Molahidatidosa from Pathophysiology to Clinical: Literature Review

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ABSTRACT

Hydatidiform is a gestational trophoblast disease which is histopathologically characterized by the proliferation of avascular trophoblast cells and corial villi and undergoing hydropic degeneration. The proliferation of trophoblast cells in hydatidiform moles can be in the form of cytotrophoblast, syncytiotrophoblast or intermediate trophoblast proliferation.

1. Introduction

Molahidatidosa may occur due to cytogenetic abnormalities, abnormalities in gene / protein expression and nutritional factors.¹ Genetic studies of molahidatidosa show that molahidatidosa can originate or occur from androgenetic fertilization but also normal fertilization.¹ Complete and partial molahodatidosa has histology, morphology, clinical features or causes. different. Complete hydatidose, diploidy with a 46-XX karyotype, the chromosomes are entirely paternal. Some cases have a triploidy or tetraploidy karyotype. There are no embryos or fetuses clinically, the fetus can only be seen if the pregnancy is multiple / multiple pregnancies with one fetal pregnancy and one being a non-malignant. Partial molahidatidosa generally with triploidy karyotype (69 chromosomes), paternal and maternal factors.¹⁻²¹

Pathophysiology of molahidatidosa is still unclear, chromosome analysis of molahidatidosa tissue yields several possibilities that occur in the fertilization process.¹ ²²⁻²⁴ Fertilization of hydatidiform mole occurs due to the absence of chromosomes in the ovum, chromosome analysis of complete hydatidiform mole trophoblast tissue only expresses paternal chromosomes (father chromosomes), maternal chromosomes are only found on partial trophoblast mole hydatidose chromosomes.¹,²⁵ Initially it was thought that molahidatidosa was a continuation of the blighted ovum, but in the study it was found that the mother and father DNA contained the mother's and the father's DNA, while the hydatid was not the mother's DNA. This study disputes the relationship between blighted ovum and
Gene / Protein Expression Abnormalities

Several other studies were conducted to determine the pathophysiology of molahidatidosa by looking at differences in gene expression in molahidatidosa trophoblast cells with normal placental trophoblast cells. Increased expression of genes in proto-oncogenes or decreased expression of tumor suppressor genes on trophoblast cells. Mutations may lead to degeneration of the corial villi and proliferation of trophoblast cells. This expression abnormality only answers molahidatidosa with paternal and maternal DNA but has not answered molahidatidosa which only comes from paternal DNA.¹

Meanwhile, 90% of molahidatidosa have only paternal DNA without having maternal DNA. Research on the expression of type IV collagen protein, which has a role in the stability of cell adhesion in tissues, found that the difference in type IV collagen expression was higher in molahidatidosa trophoblast cells compared to placental trophoblast cells. However, there was no difference in the expression of collagen types I and III. Collagen protein expression also increases in the wound healing state, collagen protein increases in the healing process to increase adhesion and regeneration of injured tissue. Whereas in hydatid mole, the collagen protein increases due to cause or as a result of hydatid mole.¹

Nutritional Factors

Another possibility that explains the occurrence of molahidatidosa is a factor of vitamin A deficiency. Vitamin A is a vitamin that has a role in regulating cell proliferation, cell differentiation, and apoptotic activity. Low levels of vitamin A cause interference with the control mechanism for cell proliferation and differentiation.¹ ²⁷ ²⁸

How vitamin A works on cell proliferation or differentiation is still unclear. It is suspected that the role of vitamin A in controlling proliferation is through p53 which causes G1 arrest, pRb which causes S-phase arrest. And there are many more mechanisms that are affected by vitamin A.¹ ²⁸

Research on vitamin A levels in molahidatidosa patients, got lower levels of vitamin A in molahidatidosa patients compared to normal pregnant women, and found that the risk of developing molahidatidosa in women suffering from vitamin A deficiency increased to 6.29 times.¹

Molahidatidosa diagnosis

Symptoms and signs of pregnancy in general, but there are specificities in the form of nausea, vomiting that is excessive or more severe than pregnancy in general, symptoms of bleeding in early pregnancy with mild to heavy bleeding. In some cases accompanied by symptoms of thyrotosikosis.¹

Clinically an enlarged uterus that is greater than the gestational age. Uterine size greater than gestational age occurs in 50% of cases of molahidatidosa mole, one third of whom have a uterus smaller than their gestational age. Hyperemesis gravidarum is found in 5-25% of cases of molahidatidosa mole. Hyperemesis is usually in a molahidatidosa pregnancy with a large uterus and high HCG levels. Preeclampsia is found in 12-27% of cases of molahidatidosa mole. Preeclampsia is rare in molar pregnancies with a small uterus. Symptoms of thyrotoxicosis (tachycardia, febrile, tremor and other symptoms of thyrotoxicosis) are found in 2-4% of cases of molahidatidosa mole. Most cases of molahidatidosa having thyrotoxicosis have a large uterus. Thyrotoxicosis sometimes causes heart failure.¹

Symptoms of impaired lung function occur in 2% of cases of molahidatidosa mole. Lung function disorders generally occur after evacuation, this condition may be due to trophoblast pulmonary embolism.¹
On ultrasound examination has a fairly specific picture. Ultrasound examination is a noninvasive examination used to detect early hydatidosis. Theca lutein cysts are common in molahidatidosa mole. Some of the lutein cysts are 6 cm in size, 14% of cases have cysts larger than 8 cm, uterine rounds that do not see prisoners, and discharge of hydatid bubbles are pathognomonic clinical signs.¹

**Histologic Diagnosis**

Histologic diagnosis is possible on molahidatidosa mole, histopathological examination with molar tissue specimens obtained during the evacuation. Evacuation is enough to do once, but if with one evacuation there is still residue (clinical and imaging) then a second curette can be performed.¹

The trophoblast cells in the residue cause bleeding, infection and allow the trophoblast cells to survive. On histopathologic examination, complete molahidatidosa has characteristics of hydropic chorial villi degeneration and trophoblast cell proliferation without embryonic components. Partial molahidatidosas have an embryonic or fetal component. In some dubious circumstances, then immunohistochemical examination and kariotype examination can help.¹

Molahidatidosa trophoblast cells consist of cytotrophoblast, syncytiotrophoblast and intermediate trophoblast. Cytotrophoblasts have proliferative activity, proliferative activity is the main activity, cytotrophoblast cells will degenerate into syncytiotrophoblast cells having hormonal activity, and hormonal activity is the main activity of syncytiotrophoblast cells. Syncytiotrophoblast cells will degenerate into trophoblast intermediate cells, the main activity of trophoblast intermediate cells is invasion and migration.¹

**Kariotype Diagnosis**

The diagnosis of non-molahidatidosa generally can be determined based on clinical and histological examination. Sometimes the diagnosis is still difficult to determine, then a karyotype can strengthen the diagnosis. Ninety percent of cases of complete molahidatidosa have a 46XX karyotype resulting from duplication of the father’s X chromosome. In 6-10%, complete molahidatidosa has 46 XY chromosome. Thus, if the 46XX or 46XY karyotype is paternal without a maternal chromosome, a diagnosis of molahidatidosa can be determined, but if a 46XY karyotype is with paternal and maternal chromosomes, it is not necessarily a non-fatal form, maybe even a normal pregnancy.¹

Gynetic examinations are not required in routine care, either for diagnosis or management of non-biological pathogens. This is because in the management of molahidatidosa mole, the most important thing is the observation to detect the occurrence of postmenidatidiform malignant degeneration.¹ 29

**Molecular Diagnosis**

In some circumstances it is difficult to distinguish molahidatidosa trophoblast cells from trophoblast cells in normal pregnancy with hydrophic degeneration. Examination of protein or gene expression may be performed to distinguish a molahidatidosa tissue from normal placental tissue.¹

One way to distinguish molahidatidosa trophoblast cells from normal pregnancy placental trophoblast cells can be done by examining Cytokeratin 20 (CK20) by means of immunohistochemical examination. Molahidatidosa trophoblast cells will express CK20, whereas normal placental trophoblast cells will not express CK20.¹ 30

P53 gene expression can also be used to differentiate trophoblast cells, non-mutant p53. In this study, by analyzing the DNA sequencing of the p53 gene, there was no mutation or mutant p53. The results of this study showed the high expression of non-mutant p53 in molahidatidosa
trophoblast cells compared to normal placental trophoblast cells. To differentiate trophoblast cells by examining p53 certainly does not have high specificity because normal trophoblast cells express non-mutant p53 even though the numbers are not many. Thus, semquantitative examination of p53 can still be used to distinguish trophoblast cells from molahidatidosa with trophoblast cells from normal placenta.  

In the histochemical examination, examining and analyzing cells that experience apoptosis (TUNEL histochemical examination) shows the apoptotic process that occurs mainly in cytotrophoblast cells and stromal cells. Thus there is a possible role for p53 in cytotrophoblast cells, especially in apoptosis mechanisms.  

In complete molahidatidosa and chorio carcinoma, there was an increase in the expression of c-myc, c-erbB2 and BCI-2, while the expression of c-mfs was not found any difference in expression in normal pregnancy placental trophoblast cells and malignant trophoblast disease. Expression of EFGR (epidermal growth factor receptor) was increased in molahidatidosa trophoblast cells and choriocarcinoma compared to normal placental trophoblast cells. Choriocarcinoma has an invasive nature, this property is consistent with extracellular protein analysis. In karyocarcinoma, there is an increase in the expression of MMP-1 and MMP-2 (matrix metalloproteinase) and there is a decrease in the expression of the MMP-1 inhibitor (TIMP-1) compared to normal molahidatidosa trophoblast cells and placenta.  

A proto-oncogene GTPase-activating protein (GAP) is a protein that is important for regulating signal transduction in cell proliferation and cell differentiation. Theoretically, the expression of GAP may have increased in molahidatidosa tissue, but the results showed different results. In the GAP study, it was found that there was a lower expression in the corial villi of molahidatidosa tissue compared to placental tissue in normal pregnancy. These results indicate that GAP has no role in the proliferation of trophoblast cells, and molahidatidosa corial villi tissue. Thus, examination of GAP racial expression can also be used to differentiate molahidatidosa tissue from normal placental tissue, because GAP is thought to play an active role in the formation of corial villi in normal pregnancy.  

**Differential Diagnosis**

A complete molar pregnancy can be differentiated from a partial molahidatidosa histologically. The alpha feto protein test can be used to distinguish a complete from a molahidatidosa with fetal parts.  

HPL (human placental lactogen) examination can help differentiate complete molahidatidosa from PSTT (trophoblastic tumor placental site).  

**Management**

Midatid is an abnormal pregnancy, so molar tissue must be evacuated immediately. Trophoblast cells produce beta HCG so that the proliferation of trophoblast cells causes an increase in beta HCG levels.  

With the act of evacuation, the hydatid tissue is removed. This evacuation or discharge still has trophoblast cell residues, both local cell residues and cell residues that circulate systemically in the circulation. Immediately after evacuation, the HCG beta level will decrease, but because there is still trophoblast cell residue, the decrease in the HCG beta level has not yet reached normal levels. However, with multifactorial immune mechanisms, such as biological process factors and immune activity factors, the trophoblast cell residues will regress spontaneously. This situation is experienced by the majority of cases of molahidatidosa mole.  

In clinical studies, it was found that the curve for a reduction in beta HCG levels and generally HCG levels reached normal before 20 weeks after evacuation. Thus, the management of post-evacuation molahidatidosas is by clinical
observation as well as monitoring of HCG beta levels. Chemotherapy is only given if there are indications due to malignant degeneration. A total of 15-28% of cases still have trophoblast cell residues that remain alive and develop or proliferate so that the number of trophoblast cells increases.2 34

This increase in the number of trophoblast cells is clinically manifested by an increase in the blood levels of beta HCG. Trophoblast cell proliferation can occur either locally in the uterus or in the systemic circulation or perhaps both. Invasive growth in the uterus can cause bleeding complications or uterine perforation so often to overcome these problems performed surgery to remove the uterus. This causes the failure of the patient’s reproductive function, which ironically the patient still needs reproductive function.2

Conversely, if what develops is a trophoblast cell that is in the systemic circulation, it is very likely that trophoblast cell embolism will form which will implant in the body’s organs. This situation is clinically manifested as a metastatic process. The complications that result from this condition, of course, really depend on the metastatic organs that are affected.2

Because these clinical manifestations are not different from the nature of malignant cells, it is clinically referred to as Malignant Trophoblast Disease (PTG). This incident generally occurs in the first six months after evacuation. The diagnosis of PTG is determined based on clinical examination and examination of beta HCG levels. This is very good when viewed from the point of view of the management of molahidatidosa patients because it has been stated that most of the molahidatidosa patients are women of young reproductive age who still really want reproductive functions so that tissue collection for histopathological examination will be difficult to do, thus histopathological examination is not very important. 2

Clinical examination and examination of beta HCG levels are beneficial noninvasive tests. Increased HCG levels indicate an increase in the number of trophoblast cells. The presence of clinical symptoms in the form of uterine enlargement or uterine bleeding accompanied by abnormal levels of beta HCG indicates trophoblast cell activity in the uterus. Moreover, if there is a metastatic process in organs outside the uterus accompanied by abnormal levels of beta HCG, this indicates trophoblast cell activity. These clinical signs and HCG beta levels form the basis for determining the diagnosis criteria for PTG by WHO.2 35

The role of beta HCG as a tumor marker for PTG has been recognized by centers worldwide because of its high sensitivity. Therefore, beta HCG is used by centers worldwide as a tumor marker for PTG.

Prophylactic chemotherapy is not used in postgraduate patients, because the decrease in PTG morbidity and mortality is not by giving PTG therapy, the best therapy is to prevent the development of PTG. Thus, the morbidity, mortality, and cost of treating malignancies which are known to be very expensive can be reduced and avoided. This effort has been pioneered by experts working in the trophoblast field, among others, by conducting research to identify risk factors for PTG.2 36

2. References


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