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ORIGINAL ARTICLE

GESTATIONAL TROPHOBLASTIC DISEASE: A PROSPECTIVE STUDY OF 82 CASES AND UTILITY OF P57 IMMUNOHISTOCHEMISTRY IN DIFFERENTIATING COMPLETE AND PARTIAL MOLE

Surya Babu Sunkesula[1], Lingeswara Rao B[2], Tamil Arasi D. S[3]

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ABSTRACT: BACKGROUND AND PURPOSE: Gestational trophoblastic disease (GTD) is a common spectrum of abnormal placental villous trophoblastic proliferation that occurs in women of reproductive age group. The present study is undertaken to discuss about the epidemiology, clinical presentation and pathology diagnosis of each of the trophoblastic disease variants.
MATERIALS AND METHODS: The present study included 82 cases of GTD over a period of 3 years. The H&E sections of FFPE tissue were studied. Periodic acid Schiff (PAS) stain was done as an adjuvant in 5 cases of early complete mole. IHC with $p57^{kip2}$ was done in 6 cases of complete mole and 6 cases of partial mole. **RESULTS:** Hydatidiform mole (93.9%) was the most common variant of GTD with peak incidence in 21-30 years age group and more common in primigravida. There were one case of invasive mole, 2 cases of choriocarcinoma and 2 cases of persistent trophoblastic disease. Most patients of GTD were of blood group O followed by group A. Early complete mole, complete mole and partial mole were differentiated by examining H&E sections. Myxoid stroma of early complete mole showed PAS positivity. p57 was negative in all the 6 cases of complete mole. Five cases of partial mole showed positivity, but one case was negative; on review, it was diagnosed as complete mole.**CONCLUSION:** The study shows the high incidence of molar pregnancies in Indian women and discusses the importance and utility of IHC in hydatidiform mole pathology.
KEYWORDS: GTD, molar pregnancy, choriocarcinoma, PAS, $p57^{kip2}$

INTRODUCTION: Gestational trophoblastic disease (GTD) represents a spectrum of lesions characterized by abnormal proliferation and pathological aberrations occurring at different trophoblastic subpopulation and stages of trophoblastic differentiation during placentation. Histologically, GTD includes complete mole, partial mole, invasive mole, placental site trophoblastic tumor and choriocarcinoma.[1] Each disease entity has distinctive clinical manifestations, biological behavior and requires different therapeutic approach.

The distinction between complete mole and partial mole is important because progression to choriocarcinoma occurs in 15-20% of complete mole and 0.5-0.6% of partial mole. Osterheld *et al* suggested a combination of histology and immunohistochemistry (IHC) as a reliable protocol for the correct diagnosis in gestational pathology.[2]

In the present prospective study of gestational trophoblastic disease, incidence of hydatidiform mole, invasive mole, choriocarcinoma and their pattern of occurrence with relation to age, clinical presentation, blood group and parity have been studied.

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In cases which are difficult to differentiate between complete and partial hydatidiform mole by light microscopy, $p57^{kip2}$, an Immunohistochemical marker has been used to differentiate between them.

MATERIALS AND METHODS: The present prospective study included 82 cases of GTD in a tertiary care hospital during a study period of January 2010 to December 2013.The material consisted of 8 hysterectomy specimens and the remaining 74 were expelled products from the uterus, uterine curettings and suction evacuation. A clinicopathological analysis of these cases was carried out.

The specimens were formalin fixed paraffin embedded (FFPE) and H&E sections were studied and reviewed by 2 pathologists. Histochemical stain for Periodic acid Schiff (PAS) was done in 5 cases of early complete mole as an adjuvant. IHC with antibody against $p57^{kip2}$ was done in 12 cases; 6 cases of complete mole and 6 cases of partial mole, for the confirmation of the diagnosis of complete mole and partial mole.

OBSERVATION & RESULTS: Out of 82 cases of GTD, 77 were hydatidiform mole, one was invasive mole, 2 were persistent trophoblastic disease and 2 were choriocarcinoma. The total number of pregnancies encountered in the 3 years period was 38,780. The incidence of GTD was 1 in 473 pregnancies. Incidence of hydatidiform mole was 1 in 503 pregnancies, incidence of invasive mole was 1 in 38,780 pregnancies and that of choriocarcinoma is found to be 1 in 19,390 pregnancies. The age group of the patients ranged from 18-40 years with peak incidence in 21-30 years accounting 75.6%. These patients presented in the gestational age of 8-32 weeks.

Among the GTD, hydatidiform mole was more common in the primigravida (42.7%) followed by para 3 and para 2. Of the 77 hydatidiform mole, complete mole constituted 54 (65.8%) cases and partial mole constituted 28 (34.2%) cases. Two patients had history of toxemia of pregnancy presented before 20 weeks of gestation, with enlarged uterus, raised blood pressure and bilateral pedal edema. Twelve patients had history of passage of vesicles per vagina. The remaining presented with lower abdominal pain, incomplete or missed abortion, and the molar pregnancy was detected by either routine ultrasound or histopathology of products of conception. Serum β-HCG levels ranged from 200-60,000 IU/ml in molar pregnancy and it was 80,000-2,00,000 IU/ml in the invasive mole and two choriocarcinoma cases.

Both choriocarcinoma cases occurred in 3^{rd} parity. One was preceded by complete hydatidiform mole and the other by term pregnancy. The interval between antecedent pregnancy and choriocarcinoma was 10 months and 2 years respectively.

When compared with blood groups, group A was found in 31 cases (37.8%) and group O was found in 34 cases (41.5%), group B in 10 cases (12.2%) and group AB in 7 cases (8.5%).

The biopsy specimens in all the cases of molar pregnancy consisted of material having multiple grape-like vesicles of varying size mixed with blood clot and decidual tissue. Vesicles had a thin transparent wall and clear fluid (Fig.1A).

Partial mole showed two distinct populations of villi; the enlarged hydropic villi and normal villi, trophoblastic pseudoinclusions, and evidence of fetal development like nucleated red blood cells in rudimentary blood vessels (Fig.1B).

Patients of <12 weeks of gestation with complete mole (early complete mole) microscopically showed numerous club shaped secondary villous sprouts from a larger villus, non-hydropic myxoid stroma, poorly demarcated central cisterns and focal hyperplasia of cytotrophoblasts and

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syncytiotrophoblast on both villi (Fig.2A). There is increased karryorrhexis and apoptosis in early complete mole. The myxoid/mucoid stroma showed PAS positivity (Fig. 2B).

Patients who presented after 12 weeks of gestational age, complete mole showed markedly distended chorionic villi with central cistern, multifocal to circumferential proliferation of both syncytiotrophoblast and cytotrophoblast and there is complete absence of stromal blood vessels.

Single case of invasive mole was identified as soft friable necrotic ulceroproliferative growth arising from the lower end of the endometrial cavity invading into the myometrium in a hysterectomy specimen. Histopathology revealed an extensive trophoblastic proliferation with enlarged villi invading into the myometrium.

Two cases were diagnosed as persistent trophoblastic disease with a previous history of complete mole. They presented with history of bleeding per vagina for 6 weeks and 8 weeks respectively and had persistent elevation of β-HCG. Suction evacuation was done and histopathology revealed a trophoblastic proliferation of cytotrophoblast and syncytiotrophoblast with features of atypia.

Hysterectomy specimens of both choriocarcinoma cases revealed an infiltrative growth within the endometrium, invading into myometrium with areas of hemorrhage and necrosis (Fig. 4A). Examination of the ovaries revealed theca-lutein cyst. Histopathology revealed a dimorphic population of mononucleated cytotrophoblasts, intermediate trophoblasts and multinucleated syncitiotrophoblasts showing nuclear pleomorphism and hyperchromasia with adjacent areas of hemorrhage and necrosis. Villi were absent (Fig. 4B).

In 12 cases comprising 6 complete mole and 6 partial mole, IHC with $p57^{kip2}$ was done. Presence of brown precipitate in the nucleus was indicated as positivity. Tissue section of a normal term placental villi was taken as positive control in our study. Intermediate trophoblasts and the decidual cells which give a positive nuclear stain serve as internal control. The $p57^{kip2}$immunostain results were interpreted as positive when the extent of staining was diffuse positive in villous stromal cells and cytotrophoblasts.

$p57^{kip2}$ IHC was done in 5 cases of early complete mole, 1 case of complete mole and 6 cases of partial mole diagnosed by histopathology. Six cases of complete mole were found to be $p57^{kip2}$ negative (Fig. 3A). Out of the 6 cases diagnosed as partial mole, 5 cases showed diffuse positivity (Fig. 3B). One case with $p57^{kip2}$ negativity, diagnosed as partial mole on histopathology, reviewed later showed diffuse positivity features of early complete mole.

Type of GTD	Number (total 82 GTDs)	Incidence (total 38780 pregnancies)	Percentage
Hydatidiform mole	77	1:503	93.9%
Invasive mole	01	1:38780	1.2%
Choriocarcinoma	02	1:19390	2.4%
PTD	02	1:19390	2.4%

Table 1: Shows the incidence of each type of gestational trophoblastic disease in the present study

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Figure 1: Shows (A) gross appearance of hydatidiform mole. Placenta with enlarged hydropic villi of varying size is seen. (B) Partial mole having villi with irregular outline and minimal trophoblastic proliferation.

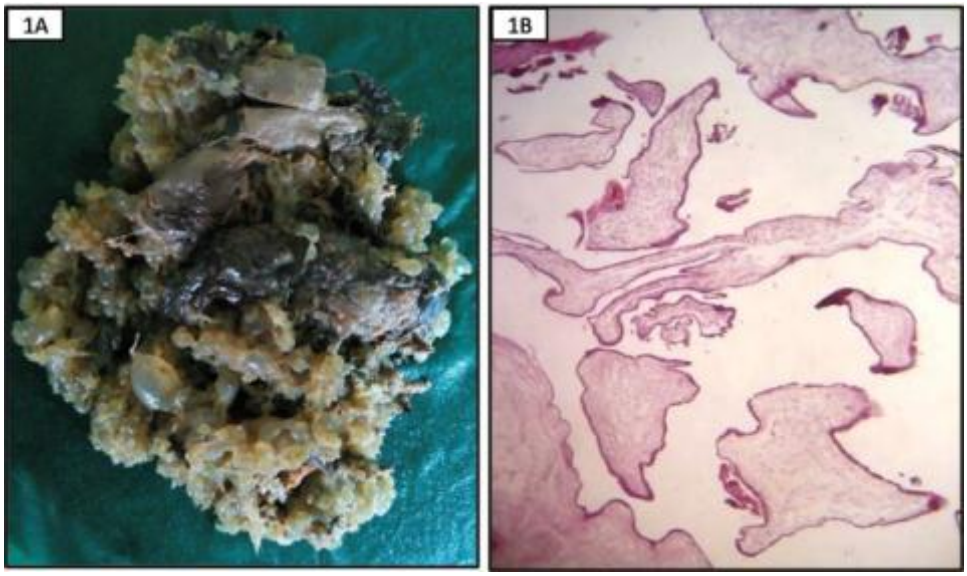

Figure 1A, 1B

Figure 2: Shows (A) villi with bulbous polypoid projections in a complete mole. (B) A villus of an early complete mole with myxoid stroma showing PAS positivity.

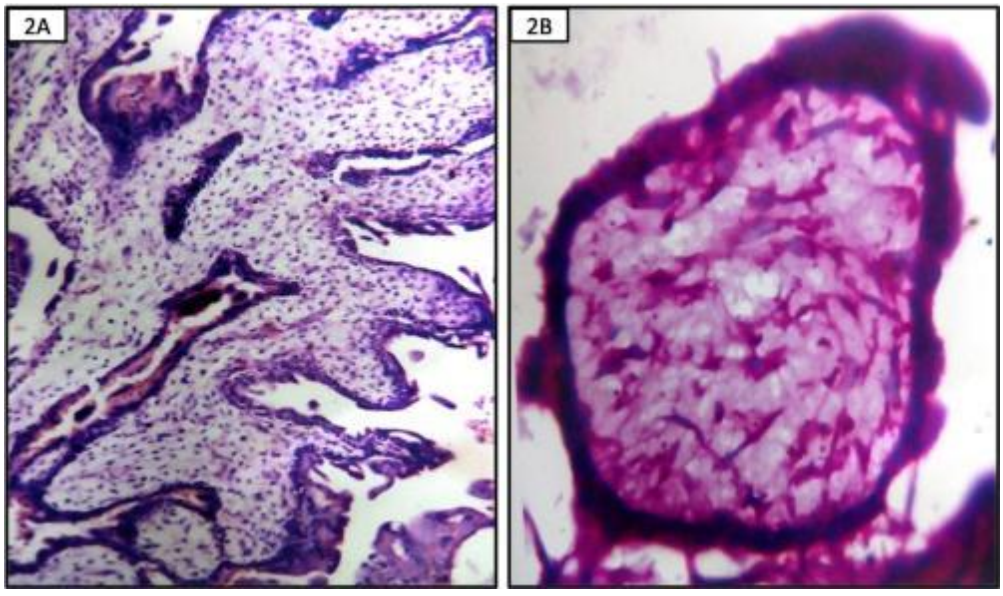

Figure 2A, 2B

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Figure 3: Shows (A) IHC for p57 in a complete mole showing negative nuclear staining in the cytotrophoblast and stromal cells. Positive staining in the decidual cells act as internal control. (B) IHC for p57 in a partial mole showing positive nuclear staining in cytotrophoblast and stromal cells.

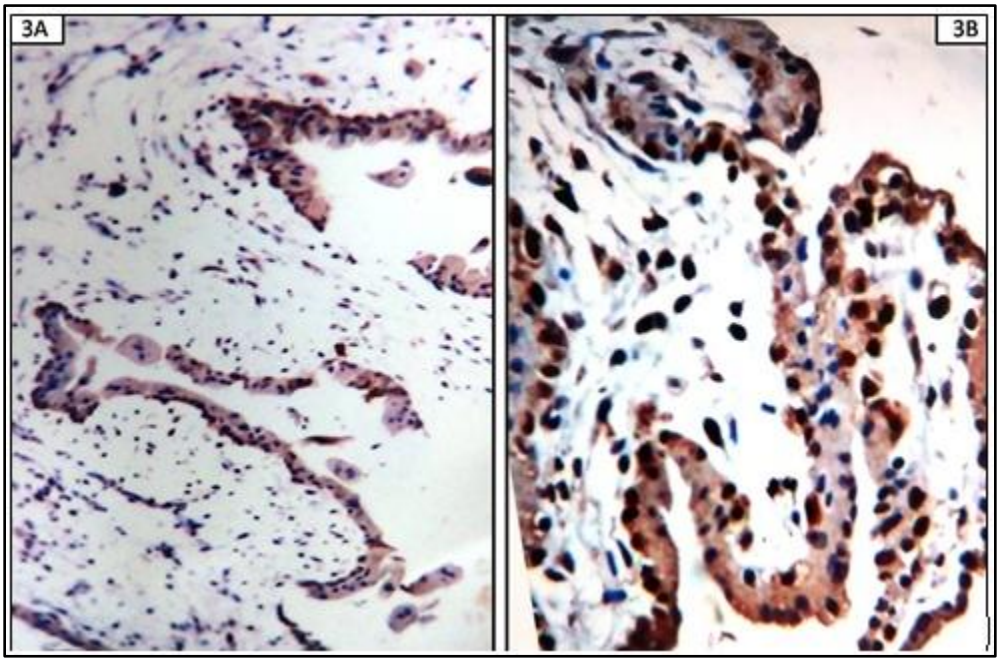

Figure 3A, 3B

Figure 4: Shows gross appearance of choriocarcinoma showing a necrotic and hemorrhagic nodular mass invading the myometrium of uterus. (B) is a photomicrograph of a choriocarcinoma showing pleomorphic trophoblastic cells with bizarre nuclei. Villi are absent.

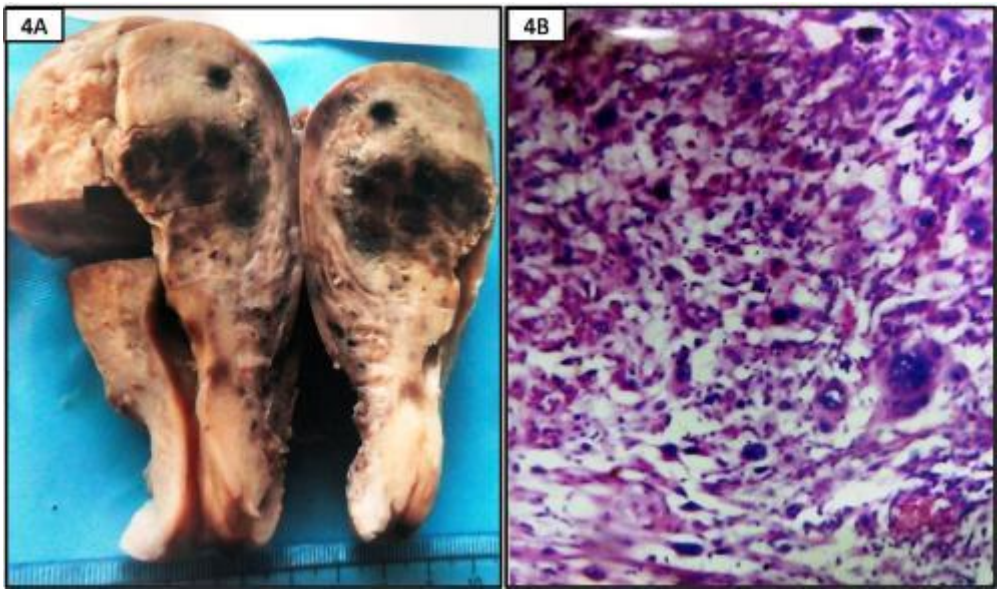

Figure 4A, 4B

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DISCUSSION: GTD constitutes a spectrum of tumors and tumor like conditions characterized by proliferation of pregnancy associated trophoblastic tissue of progressive malignant potential. In this study, the spectrum of GTD included hydatidiform mole (93.9%), invasive mole (1.2%), choriocarcinoma (2.4%) and persistent trophoblastic disease (2.4%). Shakuntala *et al* reported an incidence of 88.88% of hydatidiform mole 8.08% invasive mole and 3.03% choriocarcinoma.[3]

The incidence of GTD varied in different parts of the world. The incidence of GTD in the present study is 1 in 473 pregnancies. Smith *et al* reported an incidence of 1 in 836 pregnancies.[4] The incidence of hydatidiform mole in the present study is 1 in 503 pregnancies. In India and Middle East, the incidence is believed to be higher when compared to Europe and North America. In Asia, Indonesia has the highest incidence (1 in 77 pregnancies and 1 in 57 deliveries).[4,5,6,7]

The incidence of choriocarcinoma in the present study is 1 in 19, 390 pregnancies. This is comparatively low when compared to other studies.[8]

The peak incidence of GTD in the present study is in 3rd decade and in primigravida. Similar results were found in other studies.[3, 9, 10] Blood group O is more common in patients of GTD which correlated with other studies.[11]

The incidence of molar pregnancy in the present study is 1 in 503 pregnancies which correlates with other studies.[12]

Clinical features like passage of vesicles per vagina, lower abdominal pain etc. were correlated with that of Nizam K *et al*.[13] However, Kirk *et al* reported that many patients are asymptomatic and detected by routine ultrasonography (USG).[14]

Fifteen cases of molar pregnancy evacuated between 8-12 weeks of gestation showed histopathological features as described by David Keep *et al*.[15] Early complete moles had a mucoid/myxoid stroma which showed PAS positivity, same as reported by Kim *et al*.[16] The microscopic features of partial mole in the present study were same as reported by Rex C Bentley[17] Invasive mole constituted 1.2% of GTD and showed features of extensive trophoblastic overgrowth and penetration of trophoblastic cells and villi into myometrium.

Of the two cases of choriocarcinoma, one was preceded by complete mole and the other by term pregnancy. The latter case had metastasis to lungs and showed cannon ball opacities in chest x-ray. Both cases responded well to methotrexate chemotherapy. Smith *et al* reported that choriocarcinoma was higher between 20-39 years age group which correlates with our study.[10] Miller *et al* reported that post-term gestational choriocarcinomas have a more extensive metastatic spread.[18] Same is the case in our study. Similar to Al Sakka *et al*, the incidence of post-molar choriocarcinoma is 1 in 19,000 live births.[19]

$p57^{kip2}$, a paternally imprinted and maternally expressed gene protein which shows reduced or absent expression in cytotrophoblast and villous mesenchymal cells of complete mole, and strongly expressed in those of partial mole.[2]

$p57^{kip2}$ IHC was done in 5 cases of early complete mole and one case of complete mole. The villous stromal cells and cytotrophoblasts showed negative staining.

$p57^{kip2}$ IHC was done in 6 cases diagnosed as partial mole. Five cases showed diffuse positive staining in villous stromal cells and cytotrophoblast. One case diagnosed as partial mole on histopathology with varying villous structures and focal cytotrophoblastic proliferation, reviewed later showed features of early complete mole, and $p57^{kip2}$ negativity thus confirmed as early complete mole.

This emphasizes the importance of $p57^{kip2}$ IHC in differentiating early complete mole and partial mole, thereby assessing prognosis.

CONCLUSION: To conclude, the incidence of gestational trophoblastic disease is high in India and hydatidiform mole forms the most common type of GTD. IHC with $p57^{kip2}$ can be used as an adjuvant marker in differentiating complete mole and partial mole in difficult cases. This study also emphasizes the importance of maintaining a Trophoblastic Diseases Registry for the follow up of these patients.

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AUTHORS:

1. Surya Babu Sunkesula
2. Lingeswara Rao B.
3. Tamil Arasi D. S.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Pathology, Kurnool Medical College, Kurnool, Andhra Pradesh.
2. Senior Resident, Department of Pathology, Kurnool Medical College, Kurnool, Andhra Pradesh.
3. Professor and HOD, Department of Pathology, Kurnool Medical College, Kurnool, Andhra Pradesh.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Lingeswara Rao B,
Senior Resident,
Department of Pathology,
Kurnool Medical College,
Kurnool-518002.
Email: eswar.bathula@gmail.com

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