The association of histopathologic features and postmolar gestational trophoblastic neoplasia among patients with complete hydatidifrom mole*

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ABSTRACT

Objective: The study aims to correlate the histopathologic characteristics of patients diagnosed with complete hydatidiform moles with the risk of developing postmolar gestational trophoblastic neoplasia.

Methodology: A retrospective review of 71 histopathologically-confirmed cases of complete hydatidiform moles was made. Group 1 consisted of 65 patients who achieved normal titers and remained to have normal β-hCG titers after at least 1 year of follow up. Group 2 included 6 patients who developed postmolar gestational trophoblastic neoplasia. Histopathologic slide review was done to assess the following: trophoblastic proliferation, nuclear atypia, hemorrhage, necrosis along with measurement of the shortest diameter of the largesthydropic villus. The association of the histopathologic features and the development of postmolar gestational trophoblastic neoplasia was done using chi square. Analysis of the association of histopathologic features included in the study predictive of the development of postmolar gestational trophoblastic neoplasia was done.

Results: Analysis of several histopathologic parameters which may precisely identify which patients with complete hydatidiform moles were more likely to develop postmolar gestational trophoblastic neoplasia failed to produce statistically significant results. However, among the all the features studied, the presence of extensive necrosis favored the occurrence of postmolar sequela.

Conclusion: Trophoblastic proliferation, nuclear atypia, hemorrhage and villus size of complete hydatidiform moles do not predict progression to postmolar disease. In spite of this, all patients with complete hydatidiform moles should be considered for prophylactic chemotherapy or should be monitored closely.

Keywords: Complete hydatidiform mole, Postmolar gestational trophoblastic disease, Histopathologic features, Villus size

INTRODUCTION

Hydatidiform mole refers to an abnormal pregnancy characterized by varying degrees of trophoblastic proliferation and vesicular swelling of the placental villi associated with an absent or an abnormal fetus/ embryo.[1] Two types of hydatidiform mole have been described based on both morphologic and cytogenetic criteria: the classical complete hydatidiform mole (CHM) and the partial hydatidiform mole (PHM). The former is characterized by rapidly progressing hydatidiform change affecting the whole placenta, with widespread and gross trophoblastic hyperplasia in the absence of an embryo and its covering amnion. In contrast, partial moles demonstrate a slow hydatidiform change that affects only some of the villi in the placenta.[2]

It is now known that around eighteen to 28% of patients with complete mole develop gestational trophoblastic neoplasia or GTN. In contrast, only 2.5-4% of patients with partial molar pregnancy are at risk of GTN.[3] Clinical parameters that have been implicated to increase the risk of developing GTN after evacuation of a complete mole include those that show evidence of marked trophoblastic growth, such as a pre-evacuation βhCG level ≥ 100,000 mIU/ mL, excessive uterine growth (≥20- week size), and theca lutein cysts ≥6 cm in diameter.[1,3] Similarly, patients with an age ≥40 years, a repeat molar pregnancy, an aneuploid mole, and medical complications of molar pregnancy, such as pre-eclampsia and hyperthyroidism are also at increased risk for postmolar GTN.[1] Although these clinical factors can be used to identify women at an increased risk for the development of postmolar GTN, they lack the ability to predict the course of disease for individual patients. As a result, the search for a diagnostic test that can precisely determine which patients will develop GTN has continued. Parameters that have been investigated

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include immunostains, cytogenetic studies and histopathologic features of the molar pregnancy.

A study by Ayhan and colleagues in 1996 was carried out on 82 patients in order to define the most powerful predictors of persistent trophoblastic disease. Among the pathologic parameters, the degree of trophoblastic proliferation, marked nuclear atypia, and presence of necrosis and hemorrhage were significant forecasters of persistent disease. These findings support the idea by Hertig et al. that histopathologic evaluation of a specimen may yield additional information regarding progression to persistent neoplasia.[4] A study undertaken by Kaneki et al. in 2010 assessed whether the shortest diameter of the largest villus measured using a stereomicroscope was predictive of postmolar GTN. This study was the first to demonstrate that the size of the hydropic villi may be used as a predictor of postmolar GTD in patients with androgenetic moles.[2]

This study was undertaken to determine the association of histopathologic features of hydatidiform moles and development of postmolar GTN. Specifically, the histopathologic parameters that were investigated included the degree of trophoblastic proliferation, nuclear atypia, presence of hemorrhage and necrosis and the smallest diameter of the largest hydropic villus from complete hydatidiform moles.

Results of this study will have implications on determining which patients must be considered for prophylactic chemotherapy or at least careful β-hCG follow-up with early initiation of therapy when indicated.

MATERIALS AND METHODS

Study Design, Population and Setting

This was a retrospective cohort study involving all patients admitted at the Department of Obstetrics and Gynecology at a tertiary government hospital from January 2008 to December 2011 with histopathologically confirmed complete hydatidiform mole from specimens obtained during molar evacuation. All patients with sufficient data were included in the study. Patients with a previous history of gestational trophoblastic neoplasia, those who were lost to follow-up (less than 1 year surveillance or serial hCG monitoring less than 3 months), patients with incomplete data and those with lost histopathologic slides were excluded from the study.

Procedure

The investigators evaluated the medical records of all patients diagnosed with complete hydatidiform mole at a tertiary government hospital from January 2008 to December 2011 for possible inclusion in the study. The following clinical data of the patients were obtained by retrospective chart review: age at diagnosis, gravidity/parity, size of the uterus and the pre-evacuation β-hCG titer. All patients were categorized into two groups. Group 1 consisted of patients who achieved normal titers and remained to have normal beta hCG titers after at least 1 year of follow-up while Group 2 consisted of patients who developed post-molar Gestational Trophoblastic Neoplasia based on the following criteria: (1) High level of hCG more than 4 weeks post-evacuation (serum level of 20,000mIU/m). (2) Progressively increasing or plateauing hCG values at any time after evacuation (minimum of 3 weekly determinations). (3) Clinical or histologic evidence of metastasis at any site. (4) Persistently elevated hCG titer at 14 weeks post-evacuation. (5) Elevation of a previously normal hCG titer after evacuation provided the diagnosis of pregnancy is excluded.

Histopathologic slides of patients included were retrieved from the files of the Department of Pathology. The following histopathologic features were evaluated by a single, blinded pathologist: hydropic villus diameter, trophoblastic proliferation, nuclear atypia, hemorrhage and necrosis measurement of the smallest diameter of the largest hydropic villus in each slide using a microscope caliper was likewise carried out. Findings were then correlated with the occurrence of postmolar gestational trophoblastic disease.

Data Analysis

Data obtained was encoded using Microsoft Excel 2007 and analyzed using SPSS version 18 and Open Source Epidemiologic Statistics (OpenEpi) version 2.3.1. Continuous data were expressed as means and standard deviations. Categorical data were expressed as frequencies for populations with and without development of postmolar gestational trophoblastic disease.

The measure of the development of postmolar GTN was expressed as incidence rate, which was the proportion of subjects who develop the disease under study within a specified time period. The numerator of the rate was the number of diseased subjects and the denominator was the number of person-years of observation. The incidence rates for exposed and non-exposed subjects were calculated separately.

The chi-square was used to determine the correlation between the different histopathologic features and the development of postmolar gestational trophoblastic disease. All levels of significance were set at 0.05.

The Receiver Operator Characteristic (ROC) curve was used and the area under the curve was calculated to identify the best discriminator value for villus size. Using this cut off value, the association with postmolar gestational trophoblastic neoplasia was determined after analysis.

RESULTS

Of the 71 patients with complete hydatidiform mole, sixty five cases (91.5%) had β-hCG levels that spontaneously returned to normal after molar evacuation. On the other hand, six patients (8.5%) developed postmolar gestational trophoblastic neoplasia.

The patients ranged in age from 16 to 46 with gravidity ranging from G1 to G11. There was no apparent association between age or gravidity/parity and the subsequent disease course. Initial β-hCG titers were found to be more than 100,000 mIU/ml in 69.4% of the cases, while 29.2% had initial β-hCG levels below 100,000 mIU/ml.

Sufficient histologic material was accessible for review in 71 cases. Table 1 shows the results of the histopathologic features of both groups. The degree of trophoblastic proliferation was graded as being mild, moderate or severe (Figures 1 and 2). The incidence of postmolar gestational trophoblastic neoplasia was found to be as follows: 1.4% with mild, 2.8% with moderate and 4.2% with severe trophoblastic proliferation. (p value = 0 .61)

Table 1. Result of histopathologic readings for both groups

Histopathologic Feature	Postmolar GTN		p-value*
	Yes n=6	No n=65	
Trophoblastic proliferation			
Mild	1 (1.4)	4 (5.6)	.34
Moderate	2 (2.8)	28 (39.4)	.06
Severe	3 (4.2)	33 (46.5)	.97
Atypia			
Mild and Moderate	1 (1.4)	19 (26.8)	.51 .51
Severe	5 (7.0)	46 (64.8)	
Hemorrhage			
Present	5 (7.0)	42 (59.2)	0.35
Absent	1 (1.4)	23 (32.4)	
Necrosis			
Present	6 (8.5)	30 (42.3)	.01
Absent	0	35 (49.3)	
Villous size (9.28 + 4.26)			
Less than or equal to 10	3 (4.2)	46 (64.8)	.29
Greater than 10	3 (4.2)	19 (26.8)	

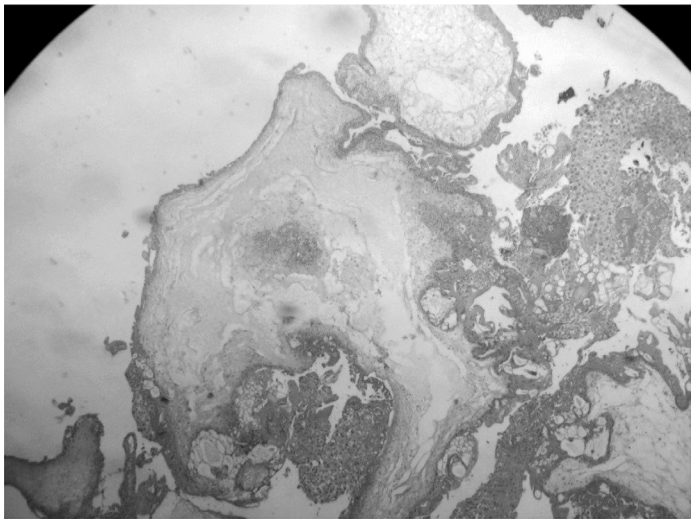

Figure 1. Multifocal trophoblastic proliferation

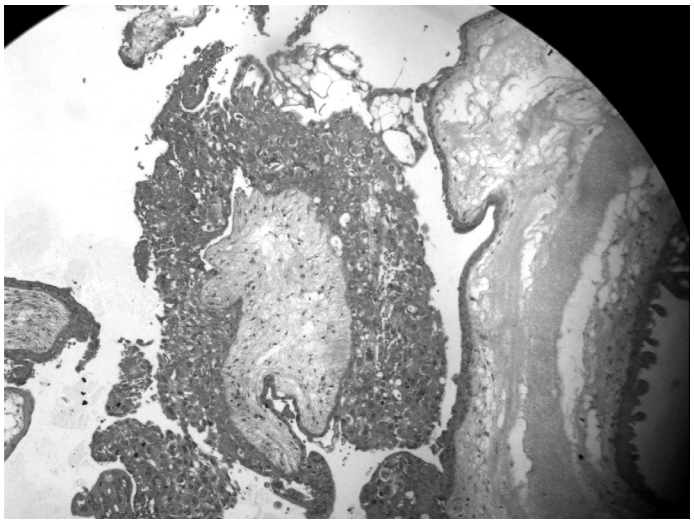

Figure 2. Circumferential trophoblastic proliferation

The degree of atypia was evaluated in the same manner as trophoblastic proliferation. (Figure 3) The results showed that there was no significant correlation between the occurence of postmolar gestational trophoblastic neoplasia and the degree of nuclear atypia. (p value = 0.79)

The presence or absence of hemorrhage and necrosis were also assessed (Figure 4). Hemorrhage was seen in 59.2% of patients without PGTN and in only 7% of patients with postmolar gestational trophoblastic neoplasia. Thus, hemorrhage was not significantly correlated with the development of postmolar GTN. (p value = 0.35) On the contrary, the presence of necrosis in 8.5% of patients with postmolar GTN and its absence in 49.3% of patients without postmolar GTN proved that necrosis is significantly associated with an increase in the incidence of postmolar gestational trophoblastic neoplasia. (P value = 0.01)

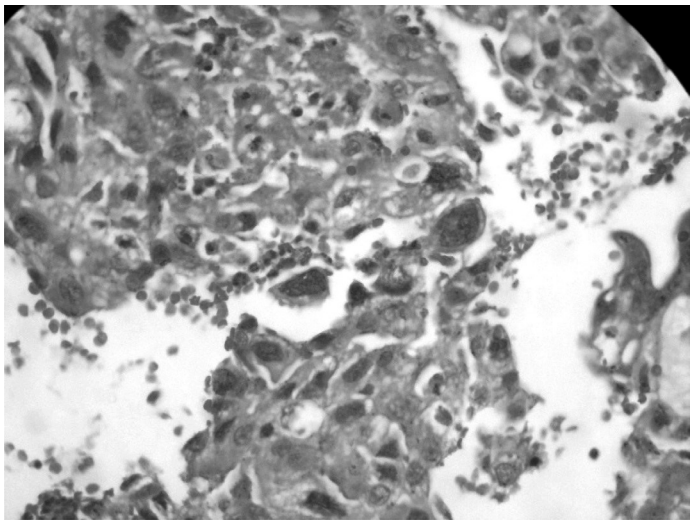

Figure 3. Nuclear atypia

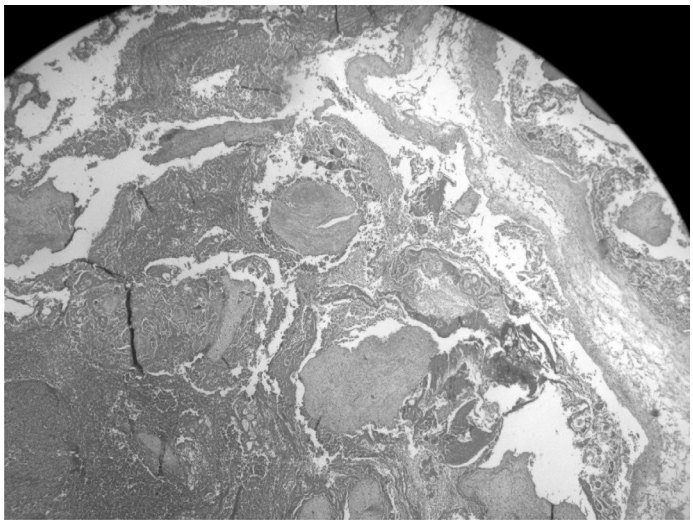

Figure 4. Hemorrhage and necrosis

Among patients belonging to Group 1, the shortest diameter of the largest hydropic villus ranged from 3 to 22 millimeters (mean of 9.09 mm). In contrast, the shortest diameter of the largest hydropic villus in patients belonging to Group 2 (with postmolar gestational trophoblastic neoplasia) ranged from 7.5 to 16.5 millimeters (mean of 12.5 mm). Using the Receiver Operator Characteristic (ROC) curve, the cut off value was set at 10 millimeters.

In this analysis, 64.8% of patients with villus size less than 10 millimeters as well as 26.8% of patients with villus size greater than 10 millimeters did not develop postmolar GTN. Regardless of the villus size, only 8.4% of the subjects developed postmolar GTN. In summary, villus size was not significantly correlated with the subsequent progression of complete hydatidiform mole to gestational trophoblastic neoplasia. (p value = 0.29)

DISCUSSION

Although the bulk of patients with a hydatidiform mole do not require further treatment after molar evacuation, an estimated 20% will develop into postmolar gestational trophoblastic neoplasia. In the current study, the incidence of postmolargestational trophoblastic neoplasia was 8.5%. Women diagnosed with a complete hydatidiform molar pregnancy are typically counseled that their risk of developing persistent gestational trophoblastic neoplasia (GTN) requiring further management with chemotherapy is 18–28%.[1] To diagnose persistent GTN promptly, patients are followed up with serial human chorionic gonadotropin (hCG) levels after molar evacuation. A plateau or rise in hCG levels indicates persistent disease and the need for chemotherapeutic management. Complete remission is typically declared if the hCG level spontaneously declines to undetectable levels and remains there during a 6-month follow-up period.[6] Investigators have tried to identify factors that would predict either persistent disease or remission to inform women and their physicians about their risk of developing persistent disease or reduce the interval between the diagnosis of molar pregnancy and the diagnosis of persistent disease. A means to predict a high risk of persistence might allow empiric chemotherapeutic management in the noncompliant patient at high risk for developing persistent disease; a method of predicting remission could reassure a woman at low risk for persistent disease.

The significant errors which would result from reliance upon histologic grading alone and the present availability of accurate methods for following hCG levels after molar evacuation have caused the histopathologic study of molar pregnancies to take on less priority. In general, histopathologic grading of hydatidiform moles appears to have merit for predicting postevacuation behavior, but as a single criterion is too limited.[5]

Several investigators have identified histopathologic features of hydatidiform moles that are associated with a higher incidence of postmolar gestational trophoblastic disease. Hertig et al. found a good correlation between the degree of trophoblastic hyperplasia and subsequent development of postmolar trophoblastic disease, while Deliqdisch et al. reported that nuclear atypia was associated with an unfavorable response to chemotherapy.[5]

In this study, we analyzed several histopathologic parameters which may precisely identify which patients with complete hydatidiform moles were more likely to develop postmolar gestational trophoblastic tumors. However, trophoblastic proliferation, nuclear atypia, presence of hemorrhage and hydropic villus size were features found not to be correlated with progressive disease. Conversely,

the destructive activity of the trophoblast as illustrated by extensive necrosis was the only parameter associated with an increase in the incidence of postmolar trophoblastic sequela.

Kaneki et al. first reported that the size of the hydropic villi may be used as a predictor of postmolar gestational trophoblastic neoplasia. They found out that the frequency of postmolar GTN was higher in patients with hydropic villi larger than 2 millimeters in their shortest diameter. These data suggest that measurement of the shortest diameter of the largest hydropic villus may be used to estimate the risk of postmolar GTN.[2] However, the present study did not find a significant correlation between villus size and the subsequent development of postmolar GTN.

Efforts to promptly identify patients with complete hydatidiform mole who are likely to progress to malignant disease without going through an extensive process have been made to be able to institute empirical chemotherapy.

The results of this analysis were contradictory to the findings of several previous studies where trophoblastic proliferation, nuclear atypia, extensive hemorrhage and hydropic villus diameter were features associated with the progression to postmolar trophoblastic tumors. The disparity in outcomes can be attributed to the small number of cases included in the study, a subjective assessment of some of the histopathologic parameters particularly trophoblastic proliferation and atypia and the preparation of the histopathologic slides that were analyzed may have affected the outcome. The retrospective nature of the study may also have a significant impact on the results.

SUMMARY AND CONCLUSION

The risk of postmolar gestational trophoblastic disease after a complete hydatidiform mole is reported as 5.7% to 36%. Several histopathologic parameters – nuclear atypia, trophoblastic proliferation, hemorrhage and necrosis are significant predictors of persistent disease. In addition, hydropic villus size may be used as a predictor of postmolar GTN. Although this study did not statistically prove that histopathologic parameters and villus size of complete hydatidiform mole predicts postmolarsequela, all patients with complete hydatidiform mole should be considered for prophylactic chemotherapy or should be monitored closely. ■

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