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Original Research

Misdiagnosis and Chemotherapy Delaying Reduces the Chemosensitivity of Choriocarcinoma Patient: Analysis of 36 Cases

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Abstract

Background: Choriocarcinoma is a curable malignant neoplasm when chemotherapy is properly implemented. However, when chemotherapy resistance occurs, disease can be fatal. Misdiagnosis is common, which may lead to delaying of the first cycle of chemotherapy and increase the possibility of chemoresistance. **Methods**: We analyzed 36 choriocarcinoma cases who were treated in our department about their clinical characteristics, and their diagnosis and treatment processes together with the serum β-hCG variation. **Results**: Analysis showed that the disease onset age, FIGO (International Federation of Gynecology and Obstetrics) stage distribution were similar to the other cohort. The primary origins were uterine canals, and the serum β-hCG elevated with or without vaginal bleeding were common, which all easily lead to misdiagnosis of benign pregnancy related diseases. Our data demonstrated that the misdiagnosis of choriocarcinoma resulted in delaying of the first cycle of chemotherapy, followed by decreased control of serum β-hCG after one chemotherapy cycle and more cycles for serum β-hCG normalization, which meant the possibility of generating chemoresistance. **Conclusions**: In summary, standardized surveillance and treatment process to decrease misdiagnosis rate of choriocarcinoma can be an effective measure to improve the prognosis of patients.

Keywords: choriocarcinoma; chemotherapy delay; chemoresistance

1. Introduction

Choriocarcinoma is one of the gestational trophoblastic neoplasias (GTN), a malignant neoplasm mostly generated from trophoblast, or from germ cells for minority. After the application of effective chemotherapy, the 5-year overall mortality rate of GTN reduced from over 90% to about 2% [1–3]. Nowadays, choriocarcinoma is curable even in patient with distant metastasis. However, drug resistant is always the biggest challenge for the gynecological oncologists to treat the disease, which becomes the most threatening factor for patient's life. The specific influencing factor is unclear, it is generally accepted that tumor heterogeneity, the inherent characteristic of malignant disease, is the root of choriocarcinoma drug resistance. Delaying of the first line chemotherapy may be one of the causes of cancer cell genetic alteration accumulation, which may increase antitumor treatment tolerance of choriocarcinoma cells [4]. However, misdiagnosis is common in gestational origin choriocarcinoma, because choriocarcinoma is a disease diagnosed mainly based on clinical manifestations, which are often lack of specificity [5].

The most common clinical manifestations of choriocarcinoma are amenorrhea, vaginal bleeding and serum β-hCG (human chorionic gonadotropin) elevating, all of which may also refer to pregnancy [6]. Besides, local or distant metastasis of choriocarcinoma often causes a wide variety of symptoms lacking of specificity. For the reasons above, misdiagnosed in choriocarcinoma patients are common, which lead to the delaying of chemotherapy. According to retrospectively analyzing the choriocarcinoma patients' data of our department, we were aimed to find out the potential health impacts of the misdiagnosis of this malignant disease.

2. Material and Methods

In this study, we retrospectively analyzed 36 cases of choriocarcinoma patients treated in our department (all were referral from lower-level medical institutions) from March 2013 to September 2020. By the means of reviewing and analyzing the clinical characteristics, and the diagnostic and therapeutic process. Because this is a retrospective study, the informed consent of the study was not available. All the patients analyzed in this study had already completed standard treatments of choriocarcinoma, the informed consent of all the treatments were given. In this article, patient anonymity are preserved. This study was approved by our hospital Ethics Committee (Ethical Review Approval No. [2022]251).

All the patients were staged based on FIGO (International Federation of Gynecology and Obstetrics) 2000 staging system, and the chemotherapy regiments were chosen after scoring with FIGO 2000 scoring system.

For clinically diagnosed choriocarcinoma, diseases were considered arisen from normal pregnancy, sponta-

neous abortion without molar pregnancy, or from molar pregnancy over 24 months after the last treatment. Every patients' specified time of disease onset were reviewed. For patient with normal pregnancy or any types of abortion as antecedent pregnancy states, abnormal vaginal bleeding or serum β-hCG elevating after termination of pregnancies was considered to be the disease onset. For patient with molar or invasive molar pregnancy, the last time of the sign of disease recurrence occurred was considered to be the onset of disease. Symptoms of specific metastasis lesion were considered for patient without any gestational related clinical manifestations [7].

We calculated the intervals from the disease onset to the first cycle of chemotherapy. T test were carried out to analyze the influence of misdiagnosis on treatments delaying.

Two index were calculated to represent the chemotherapy sensitivity, the percentage of serum β-hCG decline after the first chemotherapy cycle (% = (serum β-hCG before first cycle chemotherapy – serum β-hCG before second cycle chemotherapy) $\times$100%/serumβ-hCG before first cycle chemotherapy), and the cycle number of chemotherapy before serum β-hCG normalized.

The intervals from onset to chemotherapy were analyzed with the percentage of serumβ-hCG decline after the first chemotherapy cycle and the cycle number of chemotherapy before serum β-hCG normalized. Statistical analysis of correlation were utilized, in order to demonstrate the relationship between patients' delaying of chemotherapy and chemotherapy response.

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

3. Results

3.1 Clinical Characteristics

In these 36 cases, the age of onset ranged from 19 to 54 years old (median 32.5 years old), mean age was 34 years old. Because all patients had had sexual life, diseases were considered gestational in origin. Based on FIGO 2000 staging system, 14 cases were in stage I disease (38.9%), 3 in stage II disease (8.3%), 17 in stage III disease (47.2%), and 2 in stage IV disease (5.6%). Based on FIGO 2000 scoring system for gestational trophoblastic neoplasia, nearly half of the stage I and III patients were in low-risk group and the rest in high-risk group. All stage II patients were in low-risk group, and all stage IV patients were in high-risk group [8] (Table 1).

Choriocarcinoma can be developed from any type of gestational event, including molar gestation, and normal or abnormal pregnancy. In this series of patients, 22 were arisen from normal pregnancy, in which 11 from term pregnancy and 3 from spontaneous abortion. 7 patients were arisen from molar disease and 3 from invasive molar pregnancy. There was 1 patient who denial history of pregnancy, but had sexual life for more than 1 year [9] (Table 2).

Table 1. Characteristics of the patients.

	All patients (n = 36)	FIGO score	
		Low-Risk (n = 18)	High-Risk (n = 18)
Age, years			
Median	32.5		
Range	19–54		
FIGO stage, number			
I	14	6	8
II	3	3	0
III	17	9	8
IV	2	0	2

3.2 Primary Origins and Symptoms of Disease

The most common initial site of disease was uterine canal, with or without myometrial invasion shown in imaging examination, account for 77.8% of all the cases, the same as the data shown in other studies. Primary origin out of the uterine canal was rare, including 2 on ovary, 1 on fallopian arch, and 2 cases had lung metastasis lesion only. 2 stage IV cases with widespread metastasis were not able to identify the primary origins when diagnosed (Table 2).

Table 2. Clinical characteristics of the patients.

	All (n = 36)	Misdiagnosed	
		Yes (n = 20)	No (n = 16)
Primary origin			
Uterine Canal	28	17	11
Ovary	2	1	1
Lung	2	1	1
Parauterine or Vagina	1	1	0
Other	3	0	3
Antecedent pregnancy status			
Normal Pregnancy	22	11	11
Spontaneous Abortion	3	2	1
Molar Disease	7	5	2
Invasive Molar Pregnancy	3	1	2
No Pregnancy History	1	1	0
Disease be misdiagnosed as			
Ectopic Gestation		6	
Inevitable/Missed Abortion		9	
Molar Disease		1	
Abnormal Uterine Bleeding		1	
Endometriosis		1	
Oophoritic Cyst		1	
Upper Respiratory Tract Infection		1	

In order to analyze the difficulties of choriocarcinoma diagnosis, we reviewed the initial symptoms of these 36 patients. 42% of our patients referred to the hospital due

to abnormal vaginal bleeding, in which 4 with amenorrhea along with serum β-hCG elevating. There were also patients diagnosed because of elevated serum β-hCG during the surveillance after previous pregnancy event, including 7 normal pregnancies, 5 molar pregnancies, and 2 invasive molar pregnancies. There were 4 cases presented special initial symptoms out of the gynecological system: 1 with bellyache and then only pelvic mass was found, 1 with hemoptysis, 1 with upper abdominal pain, 2 with abnormal motor nerve dysfunction because of intracranial metastasis. Elevated serum β-hCG was the key symptoms, but differentiation from benign pregnancy related event is difficult. Furthermore, serum β-hCG examination in patients without common symptoms of gynecological diseases might be neglected.

3.3 Diagnosis and Misdiagnosis

58.3% of these 36 patients were diagnosed combined with medical history, clinical manifestations, imaging features and laboratory examinations. Notably, there were up to 9 cases diagnosed without pathology accepted vacuum extraction or uterine curettage but failed to obtain pathological samples. Among the remaining 41.7% patients who had pathological diagnosis, 7 cases accepted vacuum extraction or uterine curettage, 8 cases underwent surgical resection of the metastatic lesions.

Although pathological diagnosis is important, diagnosis based on clinical appearance is more practical and widely accepted in choriocarcinoma [7]. Because of the lack of specific clinical manifestations to distinguish different types of malignant trophoblastic disease, the diagnosis of choriocarcinoma is a big challenge for the gynecological oncologists.

Up to 20 cases in these 36 choriocarcinoma patients were misdiagnosed at their initial visits to the hospital. 9 patients had elevated serum β-hCG with or without vaginal bleeding, and the ultrasound found nothing about sign of intrauterine pregnancy, which lead to ectopic gestation diagnosis. 9 received vacuum extraction because of the misdiagnosis of inevitable abortion or missed abortion. The two patients mentioned above with giant pelvic mass and hemoptysis respectively, got misdiagnosed without testing serum β-hCG levels [10]. However, after analyzing these cases, we found that pathological diagnosis were not indispensable in all of them. 9 of them were misdiagnosis at the beginning, 2 as ectopic gestations and 5 as incomplete abortions, which resulted in unnecessary surgeries.

3.4 Consequences of Misdiagnosis

The immediate consequences of misdiagnosis were unnecessary invasive examination or even operations. In this study, only 1 in 6 patients who were misdiagnosed as ectopic gestation escaped from operation, other 5 patients suffered from laparoscopic lesion resection, including 1 extreme case who accepted laparoscopic salpingotomy twice. Patients misdiagnosed as inevitable abortion or missed abortion received 1 to 3 times of vacuum extraction or uterine curettage, including 2 cases further suffered from hysteroscopic electrocision in order to remove the intrauterine residue. All these excessive examinations or operations not only increased the suffering of patients, but also could delay the chemotherapy.

Compared to the patients who were successfully diagnosed at the initial treatment, the intervals from the disease onset to the first chemotherapy cycles of the patients misdiagnosed were inevitably extended from 5–65 days to 19–491 days (mean interval 17 days vs. 70 days, $p = 0.0078$) (Fig. 1).

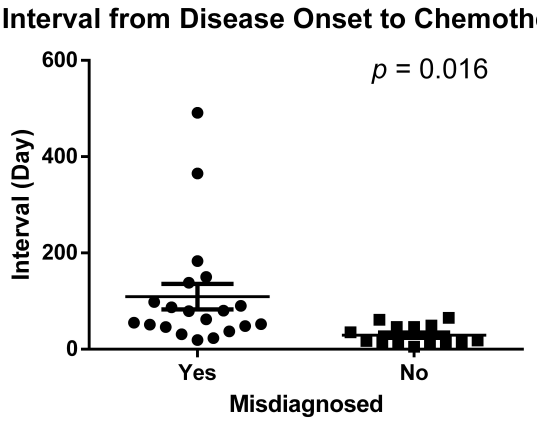

Fig. 1. Misdiagnosis delayed the chemotherapy of choriocarcinoma patient. The interval from choriocarcinoma disease onset to the first cycle of chemotherapy, the intervals of misdiagnosed patients were significantly longer than correctly diagnosed patients.

Whether the delaying of the treatment influenced the sensitivity of chemotherapy or not? The prognosis of the patients and the tumors' response to chemotherapy are suitable for evaluation. Because of the small sample size of this study, only 4 patients relapsed until now, so that we were not able to analyze the prognosis. We further analyzed the correlation between interval from disease onset to the first chemotherapy cycle and the patient's sensitivity to chemotherapy. Although the differences were not statistical significant, data showed that the longer the interval was, the less the rate of serum β-hCG decline ($r = -0.188$, $p = 0.2874$) (Fig. 2). At the same time, delaying of the first cycle of chemotherapy correlated with more cycles of chemotherapy before serum β-hCG returned to normal ($r = 0.3478$, $p = 0.0511$) (Fig. 3).

Retrospectively reviewed of every patients' chemotherapy regiments, the times of regimen changing also demonstrated that misdiagnosis would make the cure much more difficult. In patients who were misdiagnosed, more patients received more than 1 regiment because of chemoresistance (10 in 20 patients vs. 6 in 16

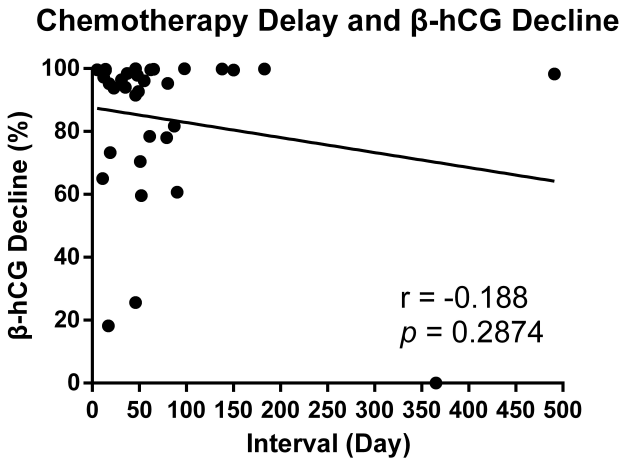

Fig. 2. Delaying of chemotherapy may reduce the drug sensitivity of choriocarcinoma patient. The interval from choriocarcinoma disease onset to the first cycle of chemotherapy were reversely correlated with the serum β-hCG decline percentage after the only one cycle of chemotherapy.

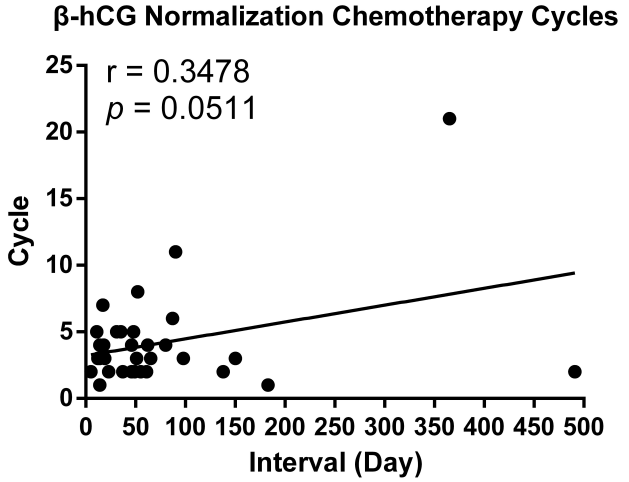

Fig. 3. Delaying of chemotherapy may increase the drug resistance of choriocarcinoma patient. The interval from choriocarcinoma disease onset to the first cycle of chemotherapy were correlated with the cycle number of chemotherapy needed for serum β-hCG normalization.

patients), although more data were needed to carried out statistical analysis.

3.5 Choriocarcinoma Treatment and Pregnancy

In our cohort, there were 5 cases of term pregnancy after the completion of choriocarcinoma treatment more than 2 years, all had healthy babies. 3 cases began with single agent Act-D (Actinomycin-D) or 5-Fu (5-Fluorouracil), in which only 1 was cured by single agent Act-D, 1 change into Act-D/5-Fu and 1 into EMA/CO regiment. Other 2 cases began with Act-D/5-Fu regiment, but adjusted to EMA/CO.

4. Discussion

Choriocarcinoma is one of the malignant trophoblastic neoplasms, which has the potential for local invasion and distant metastasis. Choriocarcinoma can be gestational or nongestational, all the 36 patients treated in our department from March 2013 to September 2020 were diagnosed as gestational choriocarcinoma. The morbidity of gestational choriocarcinoma ranged from 1 to 9.3 in 40,000 pregnancies from data of different areas [11,12]. One of the most important prognostic factors of choriocarcinoma patients is chemotherapy sensitivity. Up to now, studies for choriocarcinoma chemoresistance only mentioned about the predicted values of FIGO score and FIGO stage [13]. No study showed the influence of misdiagnosis on these patients while differential diagnosis of choriocarcinoma was complicated. As the results, we will discuss this matter in our study, in order to show the relationship between misdiagnosis and chemoresistance in choriocarcinoma patients.

Retrospect analyzed of the FIGO stage of our cohort showed the same distribution as previous studies (Table 1). Utilization of lung computed tomography scan (CT) in choriocarcinoma patient results in high sensitivity of detecting pulmonary nodule, but the relatively low specificity makes it over-diagnosed of stage III disease. Therefore, patients' FIGO staging were not able to predict their prognosis appropriately [14]. It is reported that approximately 50% of choriocarcinomas present after normal pregnancies, 25% after molar pregnancies. In our cohort the data was similar, 61.1% after normal pregnancies and 27.8% after molar or invasive molar pregnancies (Table 2).

Chemotherapy plays the vital role in choriocarcinoma treatment. Every patient diagnosed of gestational trophoblastic neoplasia (GTN) should be scored by FIGO scoring system and divided into low- or high- risk group, which will direct the choose of chemotherapy regiment. For low-risk group patients, single agent chemotherapy may be sufficient, while multi-agent chemotherapy is needed for high-risk group patients. Disease can be curable only with chemotherapy for most patients, but surgery should be considered when chemotherapy refractory disease occur. After appropriate regimen and sufficient cycles of chemotherapy, cure rate of low-risk group patient may approaches 100%. At the same time, with or without surgery and radiotherapy, the cure rate of high-risk group patient may over 90% [15].

The FIGO scoring system based on patient's age of disease onset, antecedent pregnancy status, the interval between antecedent and onset, pre-treatment, tumor size and number of metastasis is effective in predicting the patient's prognosis [16]. From the FIGO scoring we can conclude that the longer the tumor progressed, the more severe the disease will be. Therefore, the interval from disease onset to the first cycle of chemotherapy is important, which may attribute to the accumulation of mutation and tumor heterogeneity.

Chemotherapy sensitivity is one deciding factor of choriocarcinoma patient's prognosis [17]. Although the mortality rate and recurrence rate are the best indicators of chemotherapy sensitivity, our patient cohort was too small to analyze, so that we needed to find new evidence to verify the influence of treatment delaying on chemotherapy resistance [16].

Serum β-hCG level is an excellent biomarker of disease progression which reflect the tumor burden directly [18]. But the serum β-hCG level before chemotherapy alone is not able to reflect the difficulty of treatment. When the tumor cells are sensitive to the chemotherapy, only one cycle of treatment can result in sharp decline of serum β-hCG [19]. In addition, the chemotherapy cycles needed for different patients are individualized, based on how many cycles the patient are received before the serum β-hCG return to normal. When more than 4 cycles were taken but serum β-hCG is still above normal, re-scoring and therapeutic regimen adjustment is indicated. So that cycles of chemotherapy needed for the normalization of serum β-hCG can also reflect the chemosensitivity of disease [11].

In this study, we analyzed the intervals from disease onset to the first cycle of chemotherapy, data showed that when patients were misdiagnosed, their treatment would be significantly delayed (Fig. 1). We first calculated the percentage of serum β-hCG decline after one chemotherapy cycle and analyzed its correlation with treatment delay interval. And then the correlation between cycle numbers before the normalization of serum β-hCG and treatment delay intervals were also analyzed. Result demonstrated that the delay of chemotherapy for choriocarcinoma patient may result in undesirable decline of serum β-hCG and more cycles of chemotherapy for serum β-hCG normalization (Figs. 2,3), both of which implied the possibility of chemotherapy resistance. It is worth noting that there were two cases which were diagnosed after 1 year, whose disease were all arisen from molar pregnancy and the elevation of serum β-hCG during surveillance were ignored. These two patients had different reaction of chemotherapy, the poor reaction patient experienced recurrence more than once. We come to the conclusion that, promptly proper diagnosis of choriocarcinoma is crucial, while other factors were needed to be considered comprehensively.

The pregnancy outcome of our patients showed the low reproductive toxicity of the most frequently used regiments of choriocarcinoma. Choriocarcinoma patients were mostly in their reproductive age (Table 1), and chemotherapy can be the best treatment for fertility-sparing [20–22].

There were limitations of this study. First, this is a single center study, because of the low incidence of choriocarcinoma, although we had already enrolled all the patients treated in our department from March 2013 to September 2020, only 36 cases were analyzed. Second, attribute to the high chemotherapy sensitivity of GTN and good prognosis, the sample size of this study was not enough to come to a conclusion of statistically significant. More data were needed in order to increase the value of this study.

5. Conclusions

Our study demonstrated that the interval from disease onset to first cycle of chemotherapy influences chemotherapy sensitivity, and misdiagnosis not only lead to unnecessary examination and operation but also lead to treatment delaying. Because of the nonspecific symptoms, misdiagnosis of choriocarcinoma is always the challenge of the gynecological oncologist, the misdiagnosis rate was up to 55.6% according to our data. Choriocarcinoma can be early detected following the proper treatment process, such as serum β-hCG monitoring and pathological examination after abortion. Therefore, standardization of the diagnosis and treatment of normal gestation or diseases associated with pregnancy, and the surveillance after treatment is always the most important topic.

It is important to note that this study only reflect local practice. Because of the low incidence and high chemotherapy sensitivity, only 36 cases were enrolled. We need much more work to provide more reliable data.

Author Contributions

LJY—Conceptualization, Methodology, Investigation, Writing - Original Draft. YYC—Conceptualization, Methodology, Investigation, Writing - Original Draft. CXZ—Formal analysis. YZW—Data curation. GFY—Conceptualization, Writing - Review & Editing, Funding acquisition.

Ethics Approval and Consent to Participate

This study was approved by The First Affiliated Hospital of Sun Yat-sen University Ethics Committee, Ethical Review Approval No. [2022]251.

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Conflict of Interest

The authors declare no conflict of interest.

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