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The impact of ultrasonographic lesion size and initial human chorionic gonadotropin values on treatment success in cases with complete hydatidiform mole

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Abstract. – OBJECTIVE: Our aim to assess the impact of sonographically measured lesion size and initial human chorionic gonadotropin levels on treatment success in cases of complete hydatidiform mole (CHM).

PATIENTS AND METHODS: Patients with CHM diagnosed between January 2007 and January 2012 were included in the study. Clinical parameters such as patient age, fertility history, smoking, alcohol consumption, presenting symptom, pregnancy duration, ultrasonographic mean lesion size, beta-hCG level on admission, primary treatment method, beta-hCG normalization time (NT) and adjuvant treatments were recorded and analyzed.

RESULTS: One hundred-twelve cases of CHM were identified in the study period. Mean patient age was 27.3 ± 8.2 years. Suction curettage was employed as the primary treatment in all of the study cases. No perioperative complications were encountered. None of the patients were treated with prophylactic adjuvant chemotherapy. Twelve patients (10.7%) required adjuvant chemotherapy. Beta-hCG NT did not have an association with patient age and initial beta-hCG levels ($p > 0.05$). Also, patient age, gravidity, parity, smoking, initial beta-hCG and ultrasonographic mean lesion size did not predict adjuvant chemotherapy requirement ($p > 0.05$).

CONCLUSIONS: Early detection and treatment of CHM is associated with a favorable clinical outcome.

Key Words:
Complete hydatidiform mole, Gestational trophoblastic disease, Suction curettage, Chemotherapy.

Introduction

Complete hydatidiform mole (CHM) is associated with many complications such as severe vaginal bleeding, formation of theca lutein cysts, early development of preeclampsia, hyperthyroidism and malignant transformation[1]. Today, with the availability of highly sensitive human chorionic gonadotropin (hCG) assays and ultrasound, many cases of CHM are diagnosed and treated earlier[2]. This results in a great decrease of the aforementioned complications.

CHM incidence varies among different countries across the world[3-5]. The rarity of the disease has resulted in inadequacy of evidence-based data for development of appropriate management strategies. Most of our clinical practice is based upon data from single or multi-center descriptive reports. Especially optimal method of post-treatment surveillance is controversial at the time, due to lack of randomized controlled trials.

In this paper, we present the clinical analysis of CHM cases that were diagnosed and treated in a tertiary referral hospital in Ankara, Turkey within a five-year period, in an effort contribute to the limited data in the literature on this rare disease.

Patients and Methods

This retrospective study was performed in the Gynecologic Oncology Department of Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey, after gaining approval from the Institutional Review Board (Date 27.03.2012/ No: 12). Hospital pathology database was searched for CHM cases that were diagnosed between January 2007 and January 2012. For each case, patient age, fertility history, smoking, alcohol consumption, presenting symptom on admission, pregnancy duration upon admission, ultrasonographic mean lesion size, quantitative beta sub-unit of human chorionic gonadotropin (beta-hCG) level on admission, primary treatment method, beta-hCG normalization time (NT) and adjuvant treatments were recorded.

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Mean ultrasonographic lesion sizes were calculated with the formula: largest antero-posterior (AP) + superior-inferior (SI) lesion dimension divided by two. Serum beta-hCG measurements were performed using a commercial kit (ADVIA Centaur, Siemens Medical Solutions Diagnostics, Tarry Town, NY, USA). NT was defined as the time period in days, starting from the day of first intervention until detection of beta-hCG below 5 mIU/ml. Patients were divided into three groups according to age (Group 1: < 20 years, Group 2: 20-35 years, Group 3 > 35 years). Mean presenting hCG, pregnancy duration, ultrasonographic lesion size, and hCG normalization time values were compared between these groups.

Statistical Analysis

Study data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented numerically and by percentage, and continuous variables were presented as mean ± standard deviation (SD). Correlation analysis (Pearson) was used to determine the association between patient age, initial beta-hCG, pregnancy duration and NT. Logistic regression analysis was used to determine the effect of patient age, gravidity, parity, smoking, initial beta-hCG and ultrasonographic mean lesion size on post-treatment chemotherapy for treatment failure or relapse. Kaplan-Meier analysis was performed to demonstrate cumulative beta-hCG normalization curve. One-way ANOVA method was used to compare mean presenting hCG, pregnancy duration, ultrasonographic lesion size, and hCG normalization time values between age groups. $p < 0.05$ was considered statistically significant.

Results

In total, 112 cases of CHM were identified within the study period. None of the study patients were lost to follow-up. Mean patient age was 27.3±8.2 years. Mean gravidity, parity, and abortion frequencies were 2.9, 1.5 and 0.3, respectively. Forty-four cases (39.3%) were primigravidas, whereas 68 cases (60.7%) had a previous pregnancy. Sixty-four cases (57.1%) had at least one prior live birth. Twenty-two cases (19.6%) had a prior abortion and 14 of these had dilatation and curettage (D&C) for treatment. None of the cases had history of a previous gestational trophoblastic disease (GTD). Only six patients in the study population were smokers (5.4%). None of the patients had regular alcohol consumption.

Forty-four cases (39.3%) were asymptomatic on admission. Sixty cases (53.6%) presented with vaginal bleeding, and 8 cases (7.1%) presented with pelvic pain. Mean pregnancy duration according to last menstrual period (LMP) upon admission was 72.4±10.4 days. Mean ultrasonographic lesion size was 65.3±22.7 mm. Mean and median beta-hCG levels upon admission were 149,349 and 101,579 mIU/ml (minimum 551- maximum 844,441), respectively.

Suction curettage was employed as the primary treatment in all of the study cases. No perioperative complications such as uterine perforation, excessive bleeding or infection were encountered in these procedures. None of the patients were treated with prophylactic adjuvant chemotherapy. Mean and median NT of beta-hCG were 60.6 ± 23.4 and 60 days (minimum 27 – maximum 158), respectively. Mean Beta-hCG NT in cases that required adjuvant chemotherapy versus cases that did not were 82 ± 48.3 and 58 ± 17.6 days, respectively.

Cases were divided into three groups according to patient age. Mean presenting hCG, pregnancy duration, ultrasonographic lesion size, and hCG normalization time values were similar between the three groups ($p > 0.05$) (Table I).

Twelve patients (10.7%) required adjuvant chemotherapy. Ten of these received single agent (weekly intramuscular methotrexate (Mtx) – 50 mg/m^2) for persistent disease and two cases with subsequent development of gestational trophoblastic neoplasia (GTN) and lung metastasis required multi-agent (EMA/CO-etoposide, Mtx, dactinomycin, cyclophosphamide and vincristine) chemotherapy. Mean number of Mtx cycles needed for remission was 6.3 ± 2.5 (minimum 2-maximum 9). EMA/CO regimen was instituted as the frontline chemotherapy after the detection of lung metastasis in a 24 years-old and 28 years-old patients. In this cases, beta-hCG was normalized after two cycles of EMA/CO. Additional three cycles were administered for consolidation. There were no major chemotherapy related complications and none of the cases had vaginal metastasis. None of the cases relapsed after chemotherapy.

Beta-hCG NT did not have an association with patient age, pregnancy duration and initial beta-hCG levels ($p > 0.05$) (Table II). Also, patient age, gravidity, parity, smoking, pregnancy duration, initial beta-hCG and ultrasonographic mean lesion size did not predict adjuvant chemotherapy requirement ($p > 0.05$). Cumulative beta-HCG normalization curve of the study cases is presented in Figure 1.

Table I. Clinical parameters according to patient age groups.

Parameters	Age < 20 years n = 20	Age 20-35 years n = 74	Age > 35 years n = 18	p*
Initial beta-hCG ± SD†, (mIU/ml)	119952.5 ± 141776	166006.1 ± 187432	113538.4 ± 38857	> 0.05
Mean pregnancy duration (days) ± SD†	67.8 ± 8.9	72.6 ± 10.0	77.1 ± 12.4	> 0.05
Mean ultrasonographic lesion size (mm) ± SD†	63.5±26.4	64.0 ± 22.8	72.7 ± 18.4	> 0.05
Mean beta-hCG normalization time ± SD†	49.3±11.7	62.9 ± 25.4	63.5 ± 22.3	> 0.05

†SD: Standard deviation.

Table II. The correlation between patient age, pregnancy duration, initial beta-hCG and beta-hCG normalization time (NT).

Variable	Mean	Min	Max	p*
Age (years)	27.4	17	52	0.907
Pregnancy duration (days)	72.4	54	91	0.461
Initial beta-hCG (mIU/ml)	149.349	551	844.441	0.066

**p* value for correlation with beta-HCG normalization time (NT).

Discussion

Complete hydatidiform mole is a localized and non-invasive proliferative trophoblastic disorder with various incidences reported throughout the world[3-5]. In a previous study, the incidence of CHM was reported as 0.5 in 1000 pregnancies and 0.8 in 1000 deliveries[6].

Two main factors affecting GTD occurrence is maternal age and previous history of GTD. Mean maternal age in our study was 27.3 years, which is compatible with previous reports[3,7]. The risk of CHM is increased significantly in extremes of maternal age (i.e. < 20 and > 35)[7,8]. Nevertheless, most cases of CHM are diagnosed in women aged less than 35 years, due to increased birth rates in this period. In our study population, 20 patients (19.6%) were under 20 years and 18 patients (17.8%) were over 35 years of age. None of the study patients had a history of previous GTD. Due to the increased risk of GTD occurrence, patients with a history of CHM must be observed closely during subsequent pregnancies.

A significant number of cases in our population were diagnosed in the early pregnancy period (approximately 10 weeks according to LMP). Similar with previous studies, most cases presented with vaginal bleeding[9]. However, 39.3% of cases were asymptomatic at the time of diagnosis, which underlines the importance of first trimester ultrasound to confirm fetal viability. In this work, ultrasonographic mean lesion sizes were determined, and were found not to have an effect on treatment failure. A previous report discussing imaging practices in GTD has indicated the recent advances in technology[10,11]. Although these improvements may lead to increased diagnostic sensitivity, cost-effectiveness and global feasibility must be assessed before integrating these technologies to routine clinical management. Considering the widespread availability of ultrasound in many institutions, future studies on sonographic characterization of GTDs may be promising for increasing diagnostic accuracy.

All of the cases in our report were primarily treated with suction curettage, without any associated complications. As mentioned earlier, this may be attributable to early intervention, which is mostly preceded by early detection of a non-viable

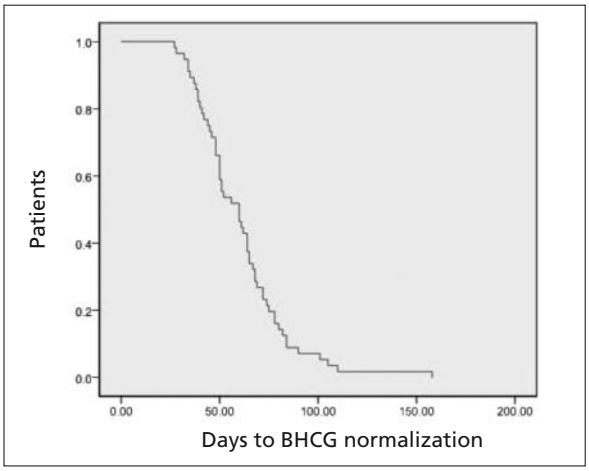

Figure 1. Days to BHCG normalization.

pregnancy. None of the cases received prophylactic chemotherapy after primary treatment and only 10% of them required adjuvant treatment.

Median normalization period (NT) after treatment was 60 days in our study. In a previous paper by Yuen et al[12] , it was reported that 50% of the cases had elevated levels of hCG 60 days after primary treatment. In women that did not undergo hysterectomy, there even were elevated levels in a maximum of 219 days. In our study, a maximum time interval after treatment was 158 days. Kizaki et al[13] referred that analysis of beta-hCG regression curves is a possible method for GTN risk assessment. In this report, the authors reported approximate beta-hCG NTs in CHM as 9.3 weeks, which is very close to our data (8.5 weeks). Also in our paper, NT was significantly longer in cases that required adjuvant chemotherapy. Interestingly, beta-hCG NT did not have an association between the age of the initial beta-hCG and pregnancy duration. The value of NT and regression rates as a prognostic marker in GTD should be evaluated in future studies.

We grouped the cases according to patient age (Table I) to further define our study population. Initial beta-hCG, pregnancy duration, ultrasonographic mean lesion size, and hCG NT was similar in these three groups. Extremes of age (especially above 35 years) constitute an important risk factor for GTD formation. Prognosis of CHM in these patients may also differ from the average aged group. In a study by Elias et al[14], the authors stated that CHM had a distinct clinical course in women aged 40 to 49 years. They reported that aggressive primary therapy (hysterectomy or prophylactic chemotherapy) was associated with shorter hCG NTs, and decreased need of surgical or chemotherapeutic intervention. Although we could not detect a variable clinical course in women above 35 years, future studies are required to establish management guidelines in this special age group.

Considering the rare occurrence of this disease, we believe that accumulation of complete moles by nation-wide investigation is required to improve the diagnosis and management of CHM.

Conclusions

Early detection and treatment of CHM is associated with a favorable clinical outcome. Initial beta-hCG levels and ultrasonographic mean lesion size did not predict adjuvant chemotherapy requirement and did not change the type of treatment.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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