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Original Article

The management of hydatidiform mole with lung nodule: a retrospective analysis in 53 patients

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ABSTRACT

Objective: To investigate the significance of lung nodule in hydatidiform mole, we retrospectively compared the clinical outcomes of those patients treated with different strategies.
Methods: The patients were divided into three groups: chemotherapy immediately once lung nodule was detected (group 1, n=17), delayed chemotherapy until human chorionic gonadotrophin (hCG) level met the diagnostic criteria for gestational trophoblastic neoplasia (GTN) (group 2, n=18), and hCG surveillance alone until hCG level was normalized spontaneously (group 3, n=18). The clinical parameters of these patients were collected and analyzed.
Results: Totally 53 (4.0%) patients were included from 1,323 cases with molar pregnancy during past 16 years. Among them, the diameters of lung nodules were 0.3–2.5 cm. Chemotherapy cycles for achieving hCG normalization and the failure rate of first-line chemotherapy in group 1 were significantly increased than that in group 2 (5 vs. 3 cycles, p=0.000, 58.8% vs. 11.1%, p=0.005). The hCG level of all 18 cases in group 3 was normalized spontaneously within 6 months. Of those, lung nodules of 9 patients disappeared spontaneously, accounting for 25% (9/36) of patients who initially selected observation. The proportion of single nodule in group 3 was significantly higher than that in group 2 (10/18 vs. 2/18, p=0.012).
Conclusion: Our results suggest that lung nodule alone is not an adequate indication of chemotherapy in molar pregnancy. hCG surveillance is safe for patients with lung nodule, especially with single nodule, as long as their hCG levels do not meet International Federation of Gynecology and Obstetrics diagnostic criteria for GTN.

Keywords: Hydatidiform Mole; Pulmonary Nodule; Chemotherapy; Gestational Trophoblastic Neoplasia; Chorionic Gonadotrophin

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with abnormal pregnancy. In this group, molar pregnancy includes complete hydatidiform mole (CHM), partial hydatidiform mole (PHM), and invasive mole, according to World Health Organization classification of tumors of female reproductive organs (2014) [1,2]. A part of hydatidiform moles, after evacuation, will progress to gestational trophoblastic neoplasia (GTN) including invasive hydatidiform mole and choriocarcinoma, accounting for 15%–29% for CHM [3] and 0.5%–5% for PHM [4]. Usually, the postmolar GTN can be diagnosed depending on abnormal human chorionic gonadotrophin (hCG) level during follow-up [3].

Lung is the most common metastatic site of GTN, which manifests as pulmonary nodule detected by chest X-ray and/or lung computed tomography (CT). The lung metastases detected by chest X-ray was regarded as one of the clinical diagnostic criteria for GTN in International Federation of Gynecology and Obstetrics (FIGO) 2012, but was withdrawn in FIGO 2015 [2,3]. Lung nodule sometimes can be detected by X-ray or CT at or after suction evacuation of molar pregnancy, even in normal pregnancies [5]. In addition, going with improved quality of CT scan, much smaller lung nodule can be visualized [6]. Thus, the clinical significance of lung nodule in hydatidiform mole patients, especially those detected by CT scan alone, has become a controversial issue.

Despite the role of chest X-ray as diagnostic criterion of GTN was retracted in FIGO 2015, pulmonary radiologic examination is still retained for GTD [2]. It would cause confusion when the doctors manage the patient with radiological suspected lung metastasis who does not meet the hCG diagnostic criteria. As we know, delayed chemotherapy may result in disease progression of GTN [2,7,8], although over 90% of patients with GTN have good prognosis[9,10]. Thus, early diagnosis and prompt treatment is needed for GTN patients with real lung metastasis. On the contrary, those women with non-metastatic or transient lung nodule would encounter unnecessary chemotherapy, if they were mistreated as metastasis. Most of patients with GTD are young and desire childbearing, avoidance of unnecessary chemotherapy is obviously beneficial for them. Thus, an appropriate management is vital for molar pregnancy patients with lung nodule.

In the present study, we retrospectively collected the clinical parameters of 53 molar pregnancy patients with lung nodule and compared their clinical outcomes depending on different management methods, in order to provide clinical evidences for the appropriate management of molar pregnancy with lung nodule.

MATERIALS AND METHODS

1. Study design

This is a retrospective study on patients with molar pregnancy who were managed between 2000.1.1 and 2016.7.31 at Women's hospital, Zhejiang University School of Medicine. The study was approved by the Ethical Committee of women's hospital, Zhejiang University School of Medicine (12/28/2017, No. 20170196). The patient who met all the following criteria was collected: the lung nodule was detected by chest X-ray and/or lung CT at the suction evacuation of molar pregnancy or during weekly hCG surveillance; the image impression was lung metastasis; and the patients did not meet FIGO diagnostic criteria (2015) of GTN

at same moment. The patients lost to follow-up were excluded. If the evacuation of molar pregnancy was not performed at our hospital, the pathologic diagnosis should be reviewed and confirmed by the pathologist in our hospital. Patients were divided into three groups depending on the treatment methods. Group 1: chemotherapy was prescribed immediately when lung nodule was detected. Group 2: chemotherapy was postponed until hCG level met FIGO diagnostic criteria of GTN. Group 3: hCG surveillance only until hCG level declined to normal spontaneously. The decision of the treatment was individually depending on the doctor's experience. A normal hCG level was identified as below 5.3 IU/L. The chemotherapy regimen was prescribed according to FIGO guideline. Failure of first-line chemotherapy was defined as an inadequate response to the initial agent, including that hCG level was elevated or not declined, and new metastasis developed. All women were followed up by clinic interview or telephone. The follow-up period was 22–208 months.

2. Variables

Collected variables included patient age (years), hCG level of pre-evacuation (IU/L), gestational age (days), pathologic classification of molar pregnancy, lung nodule detected at or after evacuation, size and number of lung nodule, the outcomes of the patients including disease relapse and patient death, and the time to hCG level normalized spontaneously. For patients undergoing chemotherapy, other variables were collected, including hCG level before chemotherapy, FIGO score, chemotherapy regimen, chemotherapy cycles to achieve hCG normalization and failure to first-line chemotherapy.

3. Statistical analysis

Continuous variables were tested by Mann-Whitney U test and median test. The χ^2 test and Fisher's exact test were used to compare proportions. The relationship between variables and chemotherapy response was evaluated by logistic regression analysis. The alpha level or significance for all tests was set at 0.05. SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses.

RESULTS

Totally 1,323 patients with molar pregnancy were diagnosed and treated in our hospital during past 16 years. Among them, 53 (4.0%) patients met the inclusion criteria of our study. The size of lung nodule ranged from 0.8–2.5cm. Group 1 included 17 patients after excluding 3 patients who lost to follow-up during chemotherapy. Group 2 included 18 patients. All patients in group 1 and 2 achieved complete remission. Group 3 included 18 patients with hCG normalized spontaneously after excluding 4 patients lost to follow-up. Only one patient relapsed in group 1 and no patients died in present study.

The clinical characteristics of patients in three groups were summarized in **Table 1**. There are no significant differences for patient age, hCG level of pre-evacuation, gestational age at first evacuation, pathologic classification of molar pregnancy, detected time and size of lung nodule among three groups. The size of most lung nodules was small (≤1.7 cm), except for one patient with 2.5 cm nodule in group 2, who developed to GTN and achieved hCG normalization after 6 cycles of chemotherapy.

Unexpectedly, there were more chemotherapy cycles for achieving hCG normalization (5 cycles in group 1 vs. 3 cycles in group 2, p=0.000) and higher failure rate of first-line

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Table 1. The clinical characteristics of patients in three groups

Variables	Group 1 (n=17)	Group 2 (n=18)	Group 3 (n=18)	p-value
Age (yr)	26 (17–53)	29.5 (17–53)	31.5 (16–54)	0.369
hCG level of pre-evacuation (IU/L)	464,672.0 (50,138.0–2,004,065.0)	152,386.0 (1,000.0–1,000,000.0)	140,880.5 (14,812.9–431,000.0)	0.107
Gestational age (day)	74 (46–147)	71 (37–270)	69 (30–112)	0.111
Pathology of molar pregnancy				0.231
CHM	17	16	15	
PHM	0	2	3	
Detected time of lung nodule*				0.281
At evacuation	12	11	8	
After evacuation	5	7	10	
The largest diameter of lung nodule (cm)	0.6 (0.3–1.7)	0.6 (0.3–2.5)	0.65 (0.3–1.7)	0.946
The quantity of lung nodule				0.018†
Single	7	2	10	
Multiple	10	16	8	

Values are presented as median (range) or number.
CHM, complete hydatidiform mole; hCG, human chorionic gonadotrophin; PHM, partial hydatidiform mole.
*This variable means the number of patients whose lung nodule detected at evacuation or after evacuation; †The p-value for the difference of the quantity of lung nodule between group 2 and 3 was 0.012 (Fisher's exact test).

chemotherapy (58.8% in group 1 vs. 11.1% in group 2, p=0.005) (**Table 2** and **Fig. 1**) in group 1 than that in group 2, although patients in group 1 immediately accepted chemotherapy when lung nodule were detected. Our results suggest that too early chemotherapy does

Table 2. The clinical characteristics related with chemotherapy in group 1 and 2

Variables	Group 1 (n=17)	Group 2 (n=18)	p-value
Follow-up of lung nodule			0.102
Disappear	8	5	
Decrease	4	11	
Persistence	5	2	
hCG level before chemotherapy (IU/L)	9,763.0 (632.1–1,144,162.0)	1,764.0 (137.1–59,843.0)	0.320
FIGO prognosis score	2 (0–8)	2 (0–8)	0.833
First-line chemotherapy			0.603
Single reagent	16	15	
Multiple reagents	1	3	
Chemotherapy cycles	5 (3–10)	3 (1–6)	0.000
Failure of first-line chemotherapy	10	2	0.005
Occurrence of relapse	1	0	-
Occurrence of death	0	0	-

Values are presented as median (range) or number.
FIGO, International Federation of Gynecology and Obstetrics; hCG, human chorionic gonadotrophin.

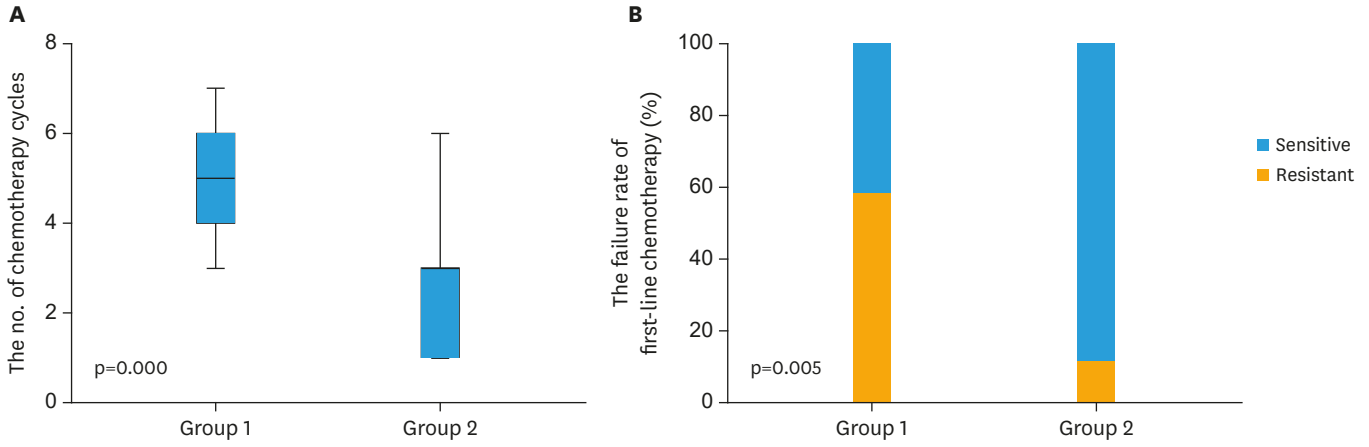

Fig. 1. The chemotherapy response for patients in group 1 and 2. (A) More chemotherapy cycles for achieving human chorionic gonadotrophin normalization were used in group 1 than that in group 2. (B) More failure rate of first-line chemotherapy in group 1 than that in group 2.

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Table 3. The response to chemotherapy for patients in group 1 and 2 by logistic regression analysis

Variables	Chemotherapy cycles		Failure to first-line chemotherapy	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.03 (0.97–1.09)	0.349	1.01 (0.96–1.07)	0.644
Gestational age	1.01 (0.99–1.03)	0.205	0.99 (0.98–1.01)	0.455
Detected time	2.18 (0.51–9.33)	0.292	0.52 (0.11–2.45)	0.407
Size	0.60 (0.14–2.56)	0.494	0.56 (0.11–2.93)	0.491
Quantity	1.71 (0.37–7.85)	0.494	0.30 (0.06–1.42)	0.128
hCG level	1.00 (1.00–1.00)	0.057	1.00 (1.00–1.00)	0.722

CI, confidence interval; hCG, human chorionic gonadotrophin; OR, odds ratio.

not improve patient's outcome. Furthermore, we analyzed the relationships between the variables and chemotherapy response by logistic regression analysis, and found that patient age, gestational age, detected time, number and size of lung nodule, and hCG level had no significant influence on chemotherapy response (**Table 3**).

In our series, the hCG level of all patients in group 3 declined to normal within 6 months. During follow-up period, lung nodules of 9 patients (0.3–1.3 cm) in group 3 disappeared spontaneously according lung CT scan, accounting for 25% of all patients who initially selected observation (group 2 and 3). The actual proportion might be higher since 6 patients in group 3 refused radiologic examinations after hCG normalization. The ratio of single nodule in these 9 patients was 66.7% (6/9). The proportion of single nodule was significantly higher in group 3 than that in group 2 (2/18 vs. 10/18, p=0.012). These data suggest that the patients with single lung nodule are more easily to achieve lung nodule regression and hCG nominalization spontaneously than those with multiple nodules. Except for lung nodule number, there were no differences of other variables between group 2 and 3, as shown in **Table 1**.

DISCUSSION

The management of molar pregnancy patients with lung nodule differs among separate GTD centers in the world [2,10-16]. European Organization for Treatment of Trophoblastic Diseases (EOTTD) recommended that the indications of chemotherapy included lung nodule >2 cm (smaller lesions may spontaneously regress) [11,12]. Gynecologic oncologists in Japan do not recommended lung CT if chest X-ray is negative for GTD patients, because small lung nodules detected by CT scan has no clinical significance [16]. But, there is still no consensus on the management for molar pregnancy with lung nodule in various areas including China, and chemotherapy is sometimes prescribed once lung nodule is detected by chest X-ray, even by CT scan. It is a challenge for professional working with molar pregnancy with lung nodule. Accurate evaluation is vital for successful treatment of GTN. Delayed diagnosis of GTN could increase the FIGO risk score as the “interval between antecedent pregnancy and start of chemotherapy” is included in the current FIGO/WHO Prognostic Scoring System, which would result in treatment with multi-drugs regimen for patients due to delayed initiation of treatment [2,7]. To assess the risk mentioned above, we compared the clinical outcome between group 1 and 2. We found that FIGO score and the rate of patients who received multiple reagents in the first-line chemotherapy were similar in both groups. Furthermore, the total number of chemotherapy cycles and the failure rate of first-line chemotherapy were not reduced in the patients with chemotherapy immediately, and even significantly higher than those with delayed chemotherapy. Due to the limitations of retrospective study, the different chemotherapy response between groups and its intrinsic mechanism needs to

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be further explored by a prospective randomized control study. In addition, patients who received hCG surveillance in group 2 and 3 presented favorable prognosis in our study, although some of them were ultimately diagnosed as GTN according to FIGO diagnostic criteria. Present study firstly reported a case series of the management of a relatively large number of molar pregnancies with lung nodule. Our data suggest that lung nodule alone couldn't be an indication of chemotherapy and early chemotherapy does not improve the prognosis of molar pregnancy patients with lung nodule. Thus, observation rather than chemotherapy is a preferred option for molar pregnancy with lung nodule until FIGO 2015 diagnostic criteria are met.

Substantial evidences suggested pulmonary nodules of molar pregnancy should be differentiated from trophoblastic embolisms and other benign status [5,6]. As early as 1968, Ring [17] put forward the concept of benign metastasizing hydatidiform moles. He pointed out that the shadow of lung might be due to a reaction of lung tissue around embolic trophoblast, but not of necessity due to trophoblast invading maternal lung tissue. Roberts et al. [18] also proposed that embolic cells might be inhibited by the activation of local thrombotic and inflammatory cascades. Even more, Hertz et al reported that GTN had a tendency towards spontaneous regression because the trophoblast was a foreign material and would be rejected via maternal immune factors [19]. In present study, we found that lung nodules (0.3–1.3 cm) of 9 patients in group 3 regressed spontaneously without any intervention, and the hCG level of all patients in group 3 (18/53) was normalized spontaneously within 6 months after evacuation. Our results supported the speculation of benign "metastasis" or trophoblastic emboli in some molar pregnancy [18-20]. Follow-up might be a suitable option for managing the molar patients with lung nodule, before the criteria of GTN is met. In addition, 27.8% (5/17) patients in group 1, 11.1% (2/18) in group 2 and 25.0% (3/12) in group 3 showed persistent lung nodules, which might represent the benign status of lung, such as lymph nodes or old granulomas [6,21]. Or rather, abnormal radiologic findings may temporarily persist after clinical improvement and hCG normalization in GTN [22]. Furthermore, we found that the proportion of single lung nodule accounted for 11.1% (2/18) of patients in group 2 and 55.6% (10/18) of patients in group 3, the difference was significant (p=0.012). And the single nodule accounted for 66.7% in 9 patients whose lung nodule regressed spontaneously. Our results suggest that hCG surveillance is safe for molar pregnancy patients with lung nodule, especially with single nodule, as long as they don't meet FIGO diagnostic criteria for GTN.

There is an ongoing debate regarding the role of pulmonary radiologic examination at or after evacuation of molar pregnancy. In 2015, The EOTTD [12] reached a formalized consensus on management of GTDs. But for the statement of the uselessness of investigations to diagnose metastases in case of hydatidiform mole, there were still no agreement to be reached even after two rounds of rating. Moreover, the opinions of different societies of trophoblastic diseases differ on this matter. The European society didn't recommend baseline chest X-ray for patients with suspected or confirmed hydatidiform mole [11,23], while Northern American society recommended pre-evacuation or baseline post-evacuation chest X-ray for hydatidiform mole in 2002 and 2004 [24,25]. In the present study, 60 (4.5%) patients with hytidiform mole presented with lung nodule at or after evacuation. This ratio might be underestimated because not all patients with molar pregnancy accepted pulmonary radiologic examination. Due to the various possibilities and the safety for observation of the small lung nodule, we supported that pulmonary radiologic detection might not be obliged at or after evacuation of molar pregnancy.

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