

ORIGINAL ARTICLE

Inter-observer variability in the histologic criteria of diagnosis of hydatidiform moles

Soheila SARMADI¹, Narges IZADI-MOOD¹, Sanaz SANII^{1,2}, Dorna MOTEVALLI³

¹Department of Pathology, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran, ²Department of Pathology, Health Sciences Center, Memorial University of Newfoundland, Newfoundland, Canada, and ³Department of Pathology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Introduction: In the event of encountering hydropic villi in products of conception specimens, pathologists will have to distinguish complete and partial hydatidiform mole (CHM & PHM) from hydropic abortion (HA). The histological diagnostic criteria are subjective and demonstrate considerable inter-observer variability. **Materials and Methods:** This study evaluated the inter-observer variability in diagnosis of CHM, PHM and HA according to defined histologic criteria. Ninety abortus conception specimens were reviewed. Representative haematoxylin and eosin-stained slides were assigned independently to two pathologists who were asked to make a diagnosis of CHM, PHM or HA, and provide a report of the identified diagnostic histological criteria. Kappa value was calculated for the inter-observer agreement. **Results:** There was a total of 36.7% disagreement between two pathologists ($K = 0.403$, Strength of Agreement = moderate), of which 24.4% and 12.2%, were differentiating PHM from CHM and PHM from HA, respectively. Among defined diagnostic histological criteria, the highest rate of agreement was observed in the identification of cistern formation and hydropic changes ($K = 0.746$ and 0.686 respectively, Strength of Agreement = substantial). **Conclusion:** There was moderate to substantial agreement rate between two pathologists in identification of two essential histologic criteria for diagnosis of molar pregnancies i.e. “hydropic change” and “trophoblastic proliferation”.

Keywords: Complete hydatidiform mole, partial hydatidiform mole, hydropic abortion, inter-observer variability, histological criteria

INTRODUCTION

Hydatidiform moles (HMs) are genetically abnormal conceptions with a prevalence of about 1 in 500-1000 pregnancies and include two distinct subtypes (complete and partial) which are diagnosed based on certain clinical, ultrasonographic, macroscopic, microscopic, and genetic criteria.^{1,2} It is very important to distinguish HMs from nonmolar specimens and also to correctly subclassify them into complete hydatidiform moles (CHMs) or partial hydatidiform moles (PHMs) since the clinical management and the actual risk of persistent or recurrent disease is different between the two. The risk for developing persistent gestational trophoblastic disease (GTD) is higher in CHM (15-20%) compared to PHMs (0.2-4%).^{3,4} It is not

uncommon for pathologists to identify hydropic changes in villi in products of conception (POC) in which case they have to determine whether they are dealing with CHM, PHM, or hydropic abortions (HAs). Although ultrasonography and serum β -hCG (Human chorionic gonadotropin) level are useful tools in identification of HMs in general, distinction between CHM, PHM, and HAs is often established only based on histological criteria identified in microscopic examination of the tissue. Microscopically, CHMs are characterised by enlarged, irregular, polypoid/lobular hydropic chorionic villi with marked circumferential trophoblastic proliferation, cistern formation, irregular cystic shape, trophoblastic inclusions, cytologic atypia, apoptotic bodies within the villous stroma,

and absence of fetal structures. Early cases of CHMs have been documented with less well-developed yet with characteristic features. PHMs usually exhibit two populations of chorionic villi (large hydropic villi and small fibrotic ones) with irregular borders (scalloping), small round trophoblastic inclusions, less pronounced trophoblastic proliferation compared to CHMs, and presence of fetal structures.⁵⁻¹¹ The nature of microscopic features creates a great degree of histologic overlap not only between the two types of molar pregnancies, but also between molar and some cases of nonmolar pregnancies such as products of conception with abnormal villous morphology, early nonmolar abortions with prominent villous hyperplasia, hydropic abortions, and mosaic/chimeric conceptions.^{3,4} In other words, regarding the sometimes ambiguous morphologic diagnostic criteria and their dependance on gestational age, histologic diagnosis of molar pregnancies could be challenging, especially regarding the fact that routine first trimester ultrasonography leads to earlier diagnosis of abnormal pregnancies and therefore submission of pathology specimens in earlier gestational ages when the previously defined histologic features are less well-developed.³

Several previous studies have shown that there is considerable inter-observer variability in distinguishing HMs from HAs.¹²⁻¹⁵ The rate of agreement between pathologists on the diagnosis of molar pregnancies ranges from 55% to 75%.¹² PHMs may be particularly difficult to distinguish from HAs since they may contain normal placenta, fetal parts and membranes, therefore, histological misdiagnosis frequently occurs between PHMs and HAs.^{14,16,17}

Diagnosis and subclassification of HM is mainly made based on histological criteria. Incorrect diagnosis will lead to mismanagement including insufficient treatment for lesions with higher malignant potential or overtreatment in low-risk lesions. The present study was conducted to assess the inter-observer reproducibility of the diagnosis of CHMs, PHMs and HAs based on common diagnostic histological criteria. Two faculty member gynaecologic pathologists were involved.

MATERIALS AND METHODS

In this study, 90 specimens of abortus conceptions comprised CHMs [N = 29 (32.2%)], PHMs [(N = 46 (51.1%)] and HAs [N = 15 (16.7%)]

were reviewed. After approval of the study by the institution Research Ethics Committee, the specimens were selected from the Department of Pathology in Women Hospital, an educational hospital affiliated to Tehran University of Medical Sciences, in Iran and were reviewed by two expert gynaecologic pathologists (Soheila Sarmadi M.D. and Narges Izadi-Mood M.D.) with 6 and 18 years of experience respectively. For each case, 3 to 6 H&E stained slides representing the morphology leading to original diagnosis were selected and examined. The slides were coded and blindly assigned to the pathologists. A questionnaire was designed containing different diagnostic histological criteria according to the common references. The different categories of defined histologic diagnostic criteria were: 1) Trophoblastic proliferation (cytotrophoblast or syncytiotrophoblast; multifocal or circumferential), evidence of atypia, presence of free cytotrophoblastic cell clusters; 2) Villous stroma with hydropic change or cistern formation, fibrotic chorionic villi, small round or irregular trophoblastic inclusions "trophoblastic inclusions are due to tangential cutting of the mentioned infoldings in villous mesenchyma and are categorised as round or irregular based on their shape" (Fig. 1),¹⁸ and nuclear debris; 3) Villous shape (scalloped, round, polypoid/lobulated); and 4) Presence of fetal structures consisting of fetus, chorionic membrane, or nucleated red blood cells.¹⁹ Five less established criteria including free cell clusters, chorionic membrane, round and irregular inclusions, were also included in this study.

No clinical data was provided for the reviewer pathologists. Statistical analysis included the evaluation of inter-observer agreement using kappa statistics with possible values between 1.00 (indicating complete agreement) and 0 (indicating no agreement). Negative values indicated less than chance agreement. "K value" was calculated for a pair of pathologists. The following interpretations of agreement were used according to Landis and Koch (20, 21): 0.00-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial and 0.81-1.00 = almost perfect (Table 1).

RESULTS

The diagnoses established by the two pathologists were compared and the rate of agreement on microscopic diagnosis were calculated (Table 2).

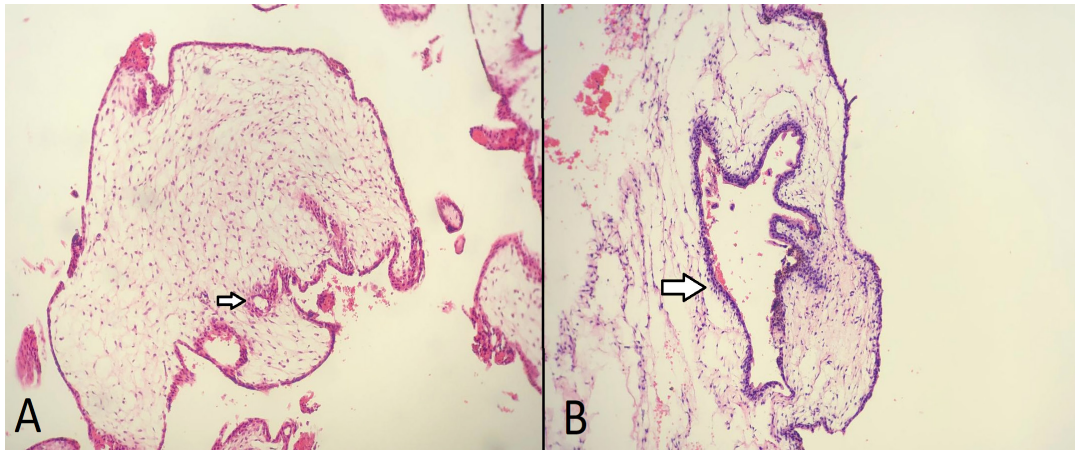


FIG. 1: Inclusions in villous stroma: (A) Round inclusion (arrow). (B) Irregular inclusion (arrow) (H&E, X40).

According to the data presented on Table 1, 33 disagreement events were observed. Twenty two events occurred in distinction between PHM and CHM, and eleven events happened in distinction between non-molar HA and PHM.

The calculated Kappa values to evaluate inter-observer agreement rate was 0.444 for diagnosis of CHM versus PHM and 0.403 for diagnosis of CHM versus PHM/HA. This is interpreted as moderate agreement ($P < 0.001$). Table 3 shows the result of Kappa test for inter-observer agreement in identification of diagnostic histological criteria.

DISCUSSION

It is well known that CHM, PHM and HA are three distinct pathologic entities. Biological variability and scarcity of available specimen, however, will sometimes create difficulties in differentiating these entities, especially in differentiating CHM from PHM or differentiating PHM from HA. Different studies, with different numbers of pathologists and case distribution, have demonstrated marked variability in diagnosis of HMs with inter-observer agreement rates ranging from 55% to 80%.³ According to

a study by Vang *et al.*³, the main diagnostic problem lies in differentiating PHMs from HAs (poor inter-observer reproducibility). Correct diagnosis of all cases of molar pregnancies on the basis of morphology is challenging even for experienced gynaecologic pathologists.³ A study by Gupta *et al.* showed that when all potential molar pregnancies were combined, correct classification by H&E morphology alone happened in 51% to 75% of cases diagnosed by individual reviewers and in 63% to 75% of cases diagnosed by consensus.⁴ Another study by Fukunaga *et al.* also showed that diagnosis based on histology alone results in poor inter-pathologist agreement ($K = 0.104$).¹⁵

The present study reveals that the calculated Kappa values to evaluate inter-observer agreement rate for differential diagnosis of CHM versus PHM and CHM versus PHM/HA were 0.444 and 0.403, respectively, and thus categorised as moderate agreement ($P < 0.001$). Various ancillary techniques have been explored in the past to improve the diagnostic accuracy of molar disease using chromosomal enumeration by karyotyping or flow cytometric DNA ploidy analysis and p57 immunohistochemical study. However, each of these specialised techniques

TABLE 1: Guidelines for strength of agreement indicated with Kappa values

Kappa Value	Strength of agreement beyond chance
< 0	Poor
0–0.20	Slight
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Substantial
0.81–1.00	Almost perfect

TABLE 2: The inter-observer comparison of diagnoses

First pathologist diagnosis / Second pathologist diagnosis	Number (Percentage)
Non-molar pregnancy / Non-molar pregnancy	5 (5.6%)
Non-molar pregnancy / Partial hydatidiform mole	10 (11.1%)
Non-molar pregnancy / Complete hydatidiform mole	0 (0%)
Partial hydatidiform mole / Non-molar pregnancy	1 (1.1%)
Partial hydatidiform mole / Partial hydatidiform mole	24 (26.7%)
Partial hydatidiform mole / Complete hydatidiform mole	21 (23.3%)
Complete hydatidiform mole / Non-molar pregnancy	0 (0%)
Complete hydatidiform mole / Partial hydatidiform mole	1 (1.1%)
Complete hydatidiform mole / Complete hydatidiform mole	28 (31.1%)

needs specialised equipment and facilities which is not available in many small laboratories. Some studies have pointed out the weakness of single conventional histological diagnostic criteria in diagnosis of molar pregnancies.^{14, 16, 22-24}

Determination of specific histologic criteria for diagnosis of molar pregnancies versus hydropic abortion is needed to improve the diagnostic agreement rate, as well as evaluation of the relationship between agreement rate and

TABLE 3: Results of Kappa statistics for inter-observer agreement in identification of diagnostic histological criteria

Category of histologic diagnosis criteria	Histological criterion	Kappa value	Strength of agreement beyond chance	P value
1) Trophoblastic proliferation	Atypia in trophoblastic cells	0.543	Moderate	< 0.001
	Trophoblastic free cell cluster	0.573	Moderate	< 0.001
	Predominant syncytiotrophoblastic proliferation	0.491	Moderate	0.002
	Predominant cytotrophoblastic proliferation	0.451	Moderate	0.005
2) Villous stroma	Cistern formation	0.746	Substantial	< 0.001
	Hydropic change	0.686	Substantial	< 0.001
	Nuclear debris in villous stroma	0.392	Fair	< 0.001
	Stromal fibrosis (fibrotic chorionic villi)	0.238	Fair	0.007
	Round inclusion	0.174	Slight	0.008
	Irregular inclusion	0.136	Slight	0.01
	Polypoid/lobulated villus	0.412	Moderate	< 0.001
3) Villous shape	Scalloping villus	0.283	Fair	0.007
	Round villus	0.321	Fair	0.001
	Chorionic membrane	0.549	Moderate	< 0.001
4) Presence of fetal structures	Nucleated RBC	0.501	Moderate	< 0.001

use of ancillary diagnostic tools.

The incidence of HM in Asia is 5 to 15 times more than western countries. Based on a recent study in Iran, the frequency of HM is 7 in 1000 pregnancies.²³ In regards to the above-mentioned difficulties and the value of pathologists' experience for diagnosis of molar disease, our primary goal was to compare the rate of agreement between two pathologists with different degrees of experience in detection of different defined histologic diagnostic criteria and to determine the histologic criteria detected with the highest agreement.

In the present study, the rate of diagnostic inter-observer agreement on established histological diagnostic criteria, was considered to be mainly in the range of moderate (Kappa = 0.549-0.412). The highest agreement rates were in detection of "cistern formation" and "hydropic changes" (significant agreement with $K = 0.746$ and $K = 0.686$, respectively) (Fig. 2).

The lowest agreement rates were related to the "shape of trophoblastic inclusions" and "round and irregular inclusions" (slight agreement with Kappa = 0.174 and $K = 0.136$, respectively). Buza *et al.* reported that, among individual parameters, villous hydrops appeared to be the most sensitive clue for diagnosis of PHM (86%); however, the specificity was low (22%). Cistern formation had

a lower sensitivity (59%) but a higher specificity (80%) for diagnosis of PHM.²² Our study showed that identification of cistern formation and hydropic changes have the highest agreement rate compared to other histological criteria for diagnosis of molar pregnancy. Some degree of trophoblastic proliferation (more significant in cytotrophoblasts) occurs in typical hydatidiform moles, especially of complete type. Since clusters of proliferated cytotrophoblastic cells become detached from the surface of chorionic villi, presence of free cytotrophoblastic cell clusters could be a key histological feature for CHM (Figs. 3&4).

In the present study, detection of free cell clusters showed a moderate rate of agreement between the two pathologists ($K = 0.573$). CHM villi are characterised by predominant cytotrophoblastic cell proliferation without differentiating into syncytiotrophoblasts; while in PHM, there is high rate of differentiation of cytotrophoblasts into syncytiotrophoblasts to the extent that it may be difficult to identify cytotrophoblastic cells. Presence of multiple circumferential collections of syncytiotrophoblasts is a very characteristic change in PHM. In our study, the rate of agreement on the "predominant cytotrophoblastic proliferation" and "predominant syncytiotrophoblastic

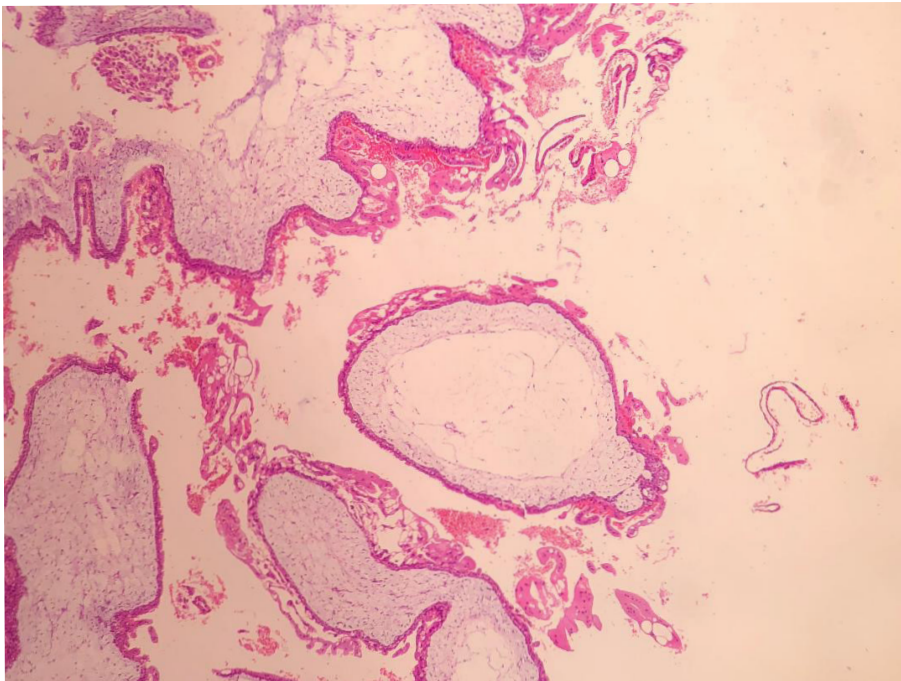


FIG. 2: Partial hydatidiform mole. Villous showed cistern formation, hydropic changes and scanty circumferential collections of trophoblasts (H&E x40).

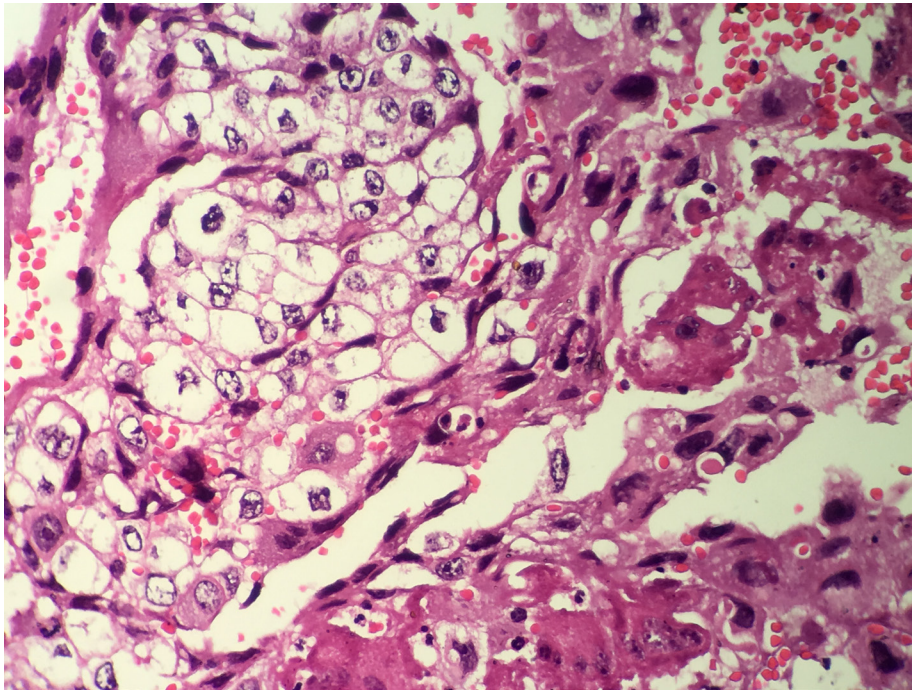


FIG. 3: Complete hydatidiform mole showed predominantly cytotrophoblastic proliferation (H&E x400).

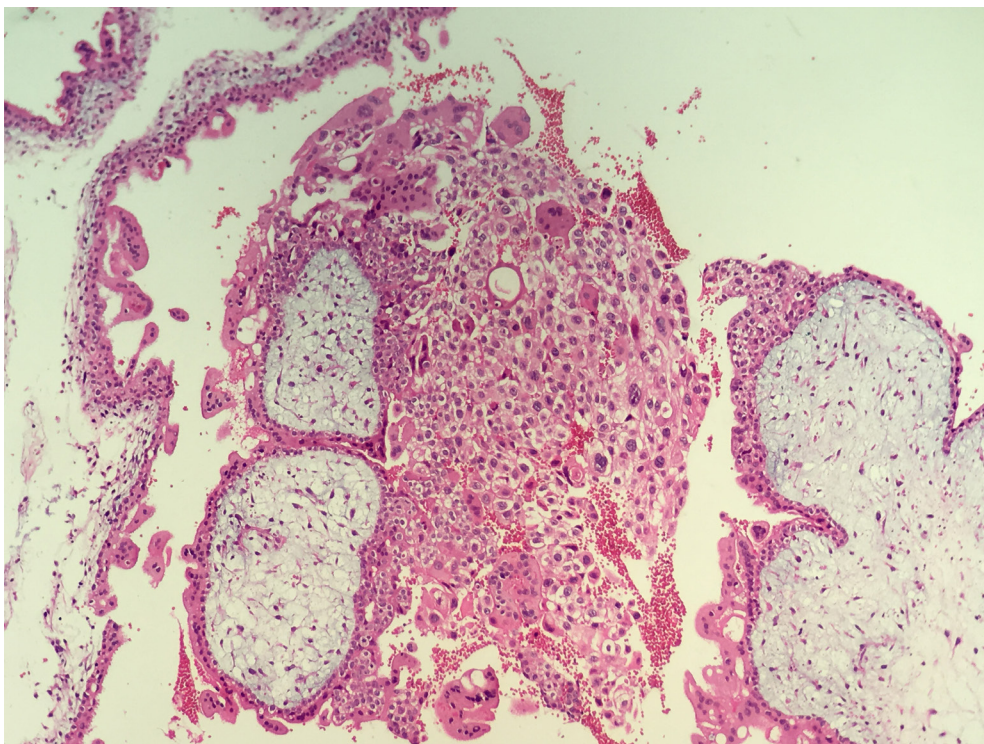


FIG. 4: Complete hydatidiform mole. Villous showed cistern formation, hydropic and myxoid changes, stromal nuclear debris (apoptosis), enlarged villi with polypoid shape predominantly cytotrophoblastic proliferation (H&E x100).

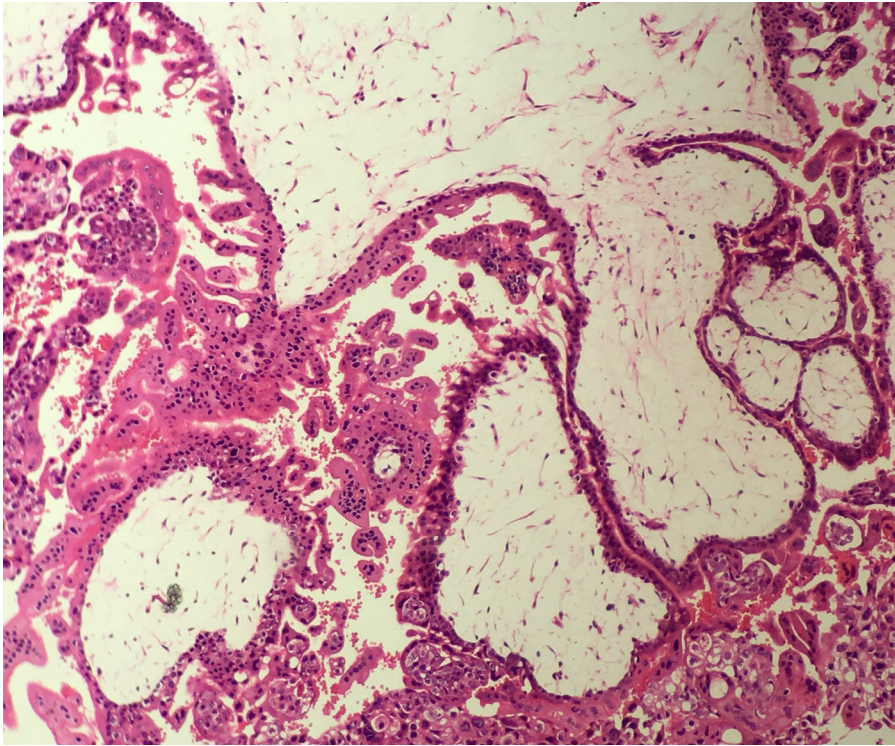


FIG. 5: Complete hydatidiform mole. Enlarged villi with polypoid shape and circumferential proliferation of cytotrophoblasts (H&E x200).

proliferation” was moderate ($K = 0.451$ and 0.491 , respectively). Therefore, trophoblastic proliferations (cytotrophoblastic versus syncytiotrophoblastic) could be considered a useful histological clue for differential diagnosis of CHM and PHM.

There are already a number of publications focusing on histological differentiation of complete and partial moles, however, compared to previous studies, this study presents a more comprehensive evaluation of the inter-observer variability in detection of defined histologic criteria for diagnosis of molar pregnancy.²⁵⁻²⁶ According to our study there is substantial to moderate agreement rate on detection of “hydropic change” and “trophoblastic proliferation” which are the two essential criteria for diagnosis of molar pregnancy.

Another feature commonly encountered in PHM is the scalloped outline of the enlarged villi. On the other hand, the outline of villi in CHM is characterised by outward projections and polypoid or round shape. In this study, detection of “polypoid shape of the enlarged villi” showed a moderate rate of agreement ($K = 0.412$), while “round” and “scalloped” outline of the villi had fair rates of agreement ($K = 0.321$ and 0.283 ,

respectively). Therefore, polypoid shape of the enlarged villi could be helpful in histological diagnosis (Fig. 5).

In PHM specimens, histologic evidence of fetal development is common, including chorionic membranes, nucleated red blood cells, umbilical cord, and fetal tissue. In this study, identification of “chorionic membranes” and “nucleated red blood cells” showed moderate rates of agreement ($K = 0.549$ and 0.501 , respectively) and showed the highest degree of agreement for presence of fetal structures (Figs. 6&7).

PHMs usually exhibit an admixture of two populations of chorionic villi: small, fibrotic, normal-appearing immature villi and large, irregular, hydropic villi. However, in our study the rate of agreement on identification of “fibrotic chorionic villi” was fair ($K = 0.238$) which might be due to small sample size. It has also been suggested in another study that up to 10 blocks may be required before a diagnosis of PHM can be excluded (Fig. 8).¹⁵

In this study, despite the fact that at least three slides were prepared for any case, agreement rates over identification of the two essential criteria for diagnosis of molar pregnancy: “hydropic change”

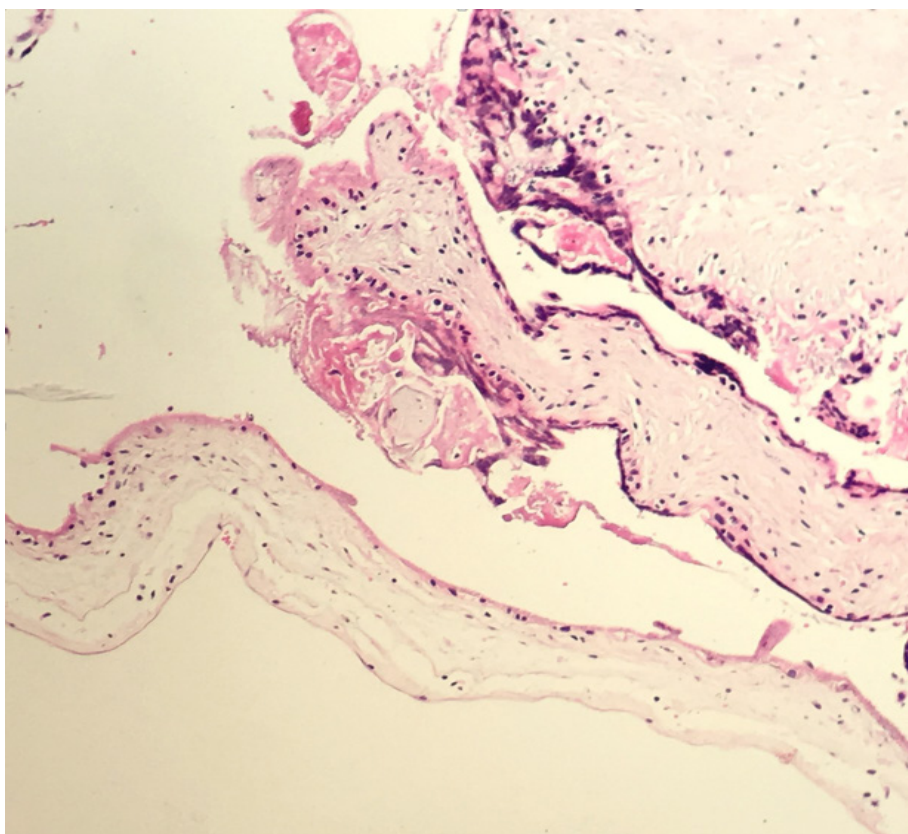


FIG. 6: Partial hydatidiform mole showed chorionic membrane and fibrotic villi (H & E X100).

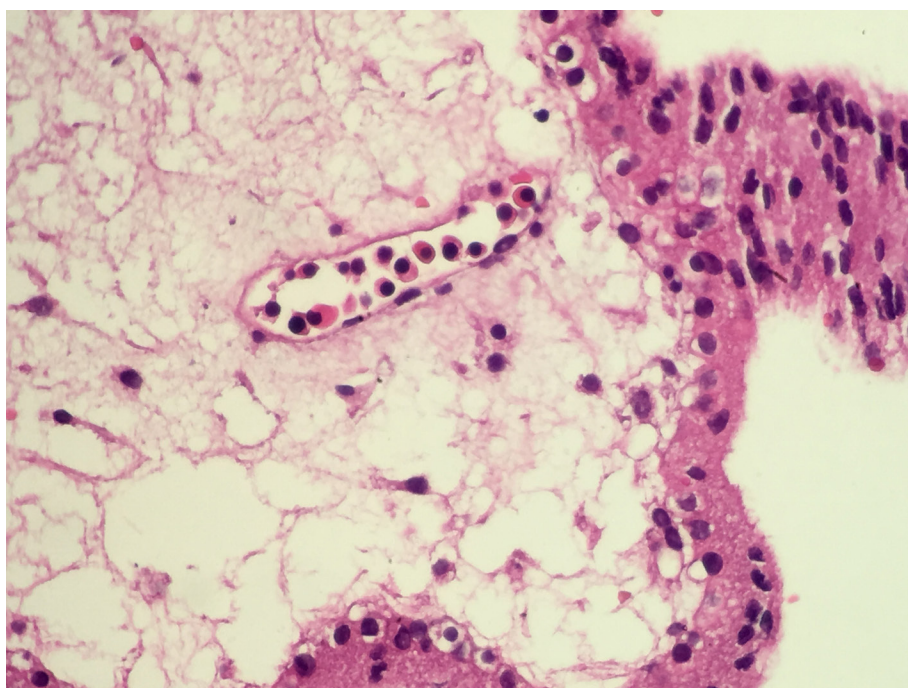


FIG. 7: Partial hydatidiform mole. Nucleated RBCs (fetal cells) in blood vessels (H&E x400).

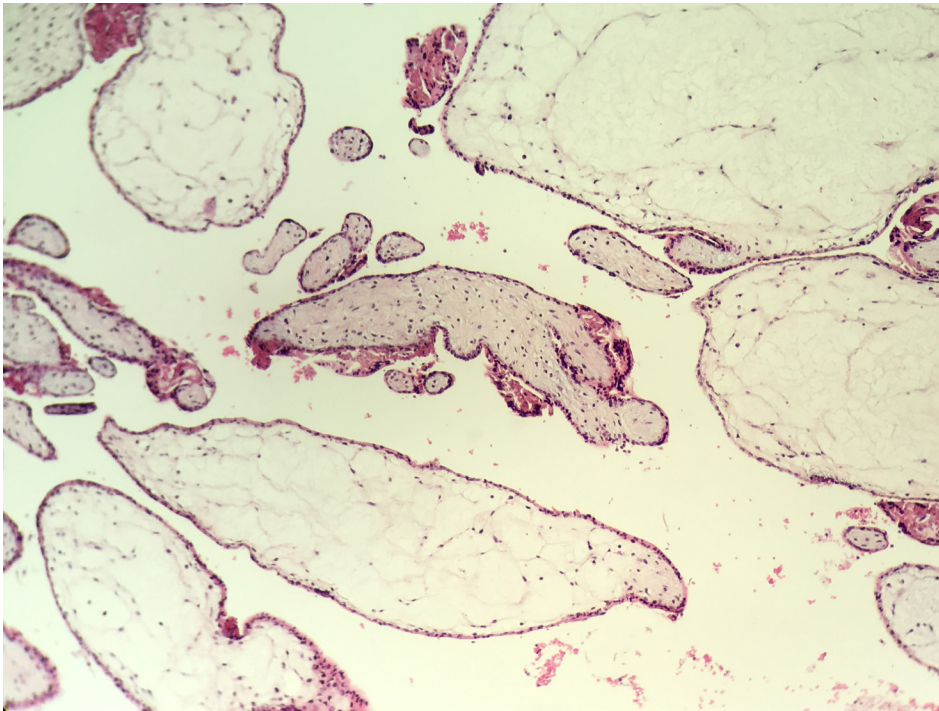


FIG. 8: Partial hydatidiform mole. Two population of chorionic villi; mixture of enlarged villi with central cisternal formation and small, normal-sized, and fibrotic chorionic villi (H&E x100).

and “trophoblastic proliferation”, are found to be in the range of substantial to moderate. The overall inter-observer agreement rate on the microscopic diagnosis of hydatidiform mole was intermediate ($K = 0.503$). This finding lies within the range of agreement rates observed in the studies by Howat *et al.* ($K = 0.104$ to 0.761) and Fukunaga *et al.* ($\kappa = 0.393$ to 0.773).^{14, 15} Of the total 36.7% disagreement between two pathologists on microscopic diagnosis, 24.4% and 12.3% were related to differentiating PHM versus CHM and PHM versus HA, respectively. CHM was readily distinguished from HA.

In general, problems in classification of molar and non-molar specimens can be attributed to several factors including imperfect histologic criteria for diagnosis of hydatidiform moles, variability in how pathologists apply the diagnostic criteria, number of prepared blocks, and the known variation in morphologic features which mainly depend on the gestational age of the specimen. The latter is especially important in this era of routine first trimester ultrasonography when abnormal pregnancies including hydatidiform moles and abortions are diagnosed early in gestational age. The specimens obtained from such pregnancies are more challenging to interpret regarding their

small quantity and less characteristic histological findings.⁴

According to Gupta *et al.*, routine microscopic evaluation without use of ancillary techniques, even in the hands of gynaecologic pathologist and even when a consensus diagnosis was used, demonstrated incorrect classification in at least 20% of cases.⁴

In conclusion, the great majority of hydatidiform moles will continue to be diagnosed on histomorphological grounds alone, while newer molecular and biological techniques will be necessary for evaluation of difficult or borderline cases. These newer techniques, however, are expensive and not available in many smaller laboratories. Based on our experience, the two most applicable histologic criteria for diagnosis of molar pregnancies versus hydropic abortions relied on by most pathologists are hydropic changes accompanied by trophoblastic proliferation. However, presence of these histologic changes is not enough and additional features including cistern formation and presence of two populations of chorionic villi is necessary to establish correct diagnosis of a molar specimen. Preparing more paraffin blocks to find more diagnostic morphologic clues might be helpful to diagnose complex cases and

to improve the diagnostic agreement rate.

Conflict of Interest: There is no conflict of interest.

Financial Disclosure: There is no financial disclosure.

Funding/Support: None declared.

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