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ORIGINAL ARTICLE

A STUDY OF *p57KIP2* EXPRESSION AND MORPHOLOGICAL FINDINGS OF COMPLETE AND PARTIAL HYDATIDIFORM MOLES

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ABSTRACT

Background: Hydatidiform mole (HM) is classified as complete and partial hydatidiform mole. The incidence of molar pregnancy demonstrated marked geographic and ethnic differences. The diagnosis is based on histopathology, karyotyping and flow cytometry. Objective of the present study was the differentiation and comparison between complete and partial hydatidiform mole on the basis of p57KIP2 expression. This comparative study was conducted in the Department of Pathology, Postgraduate Medical Institute / Lahore General Hospital, Lahore from 1st Jan 2011 to 31st Dec 2013.

Methods: The case records of all the molar pregnancy specimens during study period were analyzed regarding patient's history, clinical examination, morphological features and p57KIP2 expression. The main outcome measures included morphological features and immunohistochemical p57KIP2 expression.

Results: There were total of 50 cases which included 15 cases of complete and 35 cases of partial hydatidiform mole on H & E staining which proved to be 17 cases of complete and 33 cases of partial mole on p57KIP2 immunohistochemical expression. The commonest age of presentation of HM was 30 – 39 years.

Conclusion: Morphological findings of CHM differ from PHM on the basis of histopathological criteria. Complete hydatidiform mole showed absent expression and partial mole showed positive expression of p57KIP2 immunohistochemical staining. Thus p57KIP2 is a valuable diagnostic tool that could be used to differentiate complete and partial hydatidiform mole.

Keywords: Gestational trophoblastic disease, Hydatidiform mole, P57KIP2 IHC.

INTRODUCTION

Gestational trophoblastic diseases are a spectrum of related disorders which consist of benign trophoblastic lesions, premalignant hydatidiform moles, and neoplastic diseases.[1] The incidence of molar pregnancy is increasing in South East Asia ranges from 3.2 – 9.9 / 1000 gestation.[2] The incidence of molar pregnancy demonstrated marked geographic and ethnic differences. One possible reason for this great geographical variation is differences in diet in the different parts of the world.[3]

The diagnosis of hydatidiform mole is very important because it has great potential to give rise to choriocarcinoma.[4] The use of abdomino-pelvic ultrasound along with serial β – HCG is the best method for the prevention of morbidity and mortality of early pregnancy loss.[5] There is significant overlap in the histological features between complete and partial hydatidiform moles, resulting in considerable interobserver and intraobserver variability in the diagnosis.[6] Histological criteria for diagnosis of complete as well as partial hydatidiform moles were given by Szulman and Surti in 1978.[7,8] The following features were graded:

(a) Trophoblastic hyperplasia.
(b) Cistern formation.
(c) Pseudoinclusions of trophoblast.
(d) Fetal vessels in villous stroma.

Routine molecular analysis is impractical and unnecessary, therefore immunohistochemistry is necessary to establish the correct diagnosis of molar pregnancy.[9] *p57KIP2* is a cyclin – dependent kinase inhibitor, which is a tumor suppressor gene.[10] It is located on chromosome 11p[15.5] and predominantly is expressed from the maternal allele.[11]

Because *p57KIP2* is paternally imprinted, and both the X chromosomes in complete moles are derived from the father, it is expected that reduced or absent expression of *p57KIP2* protein is seen in complete moles.[12]

PATIENTS AND METHODS

This comparative study was conducted at the Pathology Department of the Postgraduate Medical Institute from 1st Jan 2011 to 31st Dec 2013. There were 50 spe-

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cimens of uterine curettings diagnosed as molar pregnancy. All patients having molar pregnancy with elevated ß-HCG (human chorionic gonadotropin), ultrasonic or histopathological evidence of the disease were included in the study.

Patients with incomplete history and without ß-HCG levels were excluded. Normal placental tissue was used as positive control of *p57KIP2* marker and negative controls were prepared by omission of the primary antibody.

Positive reactivity was interpreted only when distinct nuclear staining was identified. Cells with only cytoplasmic granular staining were regarded as negative. The staining of equal or more than 10% of total cytotrophoblastic cells were presumed positive and results below of this threshold were considered as negative. The data were statistically analyzed by using the Pearson's Chi-square test / Fisher exact test with SPSS software (SPSS-18).

RESULTS

There were total 50 specimens, among those 15 (30%) were found as complete and 35 (70%) were as partial hydatidiform moles on H & E staining but were found on IHC as CHM 17 (34%) and PHM 33 (66%) as shown in table 3.

P57KIP2 was strongly expressed in villous cytotrophoblast and villous mesenchyme in 33 (66%) partial hydatidiform moles. In contrast, P57KIP2 expression in villous cytotrophoblast, villous stromal cells and extravillous trophoblast was absent or markedly decreased in 17 (34%) complete hydatidiform mole (Fig. 2 and Fig. 4).

Diagnostic statistics (sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy) were applied to validate the diagnosis of hydatidiform moles on H&E staining with immunostaining. The data were gathered on a structured questionnaire, which were subsequently statistically analyzed by using the Pearson's Chi-square test / Fisher exact test with the latest version of the SPSS software (SPSS-18).

Table 1: *Types of hydatidiform mole on H & E stain.*

Type	*No. of Patients*	*Percentage*
Complete hydatidiform mole	15	30
Partial hydatidiform mole	35	70
Total	50	100

Above tests were used to compare the histopathological findings in P57KIP2 positive and negative cases of complete and partial hydatidiform moles.

Final Test Results

P< 0.05 was taken as significant.

Table 2: *Types of hydatidiform mole on IHC.*

Type	*No. of Patients*	*Percentage*
Complete hydatidiform mole	17	34
Partial hydatidiform mole	33	66
Total	50	100

Table 3: *Comparison of H&E stains with p57 KIP2 IHC results in HM.*

	No. of Cases		
Type	*Partial hydatidiform mole (IHC positive)*	*Complete hydatidiform mole (IHC negative)*	*Total*
Partial hydatidiform mole *(H&E)*	31	4	35
Complete hydatidiform mole *(H&E)*	2	13	15
Total	33	17	50

Sensitivity: - 93.9%, Specificity: - 76.4%, PPV: - 88.5%, NPV: - 86.6%, Accuracy: - 88%.

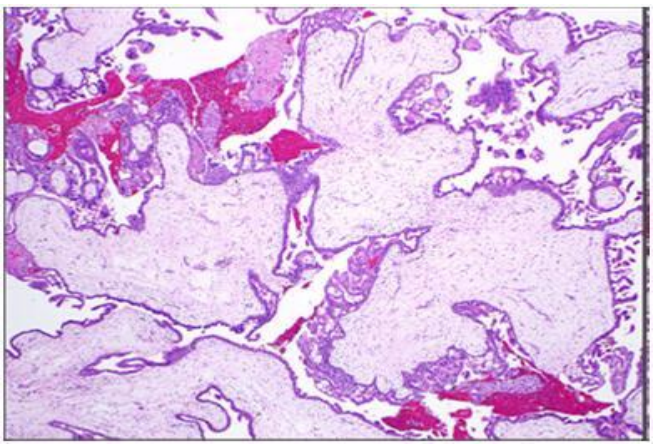

Fig. 1: *Photomicrograph of complete hydatidiform mole is showing diffuse trophoblastic hyperplasia (H&E × 100).*

DISCUSSION

A hydatidiform mole is a type of pregnancy in which the placenta has grape like vesicles. The exact incidence in Pakistan is not known but one study has repo-

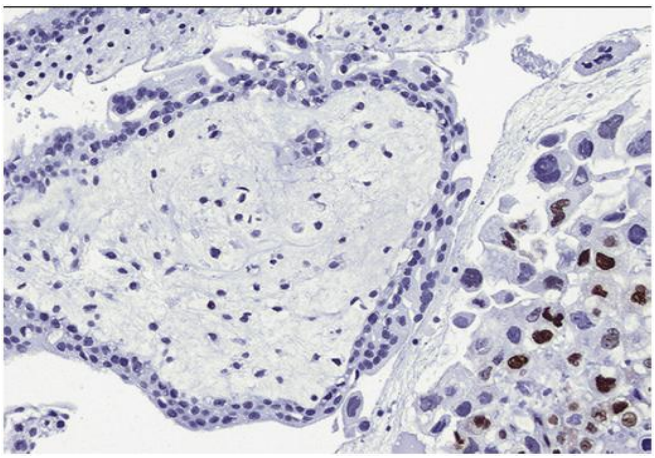

Fig. 2: *Photomicrograph of complete hydatidiform mole showing negative immunostaing with p57KIP2 in the villus (H&E × 400).*

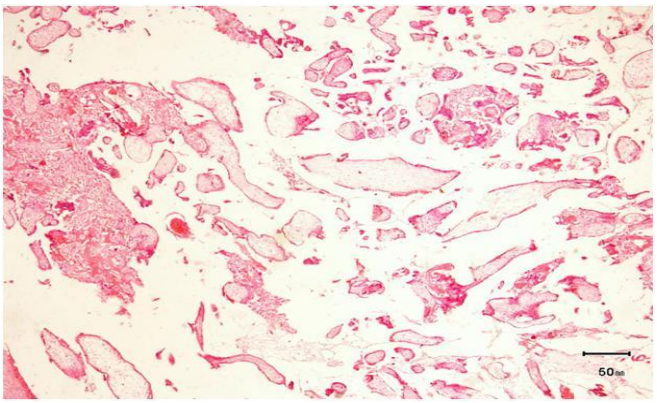

Fig. 3: *Photomicrograph of partial hydatidiform mole showing focal trophoblastic hyperplasia (H&E × 100).*

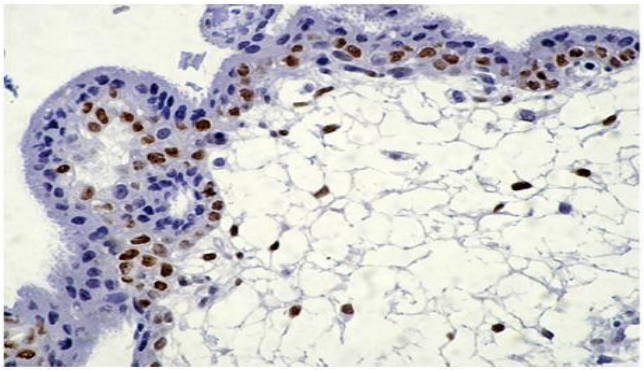

Fig. 4: *Photomicrograph of partial hydatidiform mole showing positive immunostaing with p57KIP2 in the villus. (H& E × 400).*

rted it to be 0.68 / 1000 births.[13] It has been reported that the highest incidence of molar pregnancy in Asia is generally due to low socioeconomic status and malnutrition.[14]

The present study aimed to evaluate those parameters which are commonly used for the differential diagnosis of these two conditions. Significant hyperplasia of trophoblastic tissue is required for the diagnosis of molar pregnancy. All of the above features in our study are consistent with those of criteria for diagnosis of CHM and PHM given by Szulman and Surti (1978).[7,8] Keeping in view of the limitations of morphologic assessment alone, use of immunohistochemistry is required to refine the diagnosis of molar pregnancy. The value of immunohistochemical analysis of *p57-KIP2* expression for improving the diagnosis of hydatidiform moles has been demonstrated in a number of studies.[15,16]

In the present study, we found that *p57KIP2* Immunohistochemistry could be reliably interpreted and there was excellent agreement between observers. Immunoreactivity for *p57KIP2* in cytotrophoblasts of PHM was 95% in our study. This is comparable to the study by Fukunaga (2004) and Jun et al (2003).[17,18] Thus *p57KIP2* is a diagnostic tool that could be used to differentiate complete and partial hydatidiform mole. It is shown to be a highly specific and sensitive marker.

In the present study, the following conclusions are drawn:

1) Clinical findings of HM are similar to the western world. Bleeding P/V was the most common symptom.
2) Morphological findings of CHM differ from PHM on the basis of histological criteria as diffuse trophoblastic hyperplasia was seen in most cases of CHM while partial trophoblastic hyperplasia was seen in most cases of PHM on H& E staining.
3) PHM showed absent expression of *p57KIP2* Immunohistochemical staining.
4) Thus *p57KIP2* is a valuable diagnostic tool that could be used to differentiate complete and partial hydatidiform mole.

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