Malignant gestational trophoblastic disease: a review of seventeen cases

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ABSTRACT

Objective: (a) To describe the demographic characteristics of malignant gestational trophoblasic disease (GTD) in Mosul. (b) To evaluate the classification system that stratifies the treatment of the malignant GTD. (c) To know the incidence of malignant changes of mole to malignant GTD.

Design: retrospective clinical case series study done over a period of 5 years.

Setting: Al-Batool Maternity Teaching Hospital and Ibn Seena Teaching Hospital.

Participants: The records of a series of 17 consecutively treated patients who had been diagnosed to have malignant GTD were reviewed. The records of these 17 patients were studied for their age, parity, and mode of presentation. All patients underwent staging studies which included chest x-ray and abdominal ultrasound and were classified as good prognosis group 8 patients (47%) and poor prognosis group 9 patients (53%).

Intervention(s): The good prognosis group was treated with courses of intramuscular methotrexate (50 mg on alternative days 1,3,5,7) with folinic acid rescue (7.5 mg orally on alternative days 2,4,6,8) .The poor prognosis group was treated with methotrexate (10 mg/m^2 /day) intravenously (iv), dactinomycin (0.3 mg/m^2 /day) iv, and cyclophosphamide (110 mg/m^2 /day) iv, for three-day course. Both courses were repeated according to patients' response.

Results: The mean age incidence of malignant GTD was 37.2 years; the mean parity was 4.6, equally presented from rural and urban areas. The presenting symptom of malignant GTD was vaginal bleeding in 47%, cough and shortness of breath in 41.1%, cough and hemoptysis in11.7%. The blood group was O+ve in 64.7%, A+ve in 17.5%, B+ve in 11.7% and AB+ve in 5.9%. The antecedent pregnancy for malignant GTD was complete mole in 88.2 % (the entire good prognosis group), term pregnancy in 5.9% and abortion in 5.9% (both of them in the poor prognosis group). The mean duration between the antecedent pregnancy and treatment of malignant GTD was 5.7 months. Complete response rate without recurrence was 75% for the good prognosis group and 44.4% for the poor prognosis group. The mortality rate was 0% for the good prognosis group and 33.3% for the poor prognosis group giving an overall cure rate of 58.8%. Hysterectomy was needed in 2 patients (22.2%) of the poor prognosis group. The ratio of changes from complete mole to malignant GTD was about one to nine.

Conclusion: Malignant GTD usually complicated complete mole and presented as poor prognosis type in nearly half of the patients. Classification into good and poor prognosis groups is a successful way for treatment selection.

Key words: Gestational trophoblastic disease, hydatidiform mole, neoplasm staging.

الخلاصـــة

الهدف:(ا) وصف الصفات السكانية لمرضى سرطان السخد في الموصل.(ب) تقويم طرق التصنيف لغرض العلاج. (ج) معرفة نسبة تحول الحمل العنقودي الى سرطان السخد.

الطريقة:دراسة سريريه راجعة لحالات متسلسلة.

المكان والمشاركون:تمت الدراسة في مستشفى البتول التعليمي لامراض النسائية والتوليد و مستشفى ابن سينا التعليمي وذلك بدراسة سجلات (17) حالة مشخصة كحالات سرطان السخد خلال فترة 5 سنوات.

المداخلات العلاجية:تم تجميع المعلومات السريرية كالعمر،عدد الولادات،وطريقة ظهور الأعراض،وقد اجري لكل المرضى أشعة الصدر ومسح الأمواج فوق الصوتية للبطن لغرض التصنيف.

القياسات المستخرجة : تم تصنيف المرضى إلى مجموعتين مجموعة الحالات ذات التكهن الجيد وعددها 8 حالات (47%) تمت معالجتها بدواء ميثوتريكسيت لوحده مع فولينك اسيد، ومجموعة الحالات ذات التكهن الفقير وعددها 9 حالات (53%)وقد تمت معالجتها بدواء الميثوتريكسيت مع اكتينومايسين وسايكلوفوسفامايد.

النتائج:كان معدل عمر الإصابة بسرطان السخد هو 37,2 سنة ،ومعدل عدد الولادات هو 4,6،وكان تقسيم المرضى بصورة متساوية تقريبا بين الريف والمدينة.كان العارض الرئيسي لسرطان السخد هو النزف الرحمي في 47% من الحالات،يليه سعال وضيق في التنفس في 41.1% ثم سعال وتنخم دموي في 11.7%.كان صنف الدم السائد لمرضى سرطان السخد هو (O) موجب في 64.7% و(A) موجب في17,5% ،يليه (B) موجب في 11,7% ثم(AB) موجب في 5,9% من الحالات .كان الحمل السابق لسرطان السخد هو حمل عنقودي كامل في 88,2 %(وهم يمثلون الحالات ذات التكهن الجيد) يليه حمل كامل في 5,9 % و إسقاط في 5,9 % والأخيرين يقعان في مجموعة الحالات ذات التكهن الفقير.كانت نسبة تحول الرحى الحويصلية التامة إلى سرطان السخد تقريبا 1 من 9.كانت الفترة بين البدء بالعلاج والحمل الأخير 5,7 اشهر.كانت الاستجابة التامة للعلاج 75% للحالات ذات التكهن الجيد و 44,4% للحالات ذات التكهن الفقير ،كانت نسبة الوفيات صفر% للحالات ذات التكهن الجيد 33,3 % للحالات ذات التكهن الفقير.أما نسبة الشفاء الكلي فقد كانت 58,8 %،وكان عدد استئصال الرحم 22,2% من الحالات ذات التكهن الفقير.

الاستنتاج:سرطان السخد يحدث غالبا بعد الإصابة بالحمل العنقودي الكامل ويكون عادة من النوع ذي التكهن الفقير في اكثر من نصف الحالات.إن تقسيم المرضى إلى حالات ذات التكهن الجيد و حالات ذات التكهن الفقير هي طريقة ناجحة لاختيار طريقة العلاج.

Gestational trophoblastic disease (GTD) defines a heterogeneous group of interrelated lesions that represented an aberrant fertilization event that leads to a proliferative process and potentially, to an invasive neoplasm[1]. Gestational trophoblastic disease includes partial and complete mole; persistent/ invasive gestational trophoblastic neoplasm (also called chorioadenoma destruens); choriocarcinoma; placental site trophoblastic tumor; and epithelioid trophoblastic tumor[2,3].

Malignant GTD, most commonly develops after a molar pregnancy, but can be seen after any gestation[4] .In contrast to other more common malignancies in women, malignant GTD is curable in 85 to 100 percent of cases when appropriately treated and monitored, even in the presence of advanced disease[5].

Increased serum concentrations of the beta unit of human chorionic gonadotrophin (beta- hCG) are associated with all forms of GTD[6]. Persistent elevation of serum beta-hCG following a nonmolar pregnancy (e.g. miscarriage or ectopic or term pregnancy) is always due to choriocarcinoma[7]. Besides the traditional markers such as (hCG) or human placental lactogen (hPL), several markers have been recently found to be useful as trophoblastic markers such as inhibin-alpha[3].

Choriocarcinoma occurs with a frequency of approximately 1 in 16,000 normal gestations, 1 in 15,000 abortions, and 1 in 40 complete molar pregnancies[8]. The risk factors for developing malignant GTD include, nilliparity; extremes of maternal age (under 26 and over 35 years); the presence of enlarged theca lutein ovarian cyst (> 6cm); a history of previous abortion; a history of previous GTD; some ethnic groups; maternal blood group A and after mating between individuals of blood groups A and O than other matings[3, 9-11]. Familial molar pregnancy and malignant GTD were reported although very rarely [12].

It is important to mention that malignant GTD is the fourth common gynecological malignancy in Iraq after carcinomas of the ovary, endometrium and cervix[13] or after carcinomas of the cervix, ovary and endometrium[14].

Cure rates for malignant trophoblastic disease as high as 98% have been observed among patients whose disease was diagnosed early and treated adequately, even in the presence of metastatic disease. In contrast, patients with long-standing and widely disseminated disease can only expect a 20 to 25% remission rate[15].

Patients and methods

This is a retrospective study done in a period of 5 years at Al-Batool Maternity Teaching Hospital and Ibn Seena Teaching Hospital; the records of 17 patients with some form of malignant GTD were reviewed. There were 130 patients with complete hydatidiform mole and 8 patients with partial hydatidiform mole. Of the complete mole patients 15 developed malignant changes. The diagnosis of malignant GTD was based on symptoms and signs of the disease plus sustained elevation of serum hCG level after

evacuation of a mole, or after delivery or abortion. The same criteria were used by Lurian in 1990 [16].

The records of these 17 patients were studied for their age, parity, mode of presentation, and staging investigations which included chest x-ray and abdominal ultrasound. As quantitative assay of hCG was not available during the period of this study, it was excluded from staging investigations and was only used qualitatively for diagnosis and follow-up. One of us (Dr. A. C.) was responsible for initial evaluation, staging and selection of treatment of the patients and classified them according to Hammond et al. (1973)[15] into good prognosis group (8 patients, 47%), or poor prognosis group (9 patients, 53%). Poor prognosis patients were identified by the presence of cerebral or hepatic metastases, and disease duration was greater than 4 months[15].

The patients with "good prognosis" were all treated with systemic single agent chemotherapy which was intramuscular methotrexate (50 mg on alternate days 1, 3, 5, 7) with folinic acid rescue (7.5 mg orally on alternate days 2, 4, 6, 8). The regimen was repeated at 7-day intervals after completion of the previous course for as long as the hCG titer remained elevated. Those patients with poor prognosis were treated with triple agents chemotherapy composed of methotrexate (10mg/m^2 /day) iv, dactinomycin (0.3 mg/m^2 /day) iv, and cyclophosphamide (110mg/m^2 /day) iv, for three-day course. Courses were repeated at 12 to 14 day intervals, depending on hematopoietic recovery and other toxicities. This regimen was also used by Hammond et.al. (1978)[17].

After two courses of chemotherapy the hCG became negative in some of these patients. Most of these patients had one to three courses of chemotherapy after a negative titer was first achieved. Complete remission was diagnosed in this study only after three consecutive negative weekly hCG assays. This is according to Lurian et. al (1982)[18].

After remission had been achieved, patients were allocated for follow-up schedule. Such follow-up consisted of clinical general and pelvic examinations plus measurement of hCG every 2 weeks for 3 months, monthly for 3 months, and then every other month for 6 months, then at 6-month intervals for 2years. Pregnancy, where possible, was contraindicated for at least 1 year after remission but was allowed after this interval. This follow up had been also adopted by Hammond et.al. (1973)[15].

Results

Malignant GTD were diagnosed in17 cases, complicating 11.6% of complete mole or one in every 9 complete moles (which is the percentage of persistent disease after evacuation).

Table 1 shows the demographic characteristics of the 17 patients with malignant GTD under the study. The mean age of the patients was 37.2 years, with 44.4% were over 40 years old, no one was below 25 years old. The mean parity was 4.6(range 0-8). Nearly equal number of the patient was urban (9 patients, 53 %) or rural (8 patients, 47%). The presenting symptom was vaginal bleeding in 8 patients (47%), cough and shortness of breath in 7 (41.1%), and cough and hemoptysis in two (11.7%).

Blood group was O+ve in 11 patients (64.7%), A+ve in 3 (17.5%), B+ve in 2 (11.7%), and AB+ve in only one patient (5.9%). The risky blood groups O+ve and A+ve were present in 82.2% of cases.

The antecedent pregnancy was mole in 15 patients (88.2%), term pregnancy in one (5.9%) and abortion in one patient (5.9%). In no patient the antecedent pregnancy was ectopic gestation. The duration between the antecedent pregnancy and treatment was 1-14 months with a mean of 5.7 months.

The nature of the antecedent pregnancy versus each group of the disease in the17 patients under the study is shown in table 2. All the patients (8, 100%) in the good prognosis group had hydatidiform mole as the antecedent pregnancy. In the poor prognosis group 7 patients (77.7%) had complete mole as the antecedent pregnancy, one patient (11.2%) had term pregnancy as the antecedent pregnancy, and another one patient (11.2%) had spontaneous abortion as the antecedent pregnancy. In both groups complete mole was the antecedent pregnancy in 88.2% of cases.

Table 3 presents the overall statistics in the treatment of the two groups of GTD as seen in 17 patients in this study. There were 8 patients (47%) with good prognosis, 6 of them (75%) achieved remission, no mortality was recorded, and 2 patients (25%) escaped from the study. There were 9 patients (53%) in the poor prognosis group, 4 of them (44.4%) achieved remission, death occurred in 3 patients (33.3%) and 2 patients (22.2%) escaped from the study. The cause of death in these cases was due to multiple distant metastases.

Table (1): *The demographic characteristics of 17 patients with malignant GTD included in the study.*

Characters	Range (mean), (percentage)
Age	25-48years (37.2 Years)
Parity	0-8 (4.6)
Residence	
Urban	9 patients (53%)
Rural	8 patients (47%)
Presenting symptoms	
Vaginal bleeding	8 (47.1 %)
Cough and shortness of breath	7 (41.17%)
Cough and hemoptysis	2 (11.76%)
Blood group and Rh	
O+ve	11 (64.7%)
A+ve	3(17.5%)
B+ve	2(11.7%)
AB+ve	1(5.9%)
Antecedent pregnancy	
Complete mole	15(88.2%)
Term pregnancy	1(5.9%)
Abortion	1(5.9%)
Duration between antecedent pregnancy and treatment	1-14 months (5.7 months)

The overall results in both groups were as follows: remission rate was 58.8%, death in 17.6% and 23.5% of the patients escaped from follow-up. Hysterectomy was needed in 2 patients (11.7%) both of them in the poor prognosis group; both of them died. The indication for hysterectomy in both cases was to control heavy bleeding.

Pregnancy was successfully achieved in one patient of the good prognosis group after two years of follow up. Other patients were lost before completing two years of follow up after remission.

Discussion

The incidence of malignant GTD varies in different studies; reported geographical variations in the incidence ranged from 1 per 1000 pregnancies in the United States, to 2 per 1000 pregnancies in Japan[16]. In Malaysia, the incidence of molar pregnancy and malignant GTD is 2.8 and 1.59 per 1000 deliveries respectively[19].

Few indices have been found to be useful in predicting the progression of hydatidiform mole to persistent trophoblastic disease. Essentially, the hCG regression pattern remains the most specific prognostic indicator[3].In this study hCG was used for the diagnosis of malignant GTD.

Malignant GTD most commonly develops after a molar pregnancy, and it was estimated that 50% of gestational choriocarcinomas were preceded by a complete mole, the other 50% by abortions, normal or even ectopic pregnancies[4,11,20]. In our study malignant GTD developed mostly after molar pregnancy (88.2%), this is in agreement with Lurian study[16]. The incidence of malignant GTD after normal pregnancy in this study was very low compared to that reported by Brewer and his colleagues and slightly lower after abortion, but higher after complete mole (1in 9 versus 1in 40 moles) [8]. This could be due to the high parity and old maternal age and high prevalence of blood group O+ve and A+ve (82.2%) of those with GTD in this study.

Table (2): *The nature of the antecedent pregnancy versus the group of the disease in 17 patients with malignant GTD.*

Group of the disease	Nature of antecedent pregnancy			
	Hydatidiform mole	Term	Abortion	Others
Good prognosis G.T.D(n=8)	8(100%)	-------	------	------
Poor prognosis G.T.D(n=9)	7(77.7%)	1(11.2%)	1(11.2%)	-----
Total (n=17)	15(88.2%)	1(5.9%)	1(5.9%)	

Table (3): *Overall statistics in the treatment of patients with malignant GTD, by group of the disease.*

Group of the disease	No. of patients (%)	Remission (%)	Hysterectomy	Death (%)	Lost (%)
Good prognosis	8(47%)	6(75%)	0(0%)	0(0%)	2(25%)
Poor prognosis	9(53%)	4(44.4%)	2(22.2%)	3(33.3%)	2(22.2%)
Total	17(100%)	10(58.8%)	2(11.7%)	3(17.6%)	4(23.5%)

The mean age incidence in this study was (37.2). This age is one of the risk factors for development of malignant GTD[9]. The mean parity in this study was (4.6) with a range from nulliparity to grand multiparity. Both nulliparity and multiparity are predisposing factors for malignant GTD[9].

Malignant GTD is a highly curable disease; even when there is a metastatic disease[15]. Appropriate selection of therapy is based upon classification or staging systems that stratify by the extent of the disease. Many staging, classification, prognostic system and criteria for treatment have been applied to gestational trophoblastic disease across the world. Consequently it has been difficult to compare results of treatment from different centers[21]. In this study, in order to choose appropriate selection of therapy, the patients were classified into good and poor prognosis groups (following Hammond's criteria) to be treated by single agent or multiagents chemotherapy respectively[15].

There was nearly equal number of patients in the good prognosis and poor prognosis groups in this study. Our findings differ from those of Hammond and co-workers study (1973) in which 79% of the patients were from the good prognosis group [15]. The high incidence of poor prognosis patients in our study may be due to long duration of the disease before treatment (range 1-14 months). The average duration of the disease in this study was 5.7 months, which fulfill Hammond's criteria for poor prognosis disease (more than 4 months). The long duration of the disease had predisposed to multiple distant metastases.

Remission was achieved in 75% of good prognosis patients in this study and in 98% of the Hammond's study. This difference could be due to those patients lost from follow-up in our study. Remission was achieved in 44.4% of poor prognosis patients in this study and in 47% of the Hammond's study[15]. These are nearly equal results.

Hysterectomy decreases chemotherapy requirements for patients with low risk disease and it is frequently required to control complications [22]. In this study hysterectomy has been done to control heavy bleeding.

Patients with GTD can, in general, anticipate normal pregnancy outcome[23]. In this study pregnancy was achieved in only one patient in the good prognosis group. The lost patients from follow up could have participated in increasing this number.

It has been difficult to compare the results of this study to results from different centers because of the differences in the staging, classification and criteria for treatment in every study, so there is a prompt need for an internationally agreed staging/prognostic scoring system. Even the diagnosis of persistence after evacuation of a mole varies from center to center, which reflects the inconsistency in criteria used by various centres in the management of GTD. A review of large series in the literature indicated an incidence of persistence after the evacuation of a mole ranging from 5.6 to 36%[23-26]. The incidence in this study was within this range(11.6%).

We conclude that the system adopted in this study to classify the patients for treatment is a successful system and it had been previously adopted by Hammond et.al. in 1973 and recently adopted by the FIGO committee [15, 28]. This system is also very similar to the recent classification of low and high-risk disease adopted by Wright and Mutch[29].

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