

Correlation of p53 expression with morphological features in complete and partial hydatidiform moles

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SUMMARY

Hydatidiform mole, the most common form of gestational trophoblastic disease, presents as complete or partial form. Complete hydatidiform mole (CHM) usually presents with prominent histological criteria, whereas partial hydatidiform mole (PHM) shows a wide spectrum of presentations depending on gestational age. Molecular markers enhance the understanding of the variation and heterogeneous presentation of molar pregnancies, as well as their biological potential and behavior. This retrospective study included 50 CHM and 50 PHM specimens, terminated in first trimester via suction curettage. A second histopathological review of slides stained with hematoxylin and eosin was conducted, as well as a selection of representative tissue slides for p53 immunostaining. This study aimed to determine the precise correlation between specific morphological criteria and the patterns of p53 immun-expression.

Semi-quantitative analysis of samples for both

pathological criteria and p53 immunostaining was performed. p53 positivity was defined as follow: the percentage of positive cells/nuclei: + (10-40%); ++ (40-70%); +++ (>70%); and staining intensity was scored as: 1 – weak, 2 – moderate, and 3 – strong intensity. P53 expression was estimated on at least 200 nuclei of cytotrophoblasts per slide. Significant difference in p53 expression exist between CHM and PHM in staining intensity. CHM shows significant correlation of p53 positivity with hydrops, central cisterns and atypia. In PHM trophoblast pseudoinclusions demonstrate strong significant correlation with p53 positivity. The irregular pseudoinclusions demonstrate lower expression compared with round or oval, being consistent with benign behavior of PHM. Prominent morphological criteria strongly correlate with p53 immunoexpression for both CHM and PHM.

Key words: Hydatidiform mole – p53 expression – Trophoblast – Pseudoinclusions

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INTRODUCTION

Gestational trophoblastic disease (GTD) represents a rare spectrum of conditions arising from trophoblastic tissue. Hydatidiform mole (HM) is the most common form of GTD, presenting as either complete (CHM) or partial (PHM) molar pregnancies. Typically, HM is a unique event during a woman's reproductive period, developing as a result of disturbed conception characterized by extreme aneuploidy and an imbalance of maternal and paternal genes. Although uncommon, recurrence of HM suggests a potential genetic predisposition (Altieri et al., 2003; Ngan et al., 2018; Smith, 2003). Despite differences in cytogenetics, pathology, and clinical presentation, the management of CHM and PHM is similar (Soper, 2021).

Prominent histological criteria are sufficient for distinguishing molar pregnancies from non-molar specimens, as well as for differentiating CHM from PHM. Diffuse stromal edema and generalized trophoblast proliferation characterize the majority of complete moles. In contrast, the partial form demonstrates variable, focal edema of the villi, with scalloped edges, trophoblastic inclusions, and pseudoinclusions. Trophoblastic proliferation is less pronounced and more focal compared to complete moles (Ngan et al., 2018). Routine histological examination is fundamental for the diagnosis and differentiation of molar entities. Molar specimens evacuated during early and very early pregnancy often exhibit poorly developed histological features. This is particularly relevant for PHM, leading to potential misdiagnosis and significant intra- and inter-observer variability, with a wide spectrum of presentations depending on gestational age (Seckl et al., 2013). Histological characteristics similar to PHM can also be observed in case of single or combined trisomies (Sebire et al., 2016; Wilson et al., 2016). The well-known aberrant genomic composition of HM is recognized as the foundation for precise diagnosis, supported by several effective and powerful ancillary techniques that enable prognostic stratification of molar gestations (Hui et al., 2017; Buza, 2022).

Immunohistochemistry (IHC) is useful for confirming the diagnosis and predicting the biological potential of molar specimens. Studies have

provided data on molecular markers using the IHC method, enhancing the understanding of the variation and heterogeneous presentation of HM, as well as their biological potential and behavior (Fukunaga, 2002; McConnell et al., 2009; Sebire & Seckl, 2008). p53 is a tumor suppressor gene that plays a critical role in maintaining genomic stability and serves as a marker of proliferative activity. It ensures that cells repair DNA damage before undergoing cell division by inducing cell cycle arrest, thereby allowing time for DNA repair. If the damage is irreparable, p53 can trigger apoptosis to prevent the propagation of defective cells. Due to its central role in cellular integrity, p53 is the most frequently disrupted gene in neoplastic processes (Levine, 2020; Levine & Oren, 2009).

However, the analysis of p53 immunohistochemical staining can be challenging due to varying methodologies, such as differences in cut-off values, staining intensity, and the use of scoring systems like the H-score. These inconsistencies can sometimes make the results less clear and more difficult to interpret.

p53 has consistently been found to exhibit increased expression in CHM compared to PHM. Invasive nature of hydatidiform moles is elucidated with overexpression of p53 in villous cytotrophoblasts and dysregulation of its modulators (Ali et al., 2017; Erol et al., 2016; Bahutair et al., 2024). This study aimed to determine the precise correlation between specific morphological criteria and the patterns of p53 immunoeexpression.

MATERIAL AND METHODS

This retrospective study included 50 CHM specimens and 50 PHM specimens, all of which were obtained during the first trimester via suction curettage. To ensure diagnostic accuracy, a second histopathological review of hematoxylin-and-eosin- (H&E)-stained slides was conducted by a single, experienced pathologist.

The study was approved by the Medical Ethics Committee University Clinical Center Tuzla (Ref. No: 279/15; date: December 23, 2014, and Ref. No 04-912-74/15; date: October, 8,2015). The written consent was provided before inclusion in the study. The study adhered to the principles of the

Declaration of Helsinki, 2013.

Patohistological analysis

Semi-quantitative analysis of samples was performed in order to estimate: hydrops of villi (focal or generalized) trophoblast proliferation (focal or diffuse), trophoblast pseudoinclusions (absent, round, irregular), and nuclear atypia in villous cytotrophoblast (absent, mild, moderate, strong).

Immunostaining

Following semiquantitative analysis, representative tissue blocks/slides were selected for p53 immunostaining. The immunohistochemistry staining procedure was performed on formalin-fixed, paraffin-embedded tissue samples cut at 4µm, using monoclonal mouse antihuman antibody (DAKO, monoclonal mouse antihuman p53 protein, Clone DO-7) with a 1:400 dilution. Prior to staining, 1mM citric buffer (pH 8.0 at 100°C, 10-minute duration) was used for antigen retrieval. The Immunostaining Center, Shandon Sequenza, was used for all incubation stages. After 30 minutes of incubation with the primary antibody, samples were treated with the secondary antibody (biotin, streptavidin, and peroxidases). The sections were counterstained with Mayer's hematoxylin, and Canada balsam was used for mounting the slides. Breast cancer tissue was applied to every slide, which were treated with the same procedure that served as external positive control. A Nikon ECLIPSE E400 microscope, with magnifications of 20x and 40x, was used for the analysis of p53 expression.

p53 positivity was defined as the presence of brown color immunoexpression of the villous cytotrophoblasts nuclei, and described as negative with less than 10% positive nuclei. Semi-quantitative analysis was used in order to estimate the percentage of positive cells/nuclei: + (10-40%); ++

(40-70%); +++ (>70%), and staining intensity was scored as follows: 1 – weak, 2 – moderate, and 3 – strong intensity. p53 expression was estimated on at least 200 nuclei of cytotrophoblasts per slide.

Statistical analysis

One-factor multivariate analysis of variance (MANOVA) was used for statistical analysis and performed using the IBM SPSS software version 25. P values ≤ 0.05 were considered statistically significant.

RESULTS

The results of the semi-quantitative analysis of morphological criteria for both CHM and PHM are summarized in Table 1. Mean gestational age was estimated at 8 and 9,2 gestational weeks for CHM and PHM, respectively.

The reaction of IHH staining on the p53 protein was analyzed at the nuclear level of the villous cytotrophoblasts. The reaction appeared as varying shades of brownish color, ranging from ochre to dark brown. Although cytoplasmic reaction in the form of yellow staining was observed in most samples, it was not analyzed. In addition to the reaction at the cytotrophoblast level, a similar reaction in terms of shade was observed in the nuclei of extravillous trophoblast (internal positive control). The most common staining pattern was moderate nuclear staining (39% of all samples). The staining results for CHM and PHM are presented in Figs. 1 and 2.

Out of the total number, there were 94% positive complete and 66% positive partial molar specimen (Chi: 12,25, p<0,0005). The results of distribution of p53 expression in CHM and PHM (Table 2 and Table 3.) reveals insignificant differences in percentage of positive cells (Chi: 0.057, p>0,05), as it is recorded in staining intensity (chi:8,44; p<0,01).

Table 1. Morphological criteria in CHM and PHM

	H		TP		TPI		TA				
	F**/**	D	F	D	A	R	I	A	W	M	S
CHM (%)	6	94	2	98	74	2	24	6	28	36	30
PHM (%)	62/33*	5	100	-	42	10	48	82	16	2	0

Abbreviations: H - hydrops; TP - trophoblast proliferation; TPI - trophoblast pseudoinclusions; TA - trophoblast atypia; focal* - F* - focal hydrops with central cisterns; F ** - focal hydrops without central cisterns; F - focal; D - diffuse; A - absent; R - round; I - irregular; W - weak; M - moderate; S - strong.

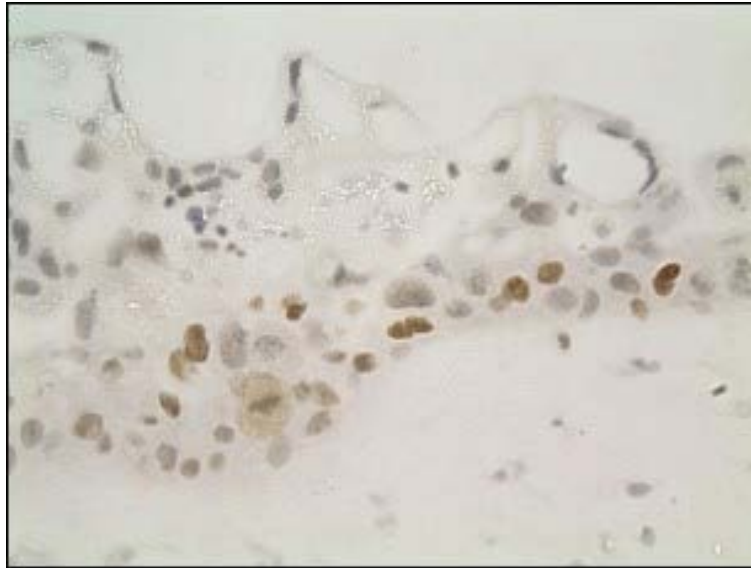


Fig. 1.- p53 expression in CHM (>70%). Magnification: x40.

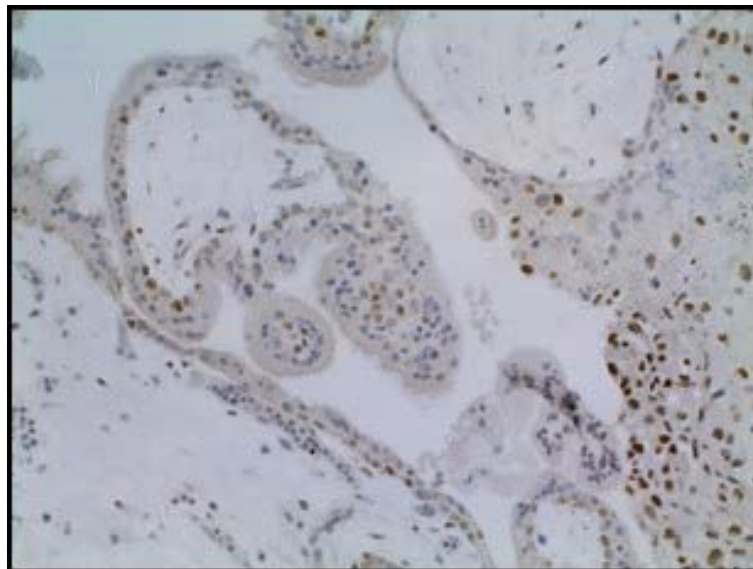


Fig. 2.- p53 expression in PHM. Magnification: x20.

Correlation of each diagnostic criteria on p53 percentage positive cells and expression intensity are presented in Table 4 to Table 8. Correlation of single diagnostic criteria and percentage of p53 positive cells in CHM. In complete moles, significant correlation of percentage of positive cells demonstrated hydrops with central cisterns (positive correlation, $p=0.028$) and atypia (negative correlation, $p=0.012$) (Table 4). In partial moles, trophoblast pseudoinclusions demonstrates strong significant positive correlation with percentage of positive cells ($p=0.003$) (Table 5).

In complete moles, significant correlation of p53 staining intensity demonstrated hydrops with central cisterns (positive correlation, $p=0.042$)

and atypia (negative correlation, $p=0.010$) (Table 6). In partial moles, trophoblast pseudoinclusions demonstrates strong significant positive correlation with p53 staining intensity ($p=0.037$) (Table 7). In partial moles, significant differences in p53 staining pattern are observed between round and irregular pseudoinclusions: irregular ones demonstrate lower p53 expression (Table 8).

DISCUSSION

Molar pregnancies develop as a result of an extreme genetic composition, which can lead to several clinical complications, such as persistence of trophoblast and progression to gestational trophoblast neoplasia. Poorly developed mor-

Table 2. Distribution of p53 positivity in CHM and PHM

% of positive ctb nuclei	CHM (n)	PHM (n)	Sig.
10-40%	36	26	p>0,05
40-70%	8	5	
>70%	3	2	
Total	47	33	

Abbreviations: ctb - cytotrophoblast

Table 3. Distribution of p53 intensity of expression in analyzed specimen

Staining intensity	CHM (n)	PHM (n)
Mild	14	14
Moderate	20	19
Intense	13	0
Total	47	33

Table 4. Correlation of single diagnostic criteria and percentage of p53 positive cells in CHM

Variables	%PC	HCC	TP	PI	AT
%PC	1.000	0.271*	.	0.069	-0.319*
HCC	0.271*	1.000	.	0.247*	-0.226
TP	.	.	1.000	.	.
PI	0.069	0.247*	.	1.000	-0.028

Abbreviations: %PS - percentage of positive cells; HCC - hydrops with central cisterns; TP - trophoblast proliferation; PI - pseudo-inclusions; AT - atypia; Values are Pearson correlation coefficients; * - statistical significance (p<0.05).

Table 5. Correlation of individual diagnostic criteria and p53 positive cells in PHM

Variables	%PC	HCC	TP	PI	AT
%PS	1.000	0.087	0.049	0.383**	-0.031
HCC	0.087	1.000	-0.036	0.148	-0.028
TP	0.049	-0.036	1.000	0.084	0.302*
PI	0.383**	0.148	0.084	1.000	0.221
AT	-0.031	-0.028	0.302*	0.221	1.000

Abbreviations: %PS - percentage of positive cells; HCC - hydrops with central cisterns; TP - trophoblast proliferation; PI - pseudo-inclusions; AT - atypia; Values are Pearson correlation coefficients; * - statistical significance (p<0.05); ** - statistical significance (p<0.01).

Table 6. Correlation of single diagnostic criteria and p53 staining intensity in CHM

Variables	IE	HCC	TP	PI	AT
IE	1.000	0.250*	-	-0.027	-0.332*
HCC	0.250*	1.000	-	0.237	-0.222
TP	-	-	1.000	-	-
PI	-0.027	0.237*	-	1.000	-0.020
AT	-0.332*	-0.222	-	-0.020	1.000

Abbreviations: IE - intensity of expression; HCC - hydrops with central cisterns; TP - trophoblast proliferation; PI - pseudo-inclusions; AT - atypia; Values are Pearson correlation coefficients; * - statistical significance (p<0.05)

Table 7. Correlation of single diagnostic criteria and p53 staining intensity in PHM

Variables	IE	HCC	TP	PI	AT
IE	1.000	0.056	0.141	0.255*	0.008
HCC	0.056	1.000	-0.036	0.148	-0.028
TP	0.141	-0.036	1.000	0.084	0.302*
PI	0.255*	0.148	0.084	1.000	0.221
AT	0.008	-0.028	0.302*	0.221	1.000

Abbreviations: IE - intensity of expression; HCC - hydrops with central cisterns; TP - trophoblast proliferation; PI - pseudoinclusions; AT - atypia; Values are Pearson correlation coefficients; * - statistical significance ($p < 0.05$)

phological criteria underlie misdiagnosis or, in case of partial mole, more often, overdiagnosis of molar pregnancies (Buza and Hui, 2013; Nagy et al., 2024). The molecular ground of molar pregnancies exposes a wide and complex genetic and epigenetic interaction, resulting from a spectrum of expression patterns of several genes and their products that influence final diagnosis, as well as understanding the disease progression and clinical outcome (Fisher and Maher, 2021; Xing et al., 2022; Bahutair et al., 2024).

This study was performed in order to identify the relationship of diagnostic criteria and p53 staining pattern. Our findings disclose that the leading criteria are sufficient for the diagnosis and distinction of both complete and partial molar specimen in the first trimester, even with CHM samples evacuated in average one week earlier than partial ones. Immunostaining results for p53 revealed significant differences between CHM and PHM. Differences in correlation of single diagnostic criteria were observed as well. We found that, in complete moles, p53 expression strongly positively correlates with hydrops with central cisterns. Furthermore, negative correlation is observed with nuclear atypia of proliferated trophoblast for both criteria. In partial moles, only trophoblast pseudoinclusions significantly correlates with p53 immunoeexpression. The irregular form of pseudoinclusions disclose lower p53 expression compared with the round/regular ones.

Analyzing morphological criteria to distinguish PHM from nonmolar trisomic gestation, Wilson et al. (2016) found that the presence of two of the following three criteria (cisterns, multifocal trophoblastic proliferation, and large trophoblastic inclusions) lead to an accurate diagnosis of PHM in 93% of cases. Irregular trophoblastic pseudoinclusions seen in PHM are presentation of villi with irregular, fjord-like indentations of proliferating trophoblast into stroma, most likely due to slower rate of change from normal to hydatidiform placental morphology (Joyce et al., 2022).

Similar to our results, immunoeexpression of p53 is detected in both molar forms, and studies disclosed significant higher p53 expression in CHM compared to PHM, suggesting its potential usefulness in distinguishing CHM from PHM (Chen et al., 2011; Kheradmand et al., 2017; Misraoui et al., 2019), and rare opposite results are reported (Khooei et al., 2019).

The majority of complete moles arise from total androgenetic conception with lack of maternal genes. One of the observations in this study renders a broad spectrum of immunostaining results, from p53 negative to strongly positive CMH samples, with more than 70% of intensively stained cytrotrophoblast nuclei, leading to the conclusion that moles' complex genetic composition may underlie complete molar specimen. In our previous study, with p57 expression we confirmed the diag-

Table 8. Correlation of trophoblast pseudoinclusions and p53 expression

	MD	SE	p	95% CI - LB	95% CI - UP
Absent vs. Present Round	0.67	0.298	0.071	-0.04	1.38
Absent vs. Present Irregular	-0.19	0.147	0.388	-0.55	0.16
Present Round vs. Present Irregular	-0.86	0.306	0.017*	-1.59	-0.13

Abbreviations: PI - pseudoinclusions; MD - mean difference; SE - standard error; 95% CI - confidence interval; LB - lower bound; UP - upper bound; * - statistically significant ($p < 0.05$)

nosis of CHM for all satisfactory immunostaining result (Lelić et al., 2017). Wide spectrum of p53 immunoexpression is described in previous studies, from overexpression of wild type to non-immunoreactive p53 in nonsense mutations, leading to confounding results in prognostic significance of p53 results (Lax et al., 2000). Therefore, observed staining intensity in CHM is more likely to be due with the significant p53 disturbance.

In correlation with nuclear atypia studies revealed that mutant p53 shows strong positive correlation with nuclear grade of atypic cells (Tang et al., 2021).

Observed negative correlation of p53 expression with nuclear atypia and trophoblast proliferation leads to the conclusion that despite significant genetic disturbance, trophoblast in moles still have well-defined limitation of their invasive growth.

Wild-type p53 protein can repair damaged cells and maintain the stability of genomes, but its half-life is short, its content in cells is low, and it is not generally expressed, while mutant p53 protein loses the ability to repair cells and promotes the development of tumors. p53 mutations found to be involved in progression of numerous proliferative tumours/conditions. Weak positive staining contributes to the p53 wild type, while forming of nontruncated protein may result with the complete lack of staining (Li et al., 2023; Yemelyanova et al., 2011).

Trophoblast pseudoinclusions were recognized as a significant feature of partial moles (Buza and Hui, 2013). However, there are no data considering the significance of their presentation either round or irregular, and our results actualize the significance in p53 immunexpression.

It has been reported that p53 gene mutation is rare in complete hydatidiform mole and trophoblastic tumors (Halperin et al., 2000; Chen et al., 1994). Cheung et al. reported a positive correlation between p53 and Ki-67 proliferation index in trophoblastic tissues of hydatidiform moles (Cheung et al., 1994). Hence, p53 overexpression may be a reflection of the higher proliferation capacity of the trophoblastic cells in molar tissues. A possible role of expression of the p53 protein in proliferative trophoblastic tissues is an attempt

to modulate the excessive proliferative activity in trophoblastic cells (Li et al., 2002). On the other hand, Halperin et al. evaluated the expression of the p53 and apoptosis in GTD and normal placenta and showed that the percentage of apoptotic cells demonstrated a significant increase in HMs compared with normal placenta and also significant overexpression of p53 in HMs compared with normal placenta, they concluded that p53 overexpression in hydatidiform moles could be the result of upregulation of apoptosis (Halperin et al., 2000). Study limitations: unicentric study, small sample size, and incomplete clinical data. Further research would be desirable to monitor complications of molar pregnancy.

CONCLUSION

The p53 immunostaining pattern in molar specimens is a reliable method for distinguishing between CHM and PHM. The leading diagnostic criteria for both CHM and PHM show a strong, statistically significant correlation with p53 staining intensity and the percentage of positive cells.

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