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The Association between Hematological Indicators and Hydatidiform Mole Progression

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ABSTRACT

Background and Objective: Gestational trophoblastic disease refers to a specific range of trophoblast proliferative disorders that originate from the placental epithelium. Recently, hematological indices are being researched and discussed as an easy and accessible method to identify patients and monitor disease progression. Therefore, the present study was conducted to investigate the relationship between the levels of hematological indicators and hydatidiform mole progression.

Methods: This cross-sectional study was conducted on 164 patients diagnosed with hydatidiform mole in two groups: complete hydatidiform mole (132 people) and partial hydatidiform mole (32 people). The diagnosis of the disease was made based on the pathology results recorded in the patients' files. Information related to hematological, biochemical and hormonal indices was collected and analyzed.

Findings: In general, there was no statistically significant difference between the group of complete hydatidiform mole and partial mole in terms of age, body mass index, uterine size, incidence rate of Theca lutein cyst and cyst size, gravida, parity, miscarriage, and history of previous mole. Of all laboratory markers evaluated (such as WBC, PLT, MPV/PLT, AST/PLT, RDW/PLT), only the mean level of triiodothyronine (free T3) in the complete mole group (1.50±2.40 pmol/L) was significantly lower compared to the partial mole group (1.90±1.30 pmol/L) (p=0.004). Free T3 threshold (1.54±0.87 pmol/L) showed good sensitivity (74.60%), specificity (51.50%) and 50% accuracy to distinguish complete moles from others.

Conclusion: This study showed that a high level of free T3 may be a good marker for the diagnosis of hydatidiform mole, which may be useful in the early detection of moles undetectable on ultrasound.

Keywords: *Gestational Trophoblastic Disease, Hydatidiform Mole, Triiodothyronine*.

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Introduction

Gestational trophoblastic disease (GTD) refers to a specific range of trophoblast proliferation disorders that originate from the placental epithelium. Furthermore, placental dysfunction leads to excessive production of gonadotropin β-subunit hCG (β-HCG) in GTD patients (1). In terms of histology, GTD is classified into benign complete or partial hydatidiform moles, malignant form of invasive moles (Chorioadenoma destruens), epithelioid trophoblastic tumor (ETT), placental trophoblastic tumor, and choriocarcinoma (2). The incidence of GTD and its distribution are different in different geographical areas. The highest prevalence of GTD has been reported in Taiwan (1/125 live births), Japan and Southeast Asia (2/1000 pregnancies), the United States (1/1500), and Europe (1/1000), respectively (3).

A complete hydatidiform mole usually presents clinically as vaginal bleeding (mostly at 6 to 16 weeks of pregnancy), and larger uterine size. However, β-hCG level testing and ultrasound are common diagnostic tools for complete hydatidiform mole during pregnancy (4, 5).

The pathological and clinical nature of complete hydatidiform mole is different from its partial type. Moreover, considering the high rate of negative and false positive results in ultrasound, especially in the case of partial moles (4, 6), it is very useful to identify suitable diagnostic or prognostic tools for timely diagnosis and treatment of hydatidiform moles. In this regard, Zhang et al. and Ghiasi et al. recently reported that hematological indices including red blood cell volume distribution (RDW), absolute lymphocyte count, mean red blood cell volume (MCV) and hemoglobin can play an important role in monitoring disease progression (7, 8). In the study of Aiob et al., it was shown that the ratio of neutrophils to lymphocytes was higher in patients with miscarriage compared to GTD patients (9). This was despite the fact that in the study of Braga et al., there was no correlation between the ratio of neutrophils to lymphocytes and the progression of GTD towards malignancy (10). Most studies have evaluated laboratory markers and compared them between GTD patients and patients with miscarriage. In addition, most studies have investigated the ratio of neutrophils to lymphocytes and the ratio of platelets to lymphocytes in patients. In this study, the association of a series of hematological and medical markers with pathological manifestations and progression of hydatidiform mole was investigated in order to identify the clinical risk factors for GTD progression and diagnostic laboratory markers.

Methods

This cross-sectional study was conducted after being approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences with the ethics code IR.AJUMS.REC.1399.734. Out of 229 patients referred to the women's oncology department of Ahvaz teaching hospitals from 2016 to 2021, 215 patients were diagnosed with hydatidiform mole. Patients with GTD who did not undergo chemotherapy and their clinical data were fully recorded were included in the study. Patients with a history of cardiovascular disease, diabetes, kidney disorders, blood disease, chronic obstructive pulmonary disease, and hepatitis B, as well as patients receiving any treatment that may affect patients' blood, were excluded from the study. Out of a total of 215 patients diagnosed with hydatidiform mole who were examined, 164 patients were eligible to enter the study and 51 patients were excluded from the study due to the history of specific diseases or lack of laboratory data. Finally, 164 eligible patients were divided into two groups of complete hydatidiform mole (132 people) and partial hydatidiform mole (32 people) based on the evaluations of pathological results and the opinion of gynecologists. All patients signed the informed consent form and voluntarily participated in this study.

About 2 mL of venous blood samples were taken from each patient with hydatidiform mole by EDTA-K2 anticoagulant tubes before receiving any treatment in the morning. A Beckman Coulter LH 780 hematology analyzer (manufactured in China) was used to analyze all measurements within 30 minutes after blood collection. White blood cell count (WBC), platelet count (PLT), mean platelet volume (MPV), red blood cell volume distribution (RDW) and aspartate aminotransferase (AST) were evaluated. The normal range for RDW was about 11-14% (11). Other demographic and medical characteristics of the patients were also recorded to compare the evaluation between the two groups.

SPSS software 26 (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis. The normality of the variables was assessed by the Kolmogorov Smirnov test. Categorical and continuous variables were presented as frequency and percentage and mean±standard deviation, respectively. Chi-square test was used to compare categorical variables and independent t-test and Mann-Whitney test were used to compare continuous variables. To evaluate the diagnostic value of important parameters, ROC curves, threshold point with 95% confidence interval and its sensitivity and specificity were used. The correlation of significant parameters with hydatidiform mole was evaluated using Spearman's correlation coefficient and $p<0.05$ was considered significant.

Results

There was no significant difference in the demographic information of the patients in the two groups in terms of age and body mass. The results showed that the mean size of the uterus and the size of the cyst in patients with complete moles were higher compared to patients with partial moles, however, this difference was not statistically significant. The ratio of MPV to PLT, AST to PLT and RDW to PLT was calculated and compared in both groups. No significant difference was observed between the two groups in terms of the mean levels of WBC, PLT, MPV/PLT, AST/PLT, and RDW/PLT (Table 1).

Table 1. Medical and laboratory information of patients

Variable	Complete mole (n=132) Mean±SD or Number(%)	Partial mole (n=32) Mean±SD or Number(%)	p-value
Age (years)	29.92±7.73	29.77±7.63	0.66
Body mass (kg/m^2)	24.75±4.24	25.16±4.22	0.62
Uterine size (mm)	101.64±19.37	79.9±19.35	0.46
Cyst size (mm)	9.91±20.82	7±15.60	0.19
White blood cells (1000 µl)	8.27±2.065	8.15±2.11	0.73
Platelets (1000 µl)	239.01±66.19	228.88±59.68	0.36
Average platelet volume/platelet	0.04±0.01	0.04±0.0	0.80
Aspartate aminotransferase/platelet	0.10±0.09	0.08±0.03	0.89
RBC volume distribution/platelet	0.06±0.01	0.07±0.03	0.70
Triiodothyronine (pmol/L)	1.50±2.40	1.90±1.30	0.004
Gravida	2.48±1.48	1.94±0.84	0.05
Parity	1.02±1.11	0.75±0.80	0.39
Abortion 0 1 2 4	 87(65.9) 31(23.5) 10(7.6) 4(3)	 25(78.1) 7(21.9) 0(0) 0(0)	0.26
Treatment Hysterectomy Methotrexate Curettage	 2(1.5) 14(10.6) 116(87.8)	 0(0) 3(9.37) 29(90.6)	0.77

The level of triiodothyronine in the complete mole group (1.50±2.40 pmol/L) was significantly lower than its mean level in the partial mole group (1.90±1.30 pmol/L; p=0.004). ROC curve was used to determine the diagnostic power of free T3 in identifying the progression of a complete hydatidiform mole, and the area under the curve was close to 70%. Using the threshold limit of 1.54±0.87 pmol/L, the sensitivity and specificity were 74.60% and 51.50%, respectively, with an accuracy of 50% (p=0.004, 95% confidence interval=0.569-0.764, Figure 1).

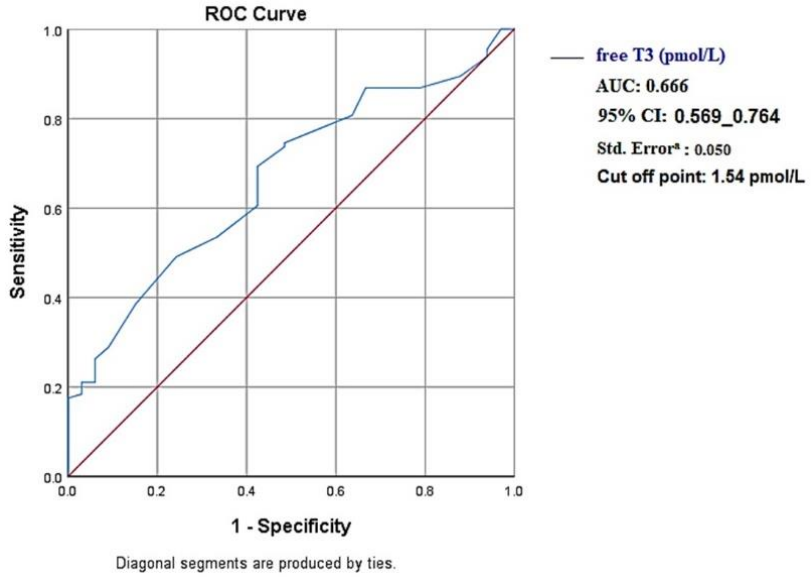

Figure 1. ROC curve to determine the efficiency of free T3 in identifying the progression of a hydatidiform mole to a complete mole. Sensitivity and specificity with 50% accuracy are equal to 74.60% and 51.50%, respectively.

Discussion

The results of this study demonstrated that there was no significant relationship between the ratio of MPV/PLT, AST/PLT and RDW/PLT and the progress of hydatidiform mole. In this regard, Soper showed that WBC and PDW levels were lower in GTD patients compared to the control group. This in turn suggests a possible weaker inflammatory response in molar pregnancy that facilitates trophoblast invasion. In addition, complete molar pregnancy may require less platelet activation compared to normal pregnancy (12). In our study, the range of WBC and PLT in patients with hydatidiform mole was almost close to their range in the study of Eskicioglu et al. (13) and was lower than the reference range. However, considering that no significant difference was observed between the partial hydatidiform mole group and the complete hydatidiform mole group in terms of mean WBC and PLT levels, it indicates that there is no relationship between WBC and PLT levels and the progress of hydatidiform mole. The difference between our results and the study of Eskicioglu could be due to the number of participants in the study and patient grouping. Because in the present study, the comparison was between complete and partial mole patients, while in the study of Eskicioglu, the comparison was between GTD patients and healthy people. In the study of Genc et al., consistent with the present study, it was shown that there was no significant relationship between RDW and the development of hydatidiform mole (14).

High levels of hCG as well as normal or slightly elevated thyroid hormones can be seen early in pregnancy. In GTD, high beta-hCG may stimulate the thyroid to thyrotoxicosis. Of course, thyroid stimulation during hydatidiform mole pregnancy can also be due to increased estrogen (15). Recently, Düğeroğlu et al. evaluated thyroid function in patients with complete or partial hydatidiform mole and showed higher fT4 and TT4 levels as well as lower TSH levels in complete hydatidiform mole patients compared to partial mole patients. They also found a relationship between complete hydatidiform mole with increasing age and more pregnancies (15). In the present study, a significantly higher level of free T3 in patients with complete hydatidiform mole compared to its level in the group of partial hydatidiform mole confirms the relationship between increased thyroid function (hyperthyroidism) and progression of hydatidiform mole. The results showed that free T3 level greater than 1.54 pmol/L is significantly associated with high risk of hydatidiform mole development. Therefore, it can be concluded that thyroid hormones, especially T3, can be used as a diagnostic factor for monitoring the progress of GTD.

Contrary to the study of Düğeroğlu et al. (15), there was no significant relationship between hydatidiform mole progression and age or parity in the present study. In this regard, the results of the study by Zhang et al. (7) regarding the relationship between hematological indices and invasive hydatidiform mole contradict our findings. They showed that low lymphocyte counts compared to platelet counts were associated with a higher risk of inflammation and disease progression. However, our study did not confirm such result in PLT and WBC count. Overall, no significant relationship was found between the development of hydatidiform mole and other medical variables, including uterine size, incidence of Theca lutein cyst and cyst size, pregnancy, delivery, miscarriage, history of previous hydatidiform mole, and previous deliveries. This difference in the results can be due to the sample size, the type of study and also the examined patients. Furthermore, in the study of Zhang et al., the aim was to investigate the relationship between inflammation and disease progression (7), while in the present study, the aim was to investigate the relationship between laboratory markers and disease progression. In a study by Guzel et al., as in the present study, no significant relationship was observed between demographic data and GTD progress (16).

Based on our findings, no significant relationship was found between the development of GTD and age, BMI, uterine size, incidence rate of Theca lutein cyst and cyst size, pregnancy, delivery, miscarriage, previous mole history and mortality rate. A high level of free T3 (more than 1.54 pmol/L) is associated with a higher risk of developing complete hydatidiform mole, while other biomarkers evaluated such as (WBC, PLT, MPV/PLT, AST/PLT and RDW/PLT) showed no significant correlation with the progress of hydatidiform mole. Considering the significant undetectable cases of hydatidiform moles in ultrasound examination as well as falsely low hCG under the influence of the Hook effect in some GTD patients, free T3 index may be useful for early diagnosis and treatment of GTD. Nevertheless, it is recommended to perform more prospective clinical trials for accurate diagnosis and prognosis of hydatidiform mole progression. Failure to investigate and compare the results of GTD patients with GTN and the effect of laboratory markers on the progression towards GTN needs to be investigated in future studies. It is also better to examine the response rate of patients to treatment based on laboratory markers.

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