathology section revealed round to polygonal to spindled cells with moderate amount of eosinophilic to clear cytoplasm splitting the muscle fibers (intermediate trophoblasts). There was absence of villi. Exaggerated placental site (EPS) constituted 03.94% of total GTD. Histopathologically, there was increased number of implantation site intermediate trophoblastic cells admixed with bundles of myometrial cells in curettage sample. Presence of normal looking villi was essential for the diagnosis. Patients were under follow up, with sequential β hCG titer and evaluation.

There were 5 cases (6.57%) of placental site nodule. All the cases were received as endometrial curettings with history of persistent rise of serum β hCG level (<1000 mIU/ml) except one hysterectomy sample. In all the cases there were proliferation of trophoblasts around lakes of extensive hyalinisation and fibrin deposition. There was no necrosis or hemorrhage. So, a diagnosis of placental site nodule was given.

DISCUSSION

Gestational trophoblastic disease is a term that describes a group of tumors that share several characteristics as follows (1) they arise in foetal chorion, (2) they produce human chorionic gonadotropin (β hCG) and (3) they respond extremely well to chemotherapy.[9] Uterine curettings containing chorionic villi or fragments of trophoblasts are commonly encountered in routine histopathological practice. Most are simple retained products of conception, but in some the trophoblast appears abnormal and the possibility of GTD must be considered. This group includes placental villus abnormalities characterized by hydropic change with abnormal proliferation and maturation of trophoblast as well as nonneoplastic and neoplastic proliferations of trophoblast unaccompanied or accompanied by villi. The various forms of GTD are defined and related to different pathologic abnormalities occurring at different stages of trophoblastic differentiation and in different trophoblastic subpopulation. These disorders mimic growth patterns encountered in normal placental development and nonmolar abortions. Further each disease entity has distinctive clinical manifestations and each requires different therapeutic approach. Therefore wide knowledge of the morphologic characteristics of gestational trophoblastic diseases is important to avoid misdiagnosis and/or under diagnosis and confusing it with normal physiologic changes of pregnancy.

Trophoblast plays a crucial role in implantation and placentation. It exhibits certain unique properties in accordance with its wide range of metabolic, endocrinologic and invasive functions.[10] Before the development of villi, the primitive trophoblast is termed previllous trophoblast. After formation of villi, at approximately 2 weeks of gestational age, trophoblasts on chorionic villi are termed villous trophoblast, whereas trophoblastic cells in all other locations are designated extravillous trophoblastic cells. The trophoblasts in villous and extra-villous locations can be broadly divided into 3 distinct populations based on morphologic, immunophenotypic and functional studies.[6] These are cytotrophoblast, syncytiotrophoblast (formed by fusion of cytotrophoblastic cells on the villous surface) and intermediate trophoblastic cells (from differentiation of cytotrophoblasts at the margin of anchoring villi). Depending on the location, intermediate trophoblasts are again subdivided into three types: villous, implantation site and chorionic type intermediate trophoblast. Hydatidifrom mole, invasive mole and choriocarcinoma are considered lesions of villous trophoblast, out of these hydatidiform mole is non-neoplastic but has an increased risk to develop into neoplastic disease. The lesions arising from extravillous trophoblast are placental site trophoblastic tumour, epithelioid trophoblastic tumour, exaggerated placental site and placental site nodule.

Out of 77 cases of gestational trophoblastic diseases in our study, hydatidiform mole accounts for 68.4 % of cases and choriocarcinoma was seen in 13.15%. Most of the hydatidiform mole cases (65.38% or 34 out of 52 cases) were seen in the age group of 21-30 years. At large, gestational trophoblastic diseases were predominantly seen in 2nd to 4th decades (64 out of 76 cases or 82.39%). But choriocarcinoma cases were seen during 3rd and 5th decades. (Table 2) In a retrospective study of 112 patients, 70% had a hydatidiform mole and 30% were diagnosed with choriocarcinoma. Of them, only 20% were above 35 years of age.[11] The incidence of hydatidiform mole is comparable with this finding but they didn't encounter any other types of GTD. Because of that, the incidence of choriocarcinoma was high in their study.

Hydatidiform mole (HM) is a nonneoplastic GTD. Estimates of the incidence of GTD vary dramatically in different regions of the world. Based on thorough pathologic review, the incidence of

complete and partial mole was found to be 1 per 1,945 and 1 per 695 pregnancies respectively. Co-existence of a fetus with molar changes of placenta is relatively rare, occurring 1 in 22,000 to 1 in 1,00,000 pregnancies.[12] We have encountered one twin pregnancy comprising of a term foetus associated with partial mole. A detail pathological autopsy was done in the dead fetus but no abnormality was noted. The cause of fetal death may be the associated molar pregnancy. It can sometimes be difficult to differentiate complete hydatidiform mole (CHM) from partial hydatidiform mole (PHM). There are clinical, pathologic, immunohistochemical and cytogenetic differences between CHM and PHM but both have the potential for persistent gestational trophoblastic disease. Histomorphologically, hyperplasia of villus trophoblast is a characteristic feature in both the conditions but the degree of hyperplasia varies. Generalised villus edema, circumferential marked trophoblastic overgrowth comprising of cytotrophoblast, intermediate trophoblast and syncytiotrophoblast are features of CHM. Finding of theca lutein cysts in ovary, incidence of medical complications and progress to gestational trophoblastic neoplasia are more in case of CHM than PHM.[13]

An invasive mole (IM) is almost invariably a sequelae of a CHM or, less likely, a PHM. The pathologic diagnosis is based on the presence of molar villi with associated trophoblastic cells in the myometrium. A clinical diagnosis of invasive mole can be suspected when β hCG titers plateau or rise after evacuation of a mole, but because choriocarcinoma can also supervene in this setting, the clinical diagnosis should be persistent trophoblastic disease. The choriocarcinoma and invasive moles were all diagnosed on clinical, hormonal and radiological criteria and confirmed histologically.

Gestational trophoblastic neoplasia (GTN) included gestational choriocarcinoma, epithelioid trophoblastic tumor and placental site trophoblastic tumor. International Federation of Gynecology and Obstetrics (FIGO) recommended for diagnosis of GTN (Ngan 2007).[14]

- β hCG plateau for > 4 values over 3 weeks
- β hCG increase of > 10% over 2 weeks
- β hCG persistence after evacuation of mole for 6 months
- Histologic diagnosis of choriocarcinoma
- Presence of metastatic disease

Gestational choriocarcinoma is a highly aggressive, malignant tumor derived from placental trophoblast. It has a high propensity for hematogenous dissemination. Choriocarcinoma may regress in the uterus without causing symptoms and metastases can be the first sign of the tumor. Typically in choriocarcinoma, the β hCG levels are high ranging from 1,000 mIU/ml to more than 1,000,000 mIU/ml. We have got one case of metastatic choriocarcinoma where the serum β hCG level was extremely high (4,20,080 mIU/ml). This case belong to stage 4 according to The official International Federation of Gynecology and Obstetrics staging of gestational trophoblastic neoplasia.[15,16] Other cases were confined to uterus, hence belonged to stage 1.

A single case of metastatic choriocarcinoma in the vaginal nodule of our series, we had done FNAC in the vaginal nodule. The USG of abdomen and pelvis showed a theca lutein cyst in ovary without any metastatic deposits in other sites. Her chest x-ray was normal. She was treated with methotrexate and leucovorin followed by total abdominal hysterectomy. Follow up for β-hCG levels of this particular patient was 290.7 mIU/ml (30th day). The patient is followed up for 1 year since treatment and the course is uneventful. Biopsy was not advised in vaginal nodule as they bleed profusely. Most common site of metastasis in choriocarcinoma are lungs (80%), vagina (30%), pelvis (20%), brain (10%) and liver (10%).

We got single case of placental site trophoblastic tumor where the patient was 45 years old and underwent hysterectomy for irregular bleeding per vaginum. The endometrial cavity showed a well circumscribed mass. Histopathology revealed infiltration of myometrium by large polygonal to spindle shaped intermediate trophoblastic cells. This condition is differentiated from choriocarcinoma due to absence of necrosis and hemorrhage and low serum β-hCG levels.

Exaggerated placental site is a benign, non-neoplastic lesion. This lesion is an exaggeration of a normal physiologic process. Based on a review of the surgical pathology files at the Johns Hopkins Hospital, this condition occurs in approximately 1.6% of spontaneous and elective abortions from the early first trimester. We have got 3 cases (03.94%) of exaggerated placental site in our study. Histomorphologically it may be very difficult to distinguish this condition from placental site trophoblastic tumour where (PSTT). These are microscopic, composed of intermediate trophoblasts without mitotic activity and are usually admixed with deciduas and chorionic villi. .

If β-hCG levels rise or plateau after molar evacuation, evaluation and treatment for malignant post molar GTN is indicated. The role of repeat dilatation and evacuation in the setting of β-hCG an rise or plateau is controversial. Some investigators have reported that repeat curettage induces remission or influences treatment in less than 20% of patients, with uterine perforation occurring in 4.8-8 % of patients. In contrast, Pezeshki and associates reported that 368 (68%) of 544 patients entered spontaneous remission after repeat evacuation with no patients requiring hysterectomy for perforation.[13] Patients with persistent histologic evidence of gestational trophoblastic disease and those with hCG levels above 1,500 International units/L, were significantly less likely to respond to the second curettage. The need for a randomized trial is obvious.[16]

GTDs were the first metastatic solid tumor to be cured using chemotherapy. Also, β hCG was the first reliable tumor marker. The GTD arise in fetal tissue, they have the potential for immunologic rejection was thought initially to explain the success of chemotherapy in this disease.[8] Abnormal bleeding for more than 6 weeks following any pregnancy should be evaluated with β hCG testing to exclude a new pregnancy or gestational trophoblastic disease. After molar evacuation, all patients should be monitored with serial β hCG determinations to diagnose and treat malignant sequelae promptly.

The present study emphasizes that histomorphological evaluation is the gold standard in interpretation of gestational trophoblastic diseases. The clinical details and serum β-hCG level can assist in definitive diagnosis of all the cases. Though immunohistochemistry can help in diagnosis, is not essential for all cases. The extremely uncommon case (Fig 4) need to be documented here and this case of invasive mole did not present as sequelae but was simultaneous with HM. It was also unusually associated with EPS reaction. Observing the severity of atypia, MIB-1 index was done to assess its biologic behaviour and it showed 5.2%. This type of high index is seen when EPS reaction

gets associated with HM, thus this patient is kept under close follow up.[17] EPS is usually associated with normal gestation with MIB-1 index nearly 0 and need not require any follow up strategy. Therefore, careful morphologic interpretation with knowledge of all types of trophoblasts and related diseases can be sufficient for definitive diagnosis.

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