Original Article

Histomorphological Analysis of Gestational Trophoblastic Disease Spectrum with Clinicopathological Correlation at a Teaching Hospital

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Abstract

Introduction: Clinically, all trophoblastic lesions are frequently combined under a broad spectrum of gestational trophoblastic diseases (GTDs) without the use of specific pathological terms. However, studies now demonstrate that various forms of GTDs demonstrate differences in etiology, histogenesis, morphology, and clinical behavior. Thus, the need for diagnostic histopathology of these lesions to distinguish gestational trophoblastic neoplasms from nonneoplastic lesions and molar pregnancies and also for early anticipation for early anticipation, risk category stratification, prognostication, management, and prediction of persistent GTD. Our study aimed to study the histomorphological patterns of various types of GTD with light microscopy and the pattern of occurrence of GTDs in relation to age, parity, and gestation. **Materials and Methods:** The present study was conducted in the department of pathology, from January 2020 to April 2022. All GTDs confirmed by histopathological examination by hematoxylin- and eosin-stained slides were included. **Results:** The spectrum of GTDs found in this study was seventy cases of hydatidiform mole (92.10%), three cases of exaggerated placental site (EPS) reaction (3.94%), and two cases of choriocarcinoma (2.63%) and one case (1.31%) of placental site trophoblastic tumor (PSTT). The most common presenting symptom was vaginal bleeding (93.42%). **Conclusion:** Hydatidiform mole forms the most common type of GTD with an incidence of complete moles more than partial moles. Histomorphological examination and analysis are helpful for confirmatory diagnosis. The most common clinical presentation of GTD was vaginal bleeding followed by amenorrhea. Emphasis on detailed descriptive morphological assessment can help in the histological distinction of benign lesions such as EPS reaction and placental site nodule and avert such cases from being erroneously diagnosed as neoplastic. The Ki-67 proliferation index helped in distinguishing the EPS reaction from neoplastic lesions such as PSTT which requires surgical intervention and chemotherapy.

Keywords: Chorionic gonadotropin, gestational trophoblastic disease, hydatidiform mole, trophoblasts

Introduction

Gestational trophoblastic diseases (GTDs) are a heterogeneous group of disorders of placental trophoblast. It encompasses a spectrum of trophoblastic proliferative disorders ranging from nonneoplastic hydatidiform mole to highly malignant choriocarcinoma.

The WHO classification of GTD as per 5th edition:[1]

1. Molar pregnancies – Hydatidiform mole
   - Complete mole
   - Partial mole
   - Invasive mole.
2. Nonneoplastic lesions
   - Exaggerated placental site (EPS) reaction
   - Placental site nodule.
3. Neoplasms
   - Placental site trophoblastic tumor (PSTT)
   - Epithelioid trophoblastic tumor
   - Choriocarcinoma.

Detailed histopathological assessment of these lesions is needed to distinguish gestational trophoblastic neoplasms

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from nonneoplastic lesions and molar pregnancies for early anticipation, risk category stratification, prognostication, and management of persistent GTD as each entity carries different therapeutic approaches. The majority of GTDs are potentially curable if the treatment is started early enough with a correct diagnosis.[2]

Extremes of maternal age and prior history of molar pregnancy are the most important risk factors associated with a molar pregnancy, apart from prolonged use of contraceptive pills, β-carotene deficiency, and racial factors.[3] Identification of hydatidiform moles and distinguishing complete and partial moles are important due to the different risks of persistent trophoblastic disease (PTD).[4] Majority of the patients with partial moles present with clinical features of incomplete or missed abortion which need the histological review of curettage specimens for a correct diagnosis.[3] Furthermore, GTD lesions mimic the growth pattern seen in early normal placental development, nonmolar abortions, and nontrophoblastic lesions; therefore, the histomorphological study is important to differentiate GTDs from their mimickers.

The present study aimed at analyzing the histomorphological patterns of various types of GTD with light microscopy and their pattern of occurrence in relation to age, parity, and gestation.

Materials and Methods

Study design

This was an observational study.

Sample

All abnormal gestational-related histopathological specimens received in our department were included in the study. Nongestational specimens were excluded from the study.

Sample size

The sample size was 76.

Study duration

The study was carried out from January 2020 to April 2022 (2 years 3 months).

Procedure

Clinical details were taken from the record room. The details of gross examination and hematoxylin- and eosin-stained slides prepared from paraffin-embedded blocks were studied in detail. GTDs were classified per a recent WHO scientific group. The data were entered and interpreted in Microsoft Excel. The analysis was done in percentages and proportions and was represented in tables and graphs wherever necessary.

Results

A total number of 8860 gynecological samples were received during the study period. The material consisted of 884 products of conception samples, uterine curetting, and suction evacuation material including two hysterectomy specimens. Seventy-six cases (9.97%) were diagnosed as GTD [Chart 1]. Histopathological examination revealed seventy cases of hydatidiform mole (92.10%) and three cases of EPS reaction (3.94%). There were two cases of choriocarcinoma (2.63%) and one case (1.31%) of PSTT. Complete mole and partial mole constitute 44 (57.89%) and 32 (42.10%), respectively, of hydatidiform mole cases. A clinicopathological analysis was carried out.

The distribution of GTD according to age is given in Table 1. The age ranged from 16 to 35 years with a mean age of 23.8 years. The majority (55.26%) of patients were in the age group of 20–25 years, followed by 17 (22.36%) patients in the age group of 26–30 years and 9 (11.84%) patients in the age group of >30 years of age. The youngest is 16 years and the eldest is 45 years.

Majority of the patients (93.42%) presented with vaginal bleeding which is the most common clinical presentation [Table 2] in our study following amenorrhea comprising 82.89%. Pain abdomen was seen in 59.21% of cases. Grape-like vesicle discharge was seen in 13.15% of the patients.

A high proportion of hydatidiform mole cases were presented during the first trimester (57.89%) followed by 34.21% of patients in the second trimester [Table 3]. Choriocarcinoma and PSTT were diagnosed in the postgestational period. One case of an EPS presented with severe postpartum hemorrhage requiring peripartum hysterectomy.

The relation of blood groups with GTD is shown in Table 4. A high incidence of GTD was noted in patients with blood Group A (60.52%) followed by blood Group O (25%). The beta-hCG levels were between 50,000 and 100,000 in a majority of cases.

The biopsy specimens in all the cases received had material ranging from 2 to 8 cc admixed with blood clots, decidual tissue, and multiple grape-like vesicles of varying sizes. Gross examination of the two hysterectomy specimens showed a bulky uterus, and on the cut surface, endometrial cavity was dilated, spongy, and edematous in case of an EPS. The other hysterectomy specimen of choriocarcinoma revealed

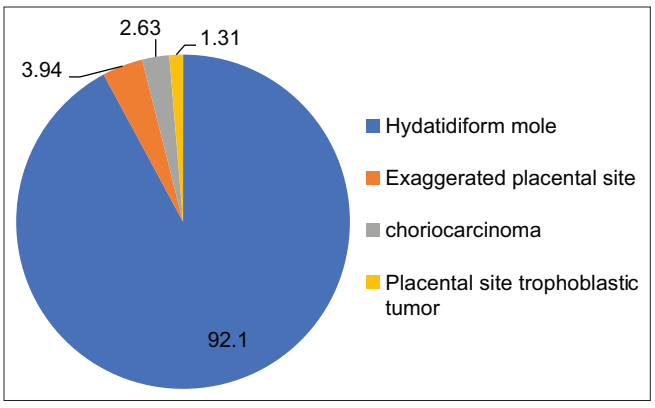

Chart 1: Spectrum of GTDs. GTD: Gestational trophoblastic disease

Table 1: Distribution of gestational trophoblastic diseases according to age

Age group (years)	Hydatidiform mole	EPS	Choriocarcinoma	PSTT	Total (%)
<2	8	0	0	0	8 (10.52)
20–25	40	2	0	0	42 (55.26)
26–30	14	1	1	1	17 (22.36)
>30	8	0	1	0	9 (11.84)
Total					76

EPS: Exaggerated placental site reaction, PSTT: Placental site trophoblastic tumor

Table 2: Various clinical presentations of gestational trophoblastic diseases

Clinical presentation	Hydatidiform mole	EPS	Choriocarcinoma	PSTT	Total (%)
Vaginal bleeding	66	0	2	1	71 (93.42)
Amenorrhea	69	2	0	0	63 (82.89)
Hyperemesis gravidarum	14	1	0	0	15 (19.73)
Pain abdomen	42	0	2	1	45 (59.21)
Passage of grape-like vesicles	10	0	0	0	10 (13.15)

EPS: Exaggerated placental site reaction, PSTT: Placental site trophoblastic tumor

Table 3: Distribution of gestational trophoblastic diseases according to gestational weeks

Trimester	Hydatidiform mole	EPS	Choriocarcinoma	PSTT	Total (%)
I	44	0	0	0	44 (57.89)
II	26	0	0	0	26 (34.21)
III	0	1	0	0	1 (1.31)
Postgestation	0	2	2	1	5 (3.3)

EPS: Exaggerated placental site reaction, PSTT: Placental site trophoblastic tumor

Table 4: Relation of different blood groups with gestational trophoblastic diseases

GTD	Blood group (ABO type)			
	A	B	AB	O
Hydatidiform mole	43	9	2	16
EPS	2	0	0	1
Choriocarcinoma	1	0	0	1
PSTT	0	0	0	1
Total cases (%)	46 (60.52)	9 (11.84)	2 (2.63)	19 (25)

GTD: Gestational trophoblastic disease, EPS: Exaggerated placental site reaction, PSTT: Placental site trophoblastic tumor

an infiltrative growth within the endometrium invading the myometrium with areas of hemorrhage and necrosis.

Histopathological examination of:

i. Complete mole showed numerous markedly distended chorionic villi with a circumferential proliferation of cytotrophoblast and syncytiotrophoblast and central cistern formation. Stromal blood vessels were absent [Figure 1].
ii. Partial mole showed two populations of enlarged hydropic villi and normal villi with focal areas of trophoblastic proliferation and few nucleated red blood cells. Trophoblastic inclusions were seen [Figure 2].
iii. EPS reaction showed hypertrophied smooth muscle cells with implantation site intermediate trophoblast infiltrating into the myometrium [Figure 3].
iv. PSTT showed proliferation of implantation site intermediate trophoblast cells infiltrating the myometrium with high nuclear atypia, mitotic activity, focal necrosis, and extracellular fibrinoid material deposition.
v. Choriocarcinoma reveals a biphasic pattern of mononucleated cytotrophoblast, intermediate trophoblast, and multinucleated syncytiotrophoblasts. Nuclear pleomorphism and hyperchromasia are seen with areas of hemorrhage and necrosis [Figure 4].

Discussion

GTD constitutes a spectrum of tumor and tumor-like conditions characterized by abnormal proliferation of trophoblastic tissue. The spectrum of the GTD lesions we observed during the study period includes hydatidiform mole, EPS reaction, PSTT, and choriocarcinoma. All the cases were uterine GTD and no case of extrauterine GTD was noted.

The majority (55.26%) of patients were in the age group of 20–25 years, followed by 17 (22.36%) patients in the age group 26–30 years and 9 (11.84%) patients in the age group of >30 years of age. This correlates with the study conducted by Jagtap *et al*., who reported that the majority of GTD patients are of 20–25 years, comprising 57%.[5] The other study done by Taboo showed a high prevalence of GTD in the age group of 20–25 years.[6] However, in a study by Almohammadi, the distribution of GTD cases was highest in the fourth decade.[7]

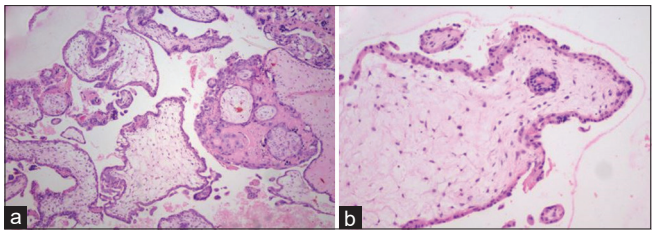

Figure 1: Partial mole. (a) Two populations of villi, large hydropic villi and small fibrotic villi (H and E, ×10). (b) Focal and mild trophoblastic hyperplasia with trophoblastic pseudo inclusion (H and E, ×40). H and E: Hematoxylin and eosin

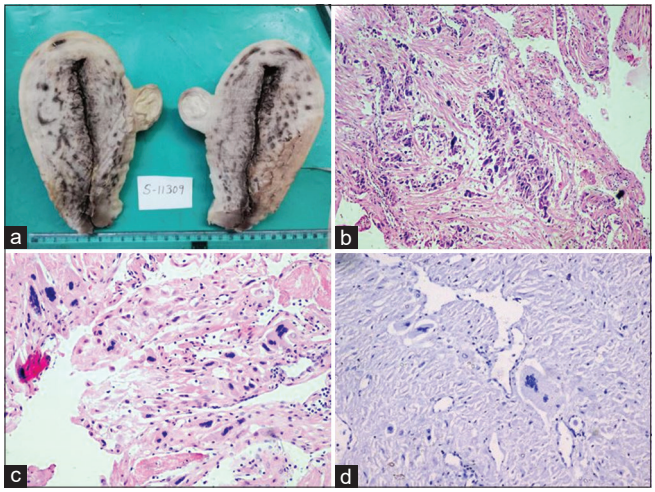

Figure 3: Exaggerated placental site. (a) Gross specimen of EPS. (b) Increased number and extensive infiltration of myometrium by intermediate trophoblasts (H and E, ×10). (c) Predominance of multinucleated giant implantation site-type intermediate trophoblastic cells (H and E, ×40). (d) Ki-67 index of near 0 seen in EPS (IHC for Ki-67, ×40). EPS: Exaggerated placental site, H and E: Hematoxylin and eosin

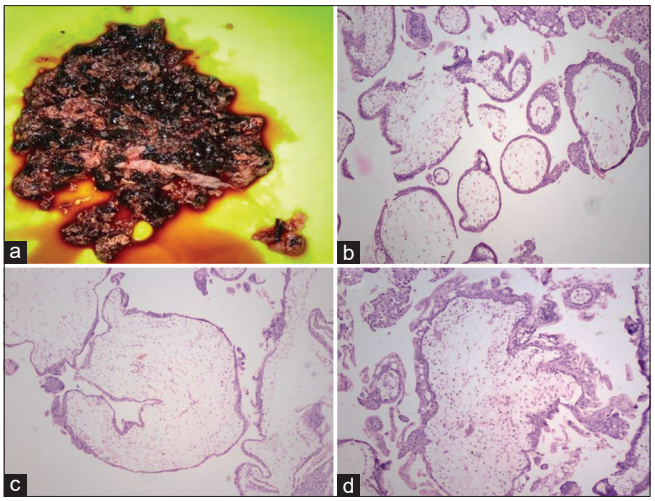

Figure 2: Complete mole. (a) Bulky bloody tissue with vesicles of variable size. (b) Diffuse enlargement of villi (H and E, ×10) (c) Hydropic villi lined by attenuated trophoblasts. (H and E, ×40). (d) Trophoblastic hyperplasia in circumferential pattern (H and E, ×40). H and E: Hematoxylin and eosin

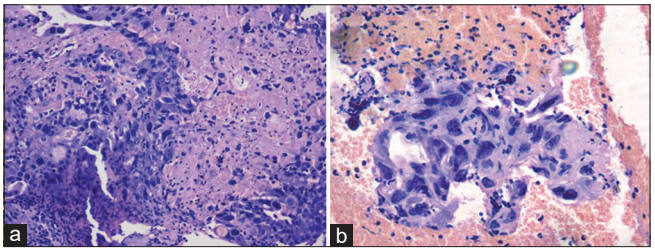

Figure 4: Choriocarcinoma. (a) Biphasic pleomorphic population of mononuclear and multinucleated cells with necrosis. Chorionic villi are absent (H and E, ×10). (b) Atypical trophoblastic cells with areas of hemorrhage (H and E, ×40). H and E: Hematoxylin and eosin

The mean age in the present study was 23.6 years which also correlates with the study conducted by Agrawal *et al*.[2]

The clinical presentation of GTD varies, and the ultrasound in pregnancy is credited to the early diagnosis of GTD. The most common clinical presentation in our study was bleeding per vagina which constitutes about 93.42% of patients, followed by amenorrhea with 82.89%. 13.15% of patients presented with a history of passing grape-like vesicles. This is in coordination with the study conducted by Aziz *et al*.[8] Furthermore, Solo stated in his study that 63.3% of patients presented with vaginal bleeding and passing grape-like vesicles is the least presentation contributing only 5%.[9]

Apart from the above clinical presentations, GTD has been associated with short-term psychological consequences. Blok *et al*. in their study described the psychological effects such as anxiety, depression, and distress which are common after a diagnosis of GTD and suggested that the diagnosis of GTD could be considered a traumatic event causing serious adaptation problems.[10]

ABO blood groups are included as one of the prognostic factors in GTD in the WHO prognostic scoring system. Blood Group A showed a high incidence of GTD in this study followed by blood Group "O" and the least were noted in blood Group "B." Among them, 59 were (77.63%) Rh positive. Many studies stated that GTD was found to be more prevalent in blood Group A and similar results were encountered in our study.[5]

The majority of all GTDs showed beta-hCG levels between 50,000 and 100,000 mIU/ml. None of the cases had a level below 50,000 mIU/ml. As serum beta-hCG is most sensitive and specific for trophoblastic lesions, its serial and regular estimations of levels in women diagnosed with complete or partial mole are very essential to predict the occurrence of persistent GTD. An increasing level of beta-hCG is considered diagnostic of invasive trophoblastic disease and choriocarcinoma. It also helps in the determination of treatment response and recurrence of the tumor.[5,11,12]

Hydatidiform mole

Hydatidiform mole constituted the most common form of benign GTD in our study. These are the nonneoplastic proliferation of the villous trophoblasts, characterized by enlarged hydropic villi along with trophoblastic hyperplasia.[13] The two entities in hydatidiform mole are complete and partial

mole based on histopathological and genetic criteria. Among the molar pregnancies, complete mole is the most common entity 44 (57.89%) and partial mole constituted the rest 32 (42.10%). Similar findings were seen in the study conducted by Taboo who reported an increased incidence of a complete mole than the partial mole.[6] The study conducted in India by Sankaran and Shanthi and Almohammadi also shows similar findings.[10,14]

On histopathology, a complete mole shows the involvement of all chorionic villi, pleomorphism of trophoblastic tissue, and villous stromal apoptosis. A partial mole is distinguished from a complete mole by the presence of two populations of chorionic villi, fetal parts, and enlarged villi with central cavitation.

Ploidy analysis helps in distinguishing a diploid complete mole from a triploid partial mole but cannot be used to make a diagnosis of hydatidiform mole *per se.* This may be achieved by flow cytometry or digital image analysis.[11]

Persistent trophoblastic disease

PTD occurs in 15%–20% of patients with complete mole and is rare following partial mole. PTD is not a histopathological diagnosis and requires rising or failing to fall beta-hCG levels on serial beta-hCG estimations.[11]

The risk factors associated with development of persistent trophoblastic disease are serum hCG levels >100,00 mUI/ml, maternal age >40 years and increased volume of retrieved endocavitary material.[12] Hydatidiform moles with telomerase activity, lower apoptotic indices, and increased expression of antiapoptotic gene Mcl-l have been known to be associated with the development of PTD. They have been studied to predict those cases of hydatidiform moles that will go on to PTD. A follow-up is considered necessary for both complete and partial hydatidiform moles.[11] None of the cases of hydatidiform mole showed PTD in our study during the study period.

Exaggerated placental site reaction

EPS reaction is a nonneoplastic exuberant infiltration of the underlying myometrium by implantation site intermediate trophoblasts. It occurs following a normal pregnancy, ectopic pregnancy, or abortion from the first trimester and sometimes leads to postpartum hemorrhage.[15,16] In our study, three EPS cases were observed. Two were curetting and one was observed in a postpartum hysterectomy performed for postpartum hemorrhage. Histopathological examination in these three cases revealed implantation site intermediate trophoblastic cells extensively infiltrating the endometrium and myometrium. Many of these cells were multinucleated and seen to infiltrate myometrium diffusely without producing necrosis. The associated chorionic villi were morphologically unremarkable.

Exaggerated placental site versus placental site trophoblastic tumor

It is important to distinguish the EPS reaction from the other intermediate trophoblastic lesions like the PSTT since the latter needs surgical intervention and chemotherapy while the EPS usually resolves spontaneously after curettage and no follow-up is required. The trophoblastic cells in EPS are often multinucleated and more widely spaced, and lack confluent growth or necrosis, unlike PSTT. The diagnosis can be confirmed by immunohistochemistry, which shows 0 Ki-67 proliferation index and absent mitotic activity which favors EPS. The Ki-67 index performed in one of the cases of EPS is near zero despite the profuse infiltration of implantation site intermediate trophoblasts.[15]

Placental site trophoblastic tumor

PSTT is a rare tumor composed of neoplastic proliferation of intermediate trophoblastic cells at the implantation site.[16] PSTTs most commonly occur following a normal pregnancy, and only 5%–8% of patients have a history of complete mole.[17,18] One case of PSTT was observed in this study in a 32-year-old patient, who presented with abnormal vaginal bleeding. Histopathology examination revealed the proliferation of large, polygonal implantation site intermediate trophoblastic cells infiltrating the myometrium and separating the muscle bundles. It lacked the biphasic pattern seen in choriocarcinoma.

Choriocarcinoma

Choriocarcinoma is a highly aggressive malignant tumor of trophoblastic tissue of any type of gestational event. Most often it is preceded by complete mole or abortion, ectopic and normal pregnancy. It is a highly vascularized tumor with metastasis to various organs such as the lungs, brain, and liver. Patients usually present with bleeding per vagina. Histopathological diagnosis rests on the recognition of a characteristic biphasic pattern of mononucleate and multinucleated trophoblastic cells, which is usually unmistakable along with hemorrhagic areas and necrosis. Persistently raised beta-HCG confirms the diagnosis.[19]

Two cases of choriocarcinoma were reported during the present study duration. The patients were 30 years old and 45 years old and both had a previous history of molar pregnancy 2.1 and 3 years back. Powles *et al*. reported that the time interval between the antecedent molar pregnancy and gestational trophoblastic tumors carries prognostic significance. Patients with >2.8 years carry poor outcomes and need aggressive treatment.[19,20]

Treatment decisions for GTD depend on multiple factors such as a desire to maintain fertility, coexisting normal pregnancy, International Federation of Gynecology and Obstetrics (FIGO) score based on prognostic factors, and the need for long-term follow-up. Various treatment modalities include suction evacuation and curettage, hysterectomy, first-line single-agent chemotherapy with methotrexate or actinomycin D for low-risk gestational trophoblastic neoplasia, and multiple-agent chemotherapy for high-risk gestational trophoblastic neoplasia, salvage therapies, radiotherapy, etc.[10]

Conclusion

Hydatidiform mole forms the most common form of GTD. The complete hydatidiform mole was observed most common type

in this study. Histomorphological examination and analysis are essential for confirmatory diagnosis. The most common clinical manifestation of GTD was vaginal bleeding followed by amenorrhea. The reproductive age group (20–25 years) is the most common age group for GTD. The Ki-67 proliferation index helped in distinguishing the EPS reaction from neoplastic lesions such as PSTT which requires surgical intervention and chemotherapy. Detailed descriptive morphological assessment with supportive ancillary techniques can help in the distinction of benign lesions like exaggerated placental reactions and avert such cases from being erroneously diagnosed as neoplastic.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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