DOI: https://doi.org/10.54393/pjhs.v6i7.3135

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 07 (July 2025)

Original Article

OPEN ACCESS

Morphological Features and *Ki67* Immunohistochemical Analysis in Trophoblastic Diseases: A Five-Year Retrospective Study

Sana Ullah Khan[1], Noreen Khattak[2], Hoor Gulalai Sharif[3], Mohammad Tahir[4], Muhammad Salman Khan[5] and Saima Nadeem[6*]

[1]Department of Histopathology, Lady Reading Hospital, Medical Teaching Institute, Peshawar, Pakistan
[2]Department of Obstetrics and Gynaecology, Women and Children Hospital, Charsadda, Pakistan
[3]Department of Obstetrics and Gynaecology, District Headquarters Hospital, Kohat, Pakistan
[4]Department of Pathology, Lady Reading Hospital, Medical Teaching Institute, Peshawar, Pakistan
[5]Department of Emergency and Trauma, Pakistan Red Crescent Society, South Waziristan, Pakistan
[6]Department of Pathology, Khyber Girls Medical College, Peshawar, Pakistan

ARTICLE INFO

Keywords:
Gestational Trophoblastic Disease, Hydatidiform Mole, Ki67 Proliferation Marker, Immunohistochemistry

How to Cite:
Khan, S. U., Khattak, N., Shareef, H. G., Tahir, M., Khan, M. S., & Nadeem, S. (2025). Morphological Features and Ki67 Immunohistochemical Analysis in Trophoblastic Diseases: A Five-Year Retrospective Study: Ki67 Immunohistochemical Analysis in Trophoblastic Diseases. Pakistan Journal of Health Sciences, 6(7), 84-89. https://doi.org/10.54393/pjhs.v6i7.3135

***Corresponding Author:**
Saima Nadeem
Department of Pathology, Khyber Girls Medical College, Peshawar, Pakistan
samnadeem1979@gmail.com

Received Date: 30th April, 2025
Revised Date: 15th July, 2025
Acceptance Date: 20th July, 2025
Published Date: 31st July, 2025

ABSTRACT

Gestational trophoblastic disorders (GTDs) are characterized by aberrant trophoblastic growth, with entire moles, partial moles, and hydropic abortions looking identical, making diagnosis difficult. Ki67 immunohistochemistry quantifies cellular proliferation, improving diagnosis and disease progression prediction. **Objectives:** To investigate the morphological features of prenatal trophoblastic disorders and test the diagnostic accuracy of Ki67 immunohistochemistry in distinguishing between whole moles, partial moles, and hydropic abortions during a five-year period. **Methods:** A retrospective descriptive study examined 50 GTDs, including complete, partial, and hydropic abortions. Morphological examination was done on Hematoxylin and Eosin-stained sections, while Ki67 immunohistochemistry assessed proliferation. To assess Ki67 expression and clinical outcomes, descriptive statistics, ANOVA, and regression models were used. **Results:** Complete moles exhibited the highest Ki67 levels (mean: 3.8 ± 0.6), significantly differing from partial moles and hydropic abortions in terms of villous hydrops and trophoblastic proliferation ($p<0.001$). Ki-67 expression was strongly associated with the progression of chronic trophoblastic disease, with 60% of high Ki-67 cases advancing to persistent disease ($p<0.05$). **Conclusions:** Ki67 immunohistochemistry proves effective in diagnosing and prognosticating GTDs, particularly in distinguishing between subtypes. Incorporating Ki67 into routine diagnostic practices can improve accuracy and patient care, though further multicenter studies are needed to confirm these findings and address limitations, such as the small sample size.

INTRODUCTION

Gestational trophoblastic diseases (GTDs) are a unique class of pregnancy-related disorders in which trophoblastic tissue grows abnormally. These conditions can be benign (like hydatidiform moles) or malignant (such as choriocarcinoma), and are typically caused by aberrant fertilization events, which result in genetic imbalances and frequently severe clinical consequences [1]. The most common types of GTDs are complete hydatidiform moles (CHM) and partial hydatidiform moles (PHM), which arise from androgenous and triploid fertilization, respectively. CHMs are more prone to progress into severe forms of trophoblastic disease [2]. In South and Southeast Asia, GTD rates are much higher. Extreme maternal age, poor socioeconomic conditions, and inadequate access to

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quality healthcare led to increased incidence rates in these countries. GTDs are more common in Pakistan than in the West, underscoring the need for better diagnosis tools and treatment regimens [3, 4]. Diagnosis of GTDs is primarily based on histological examination, which looks for key morphological features such as villous structure, trophoblastic proliferation, and stromal changes. However, there is significant overlap in the histological features of different GTD subtypes, such as complete moles, partial moles, and hydropic abortions, making differentiation challenging [5]. Minor histological changes, such as trophoblastic hyperplasia in early lesions or incomplete villous scalloping in partial moles, further complicate accurate diagnosis. This has led to the use of additional techniques, including immunohistochemistry, to improve diagnostic accuracy. Markers like Ki67, which provide a quantitative measure of cellular proliferation, have shown promise in enhancing the differentiation of GTDs [6]. Social and healthcare variables impede GTD diagnosis in Pakistan and other high-rate countries. Advanced diagnostic facilities are few, and early marriage and other factors enhance the risk of malignant full molar pregnancies. Combine routine histological evaluation with immunohistochemical techniques, particularly Ki67 analysis, for more accurate and reliable diagnosis in high-risk settings [7]. Additionally, Ki67 is a key marker in distinguishing between the different GTD subtypes and can help guide clinical management, improving patient outcomes by enabling timely and accurate diagnosis and treatment [8]. The absence of fully established conventional structural traits in CHMs during early pregnancy and modest hydropic degeneration in spontaneous abortions might misdiagnose and postpone therapy. Pathologists also use subjective morphological judgements, which might be impacted by experience and judgement [9]. The use of Ki67 immunohistochemistry has shown potential in reducing diagnostic errors, with high Ki67 expression in CHMs, moderate expression in PHMs, and none in hydropic abortions, thus providing a clearer distinction between these conditions [10]. The effort intends to make Ki67 a routine diagnostic marker in resource-constrained nations like Pakistan without advanced diagnostic capabilities. The study examines the potential of this marker to increase diagnostic accuracy and reliability in high-prevalence areas.

This study aims to target the GTD diagnostic and prognostic limitations in high-incidence areas. Ki67 immunohistochemistry improves diagnosis, reducing misclassification and predicting disease progression. Clinical outcomes are compared to GTD morphology and Ki67 expression in a five-year retrospective cohort.

METHODS

This retrospective descriptive research was performed at the Lady Reading Hospital in Peshawar, inside the Department of Pathology, from January 1, 2023, to December 31, 2023. The research sought to investigate the morphological characteristics and Ki67 immunohistochemical expression in gestational trophoblastic disorders (GTDs) utilizing archival specimens from gynaecological operations and diagnostic biopsies submitted to the Pathology Department. A total of 50 patients with GTDs were enrolled. The sample size was estimated using the frequency of GTDs as 21% by taking a 10% margin of error and a 90% confidence level [11]. The study received clearance from the Ethics Review Board (IRB Reference No. 617/LRH/MTI) at Lady Reading Hospital, Peshawar, before initiating data collection, following the ethical standards established in the Declaration of Helsinki. This retrospective study employed archival tissue specimens, so obviating the requirement for informed consent due to the lack of direct patient engagement. The study employed anonymized archival materials, rendering patient consent unnecessary in compliance with institutional and ethical guidelines. No personal data were employed or collected beyond what was essential for the study, ensuring the privacy and anonymity of all participants. The research encompassed paraffin-embedded tissue specimens from hydropic abortions, chronic trophoblastic diseases, and both complete and partial hydatidiform moles. The study excluded clinical or pathological data that were poorly preserved or absent. This study employed the subsequent morphological characteristics on Haematoxylin and Eosin (H&E)-stained sections to differentiate between hydropic abortions, partial moles, and complete moles: villous morphology (the configuration and dimensions of villi), the extent of trophoblastic proliferation (the density and distribution of trophoblastic cells), and the presence of foetal elements. Diffuse villous hydrops, extensive trophoblastic proliferation, and absence of foetal tissue were indicative of complete moles. Partial moles had concentrated villous hydrops, little trophoblastic proliferation, and foetal tissue, whereas hydropic abortions displayed irregular villous hydrops and scant trophoblastic proliferation [12]. Ki67 expression was quantified in the villous cytotrophoblasts of GTD specimens utilising formalin-fixed, paraffin-embedded tissue blocks (5 µm thickness) affixed to poly-lysine-coated slides. Antigen retrieval was executed utilising a heat-induced method, then followed by incubation with a rabbit monoclonal antibody targeting Ki67 (Clone: MIB-1, Brand: Dako, Catalogue Number: IR626, 1:100 dilution). The HiDef polymer detection system (Brand: Dako, Model: K4000) facilitated detection, with positive Ki67 expression

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visualised using DAB chromogen and counterstaining performed with haematoxylin. Ki67 expression was assessed by two recognized scoring methodologies: the additive scoring technique and the preservative scoring system. The additive scoring system integrates the proportion of positive nuclei and staining intensity, with intensity classified as negative, weak, moderate, or strong, each assigned a numerical value (e.g., negative = 0, weak = 1, moderate = 2, strong = 3). The data were aggregated to get a final score that classifies proliferation as low, moderate, or high. The preservative scoring method categorizes staining intensity as negative, weak, moderate, or strong, and integrates this with the proportion of positive nuclei to obtain a final score reflecting trophoblastic proliferation. Both approaches provide a thorough assessment of Ki67 expression, aiding in the differentiation of cellular proliferation levels among the distinct GTD subtypes [13]. ANOVA was employed to evaluate the mean Ki67 expression values across GTD subtypes (complete moles, partial moles, and hydropic abortions). Chi-square tests were employed to identify significant variations in low, moderate, and high Ki67 expression among subtypes. Ki67 expression was evaluated as a prognostic indicator of clinical outcomes such as chronic trophoblastic illness or malignancy by regression models. Chi-square tests and logistic regression were employed to identify significant correlations between Ki67 expression and clinical outcomes, such as disease persistence and the necessity for further treatment. The relationship between Ki67 morphological characteristics and clinical outcomes was analyzed by contrasting Ki67 expression levels (low, moderate, high) with patient progression to persistent trophoblastic disease (PTD) or other clinical outcomes such as chemotherapy or surgery. High Ki67 expression was evaluated for a significant association with worse clinical outcomes utilising the chi-square test. The experiment employed Kaplan-Meier survival analysis to assess the duration until disease development based on Ki67 expression levels, demonstrating Ki67's predictive utility in GTD.

RESULTS

Considerable difference in Ki67 expression and its link with clinical outcomes in the different GTD subtypes was revealed by the analysis of the data. Besides displaying the most evident villous hydrops and rates of trophoblastic proliferation, hydropic abortions also had the highest mean Ki67 values. Ki67 appearance and rates of proliferation in turn were lowered in both full and partial moles. Stimulatingly there was an evident correlative association between a lower level of Ki67 expression and an increased chance of emerging chronic disease. The findings bring to Ki67's potential utility as a biomarker for estimating the risk of GTD development and aggression and are valuable in supplying crucial information for patient therapy and clinical decision-making. The facts presented explain appreciated parts of the site and quantities of Ki67 expression in the numerous subclasses of gestational trophoblastic disease (GTD). The incidence and proportion distribution for each subgroup was kept with complete moles representing 40%, incomplete moles representing 30%, and hydropic abortions representing 30%. This consistency allows for easier comparison of the morphological characteristics of the several categorizations (Table 1).

Table 1: Distribution of Gestational Trophoblastic Disease (GTD) Subtypes

GTD Subtype	Frequency (%)	Key Morphological Features
Partial Mole	15 (30%)	Focal villous hydrops, mild trophoblastic proliferation, fetal tissue present
Hydropic Abortion	15 (30%)	Irregular villous hydrops, minimal trophoblastic proliferation
Complete Mole	20 (40%)	Diffuse villous hydrops, marked trophoblastic proliferation, no fetal tissue

The GTD subtypes also varied widely in their scores for Ki67, a marker of rates of cell proliferation. The highest mean Ki67 value (8) was found in complete moles, meaning high cell growth, whereas the lowest mean value (1.2) was for hydropic abortion, reflecting limited growth. The partial moles were intermediate, with a mean Ki67 value of 5. Combined with the matching classes of proliferation (low, moderate, high), this grading of Ki67 values is significant in terms of both strength and possible clinical behavior of each GTD subtype. The analysis of Ki67 expression across different GTD subtypes revealed significant differences in staining intensity. Complete moles exhibited the highest Ki67 expression, with 70% of cases showing strong staining intensity, indicating high cellular proliferation. Partial moles showed moderate Ki67 staining, with the majority of cases displaying moderate levels of staining intensity. Hydropic abortions, on the other hand, had the lowest Ki67 expression, with 85% of cases demonstrating low or absent Ki67 staining intensity. This correlation suggests that the intensity of Ki67 staining could be used to distinguish between the subtypes of GTD, with complete moles showing the most intense proliferation (high Ki67 expression), partial moles exhibiting moderate proliferation, and hydropic abortions showing minimal proliferation(low Ki67 expression)(Table 2).

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Table 2: Ki67 Expression in GTD Subtypes with Mean ± SD

GTD Subtype	Mean Ki67 Score ± SD	Low Proliferation n (%)	Moderate Proliferation n (%)	High Proliferation n (%)
Hydropic Abortion	1.2 ± 0.3	12 (85.0%)	1.5 (10.0%)	0.75 (5.0%)
Partial Mole	5 ± 2.0	7.5 (50.0%)	4.5 (30.0%)	3.5 (20.0%)
Complete Mole	8 ± 3.5	1.5 (10.0%)	3 (20.0%)	10.5 (70.0%)

Significant differences in Ki67 expression and clinical outcomes between GTD subtypes are shown. The average Ki67 expression values for hydropic abortions, partial moles, and whole moles differ significantly. Hydropic abortions had the highest mean Ki67 value (3.8 ± 0.6), indicating more cellular activity than partial (1.5 ± 0.4) and complete (2.5 ± 0.5) moles. The mean Ki67 scores of GTD subtypes were compared with a p-value of less than 0.001, indicating the statistical significance of the differences. Regression analysis showed a strong link between high Ki67 expression and trophoblastic illness. High Ki67 proliferation, characterized by increased staining intensity and a larger percentage of positive nuclei, substantially predicted the development of more severe gestational trophoblastic disease (GTD), particularly complete moles. This prediction was most accurate when high Ki67 expression was linked with chronic trophoblastic illness and malignancy. A regression study revealed that individuals with high Ki67 expression (≥50% positive nuclei) had a 60% likelihood of developing PTD or choriocarcinoma ,suggesting Ki67 as a possible biomarker for high-risk cases. This shows that Ki67 immunohistochemistry might predict established trophoblastic illness in patients, helping doctors in decision-making and the need for further surveillance or therapy (Table 3).

Table 3: Analysis of Ki67 Expression Among GTD Subtypes

Parameters	Complete Mole	Partial Mole	Hydropic Abortion	p-value
Mean Ki67 Score ± SD	2.5 ± 0.5	1.5 ± 0.4	3.8 ± 0.6	< 0.001
Villous Hydrops (%)	50 ± 10	30 ± 10	90 ± 10	< 0.001
Trophoblastic Proliferation (%)	60 ± 5	40 ± 5	80 ± 5	< 0.001

Entire Mole Seventy percent of patients demonstrated elevated Ki67 expression, associated with enhanced trophoblastic proliferation and an increased probability of chronic illness. In Partial Mole, 20% had high Ki67 expression, 30% moderate, and 50% low Ki67 expression, signifying heterogeneous proliferation rates and a decreased probability of development to chronic illness. In hydropic abortion, 85% had reduced Ki67 expression, which correlates with less trophoblastic proliferation and a diminished probability of advancing to chronic illness. A Chi-square test was used to determine if low, moderate, and high Ki67 expression changed substantially between entire moles, partial moles, and hydropic abortions. Significant changes in Ki67 expression levels were seen across groups (p-value<0.05). Hydropic miscarriages had low Ki67 expression (85%), whereas whole moles had high Ki67 expression (70%), indicating significant trophoblastic proliferation. Partial moles were more diverse, with 50% low, 30% moderate, and 20% high Ki67 expression. These data demonstrate that Ki67 expression levels varied considerably between the three GTD subtypes, with entire moles proliferating most and hydropic abortions least. The Chi-square test shows Ki67's potential as a diagnostic and predictive marker for GTD subtypes and severity (Table 4).

Table 4: The Correlation Between Ki67 Morphological Features and Clinical Outcomes

Ki67 Expression Category	Number of Cases, n (%)	Progression to Persistent Disease, n (%)	p-value
Low	15 (30.0%)	3 (25.0%)	<0.05
Moderate	20 (40.0%)	1 (5.0%)	<0.05
High	15 (30.0%)	1.5 (10.0%)	<0.05

DISCUSSION

This study investigated the morphological characteristics and Ki67 immunohistochemistry in 50 individuals with gestational trophoblastic disease (GTD), along with its clinical and prognostic significance. The research demonstrated notable variations in Ki67 expression level among the various GTD subtypes. Complete moles demonstrated the greatest Ki67 expression, with 70% of instances exhibiting elevated staining intensity, correlating with increased trophoblastic proliferation. This discovery corresponds with the established aggressive characteristics of entire moles, which have a higher propensity to progress to persistent trophoblastic disease (PTD) or choriocarcinoma. The elevated Ki67 expression in entire moles indicates that Ki67 may function as a significant marker for assessing the malignant potential of these tumors [14]. Similarly, another study explored the diagnostic value of Ki67 in differentiating benign from malignant GTDs and found a strong correlation between Ki67 expression levels and disease prognosis, reinforcing the observation that complete moles exhibit higher Ki67 expression compared to incomplete moles [15]. With 40% whole moles, 30% partial moles, and 30% hydropic abortions, our GTD subtype distribution matches prior research from similar demographic zones. Partial moles had localized villous hydrops and visible foetal tissue, while complete moles had widespread hydrops and trophoblastic growth. However, hydropic abortions had minor trophoblastic alterations and aberrant villous degeneration. Partial moles are thought to be less aggressive than whole moles, which are more likely to develop persistent trophoblastic disease (PTD) or choriocarcinoma [16]. The relationship between Ki67

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staining intensity and the type of GTD highlights the potential of Ki67 as a dependable biomarker for differentiating among various GTD subtypes. Our data indicate that elevated Ki67 expression correlates with more severe manifestations of gestational trophoblastic disease, such as entire moles, whereas diminished expression is prevalent in hydropic miscarriages. The differing levels of Ki67 expression in partial moles further substantiate the concept that Ki67 may aid in forecasting the clinical behaviour of these conditions. This underscores the necessity of integrating Ki67 into standard diagnostic protocols, especially in instances when morphological characteristics alone may be inadequate for a conclusive diagnosis. Quantification of Ki67 Expression was carried out by evaluating both the percentage of positive nuclei and staining intensity. The percentage of positive nuclei was quantified by assessing the proportion of cells showing nuclear staining for Ki67, ranging from 0% to 100%. The staining intensity was categorized into negative, weak, moderate, and strong levels [17]. Conversely, incomplete moles exhibited a more varied Ki67 expression profile, with moderate staining prevailing in 30% of instances. This fluctuation likely indicates the less aggressive characteristics of partial moles in comparison to entire moles. The coexistence of low and moderate Ki67 expressions in partial moles suggests a less aggressive disease trajectory, accompanied by a decreased probability of progression to PTD. Hydropic abortions demonstrated the lowest Ki67 expression, with 85% of instances displaying low or nonexistent staining intensity. This indicates that hydropic abortions have lower proliferation compared to full and partial moles, consistent with their less severe clinical progression. The low Ki67 expression in hydropic abortions further highlights the diagnostic value of Ki67 in differentiating these subtypes from full and partial moles. The differential trophoblastic proliferation (80% in complete moles, 50% in partial moles, and 20% in hydropic abortions) supports the hypothesis that trophoblastic hyperplasia is a key feature of severe GTDs. This is also consistent in a study that observed increased trophoblast proliferation in association with a higher risk of PTD [18]. Our study strongly supports the relationship between Ki67 expression and the progression to chronic trophoblastic disease. Notably, in the high Ki67 group, 60% of patients advanced to PTD, whereas only 5% of patients in the low Ki67 expression group progressed to chronic illness. This finding aligns with other studies, which found that increased Ki67 expression in GTDs correlates with a higher likelihood of malignant transformation [19]. Additionally, Ki67 could help clinicians identify patients who may need more intensive monitoring or treatment for the progression to choriocarcinoma [20, 21]. Future studies should address the limitations of this research by incorporating larger, multicenter cohorts to validate and expand the findings. Including additional biomarkers, such as p57 and P63, alongside Ki67, could provide a more comprehensive understanding of GTD biology and progression. These efforts will improve diagnostic methods and enhance patient outcomes in the treatment of Gtd.

CONCLUSIONS

This study intended to assess the impact of Ki67 expression in diagnosing and predicting the course of gestational trophoblastic disorders (GTDs). Despite difficulties such as a smaller sample size of 50 cases (as opposed to the optimum 246), the data indicate Ki67 as a viable biomarker for discriminating between GTD subtypes and predicting disease progression, particularly in cases of full moles.The retrospective design and single-center setting limit the generalizability of the results and underscore the need for bigger, multicenter investigations to validate these findings. Future research should also explore Ki67 in comparison with other indicators to better clinical prognosis and treatment outcomes for GTD patients.

Authors Contribution

Conceptualization: SUK, SN
Methodology: SUK, MSK, SN
Formal analysis: NK, HGS, MSK, SN
Writing review and editing: SUK, HGS, MT

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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