

# Pulmonary deportation of hydatidiform mole: a 12-year, single tertiary center experience in China

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## Abstract

**Background:** Pulmonary deportation of hydatidiform mole is an exceedingly rare entity. The underlying mechanisms and proper management strategies remain unclear based on sporadic case reports over the past six decades. This study aimed to investigate the clinical features and rational treatment of patients with benign molar pregnancies with pulmonary deportation based on our experience.

**Methods:** Medical records of 20 cases of hydatidiform mole with pulmonary deportation were retrospectively reviewed at Peking Union Medical College Hospital from November 2006 to May 2019. The detailed information of all patients was recorded and analyzed. Patients were divided into different groups according to their characteristics and Mann-Whitney *U* test was used to compare the duration to achieve a normal  $\beta$ -human chorionic gonadotrophin ( $\beta$ -hCG) level after the first evacuation among groups.

**Results:** Initial pulmonary computed tomography scans showed suspected bilateral, left and right chest deportation of hydatidiform mole in 12, four, and four patients, respectively, with the maximum nodular diameter ranging from 0.6 to 1.2 cm. Ten patients achieved lesion resolution while the remaining ten patients achieved decreases in the size of their pulmonary lesions. The median duration to achieve a normal  $\beta$ -hCG level after the first evacuation was 15.5 (13.0, 21.9) weeks. There was no significant difference in the duration to achieve a normal  $\beta$ -hCG level after the first evacuation between two groups based on age ( $\geq 40$  years *vs.*  $< 40$  years: 15.8 [12.2, 21.5] weeks *vs.* 15.5 [12.9, 23.0] weeks,  $Z = 0.094$ ,  $P = 0.925$ ), type of antecedent mole (partial mole *vs.* complete mole: 15.2 [12.5, 27.4] weeks *vs.* 15.9 [12.9, 21.5] weeks,  $Z = 0.165$ ,  $P = 0.869$ ), distribution of pulmonary nodules (bilateral lungs *vs.* unilateral lung: 15.2 [12.8, 22.5] weeks *vs.* 15.9 [13.2, 22.2] weeks,  $Z = 0.386$ ,  $P = 0.700$ ), maximum size of pulmonary nodules ( $> 0.5$  cm *vs.*  $\leq 0.5$  cm: 13.0 [11.3, 17.2] weeks *vs.* 16.0 [14.5, 23.8] weeks,  $Z = 1.815$ ,  $P = 0.070$ ), and number of uterine evacuations (once *vs.* twice or three times: 15.0 [13.0, 16.3] weeks *vs.* 16.0 [12.8, 23.9] weeks,  $Z = 0.832$ ,  $P = 0.405$ ). The post-molar cohort was followed up for 17 to 139 months, and no gestational trophoblastic neoplasia was observed.

**Conclusions:** No surgeries other than uterine evacuation and no chemotherapy regimens are recommended for such patients if they achieve satisfactory decreases in the level of hCG and gradual decrease or disappearance of pulmonary deportation nodules. Patients should be informed about the necessity of long-term follow-up. More collaborative international studies on this exceedingly rare condition may guide decisions regarding optimal management strategies.

**Keywords:** Hydatidiform mole; Pulmonary deportation; Human chorionic gonadotrophin; Computed tomography

## Introduction

Gestational trophoblastic disease (GTD) includes a spectrum of clinical entities, from benign hydatidiform mole (complete or partial) to malignant forms under the term gestational trophoblastic neoplasia (GTN). The use of prophylactic chemotherapy for molar pregnancies is controversial in the literature, and the greatest clinical challenges are the early detection of the possible progression to GTN and the decision to initiate chemotherapy after evacuation of the molar pregnancy.<sup>[1]</sup> Post-molar

follow-up involves the serial detection of the tumor-specific quantitative marker  $\beta$ -human chorionic gonadotrophin ( $\beta$ -hCG). Imaging tests, including ultrasonography, chest X-ray, and computed tomography (CT), may also be performed when metastatic disease is suspected. Early in 1963, nine cases of benign hydatidiform mole with deportation to the vagina and lungs diagnosed by pathology were reported by Peking Union Medical College Hospital (PUMCH).<sup>[2]</sup> Over the past half century, case reports of pulmonary deportation in patients with hydatidiform mole have been exceedingly rare, and thus,

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the underlying mechanisms and proper management strategies remain unclear. This 12-year retrospective review of 20 patients was conducted to investigate the clinical features and rational treatment for this unique group of patients.

## Methods

### Ethical approval

This study was approved by the PUMCH Ethics Committee (No. S-K711) and conducted in accordance with the *Declaration of Helsinki*. All participants provided written informed consent.

### Study design and population

This study was conducted among consecutive patients with pulmonary molar deportation who were first treated or referred to the Chinese Gestational Trophoblastic Disease Reference Center at PUMCH. Patients with either a confirmed histopathologic diagnosis of molar pregnancy after evacuation at a local hospital or a suspected diagnosis of molar pregnancy who underwent evacuation at our center were identified from center registries. This study included patients who had suspected intrapulmonary micrometastases based on the results of the chest CT scan after evacuation that spontaneously decreased in size, with normalized  $\beta$ -hCG levels during post-molar follow-up without any chemotherapy or further surgical management. One patient received positron-emission tomography (PET)-CT evaluation at the first visit to PUMCH. A repeat uterine curettage is generally indicated in patients with incomplete previous evacuation. Patients continued  $\beta$ -hCG surveillance after achieving a normal  $\beta$ -hCG level until May 2019 unless they experienced a relapse. Complete remission was defined as three normal weekly  $\beta$ -hCG values followed by six normal monthly  $\beta$ -hCG values and then normal  $\beta$ -hCG values every 6 months or 1 year. The reference value for  $\beta$ -hCG was less than 2 mIU/mL when measured at PUMCH with a Beckman-Coulter Unicel Dxl 800 system (Beckman Coulter Inc, Brea, CA, USA). Lung CTs were repeated every 4 to 8 weeks before normalization of the  $\beta$ -hCG level was achieved and every 3 to 6 months after that until the lung lesion disappeared or decreased in size along with normal  $\beta$ -hCG levels. The CT images were examined and compared with the previous results by the same group of radiologists. All clinical records were complete and available for review.

### Statistical analysis

Patients' detailed clinical characteristics were reported and analyzed. The continuous variables with non-normal distribution were presented as median (inter-quartile range). Categorical variables were presented as numbers. The durations to achieve a normal  $\beta$ -hCG level after the first evacuation were compared according to patient age, type of antecedent mole, distribution of pulmonary nodules, maximum size of pulmonary nodules and number of uterine evacuations using Mann-Whitney *U* test. Statistical analyses were performed using SPSS 26.0 (SPSS, Inc., Chicago, IL, USA). A  $P < 0.05$  was considered statistically significant.

## Results

### General patient information and clinical features

From November 2006 to May 2019, 20 patients were identified as pulmonary deportation of hydatidiform mole and included in this study at PUMCH. Their demographic data and other characteristics are listed in Table 1. Among these, nineteen patients in this group were referred from local hospitals in China, and some of the data especially chest X-ray results from local hospitals were absent when these patients were transferred to PUMCH.

Among this patient group, the median age was 29.0 (27.0, 36.5) years, the median gravidity was 2 (2, 3), and the median parity was 1 (0, 1). The median gestational age at molar pregnancy diagnosis in 14 patients was 10.3 (8.6, 12.6) weeks, and the median  $\beta$ -hCG level prior to uterine evacuation in ten patients was 267,064.5 (123,406.5, 619,346.5) mIU/mL. Relevant information was missing in the other patients. Fourteen complete moles and six partial moles were identified by immunohistochemical analyses. Pulmonary CT performed at their first visit to PUMCH showed suspected bilateral, left and right chest deportation in 12, four, and four patients, respectively, with the maximum measurable nodular diameter ranging from 0.6 to 1.2 cm. The indication of repeat curettage was mainly evidence of retained tissue. The number of uterine evacuations needed before  $\beta$ -hCG normalization was one in seven patients, two in eight patients (seven with mole residue on second curettage, one with necrotic decidua) and three in five patients (four with mole residue on third curettage, one with necrotic decidua). The median time to achieve the first normal  $\beta$ -hCG measurement after the first evacuation was 15.5 (13.0, 21.9) weeks. The median time to achieve lesion resolution on chest CT after the first evacuation in ten patients was 29.8 (17.3, 49.9) weeks. The median time to achieve lesion resolution on chest CT after the first normal  $\beta$ -hCG measurement was 11.5 (5.3, 35.4) weeks in these ten patients. The remaining ten patients achieved decreased pulmonary lesions compared to those observed on the previous chest CT scans during the ongoing follow-up. This post-molar cohort was followed up for 17 months to 139 months after  $\beta$ -hCG normalization, and none of the patients developed GTN.

### Analysis of factors associated with the duration to achieve a normal $\beta$ -hCG level after the first evacuation

As displayed in Table 2, there was no significant difference between the durations to achieve a normal  $\beta$ -hCG level after the first evacuation between the two groups based on age ( $\geq 40$  years *vs.*  $< 40$  years: 15.8 [12.2, 21.5] weeks *vs.* 15.5 [12.9, 23.0] weeks,  $Z = 0.094$ ,  $P = 0.925$ ), type of antecedent mole (partial mole *vs.* complete mole: 15.2 [12.5, 27.4] weeks *vs.* 15.9 [12.9, 21.5] weeks,  $Z = 0.165$ ,  $P = 0.869$ ), distribution of pulmonary nodules (bilateral lungs *vs.* unilateral lung: 15.2 [12.8, 22.5] weeks *vs.* 15.9 [13.2, 22.2] weeks,  $Z = 0.386$ ,  $P = 0.700$ ), maximum size of pulmonary nodules ( $> 0.5$  cm *vs.*  $\leq 0.5$  cm: 13.0 [11.3, 17.2] weeks *vs.* 16.0 [14.5, 23.8] weeks,  $Z = 1.815$ ,  $P = 0.070$ ) and number of uterine evacuations (once *vs.*

**Table 1: Clinicopathologic features of 20 cases of hydatidiform mole with pulmonary deportation in PUMCH (until May 2019) (n = 20).**

Case No.	Age (years)	Weeks before the first evacuation	β-hCG before the first evacuation (mIU/mL)	Type of antecedent mole (complete/partial)	Duration until the first visit to PUMCH (weeks)	Pulmonary lesion location on CT at PUMCH (bilateral/left/right)	Maximum pulmonary lesion size on CT at PUMCH (cm)	Duration between the first evacuation and β-hCG regression (weeks)	Duration between the first evacuation and pulmonary lesion regression or shrinkage (weeks)	Times of evacuation, n	Follow-up duration after β-hCG regression (months)
1	37	6.1	–	P	13.6	B	≤0.5	40.4	S	2	139
2*	27	–	–	C	6.1	B	≤0.5	23.7	67.4	2	123
3	22	–	–	P	10.2	B	≤0.5	15.3	S	2	110
4	33	12.9	71,000	C	14.1	L	≤0.5	42.9	S	2	107
5	49	8.6	–	C	7.6	L	≤0.5	16.6	36.9	1	106
6	28	12.2	175,813	C	3.7	R	1.2	11.1	18.6	3	104
7	26	10.2	–	C	8.7	B	≤0.5	14.7	S	2	102
8	30	10.1	220,000	C	6.0	B	≤0.5	12.7	17.0	3	102
9	27	12.7	3470	P	2.5	B	0.6	12.9	13.9	2	101
10	50	7.0	–	P	7.9	B	1.1	11.3	17.6	2	100
11	35	12.9	264,129	C	5.7	B	1.1	20.7	S	3	100
12	25	–	–	C	13.3	B	≤0.5	16.3	S	1	96
13	26	–	–	C	8.0	L	0.8	13.0	52.1	1	74
14†	27	12.5	755,195	C	0	R	1.1	16.0	47.7	2	70
15	41	10.9	–	P	17.3	B	≤0.5	23.1	38.4	3	54
16‡	50	10.3	390,000	P	4.0	B	≤0.5	15.0	22.7	1	51
17§	36	9.9	1,150,000	C	2.1	B	≤0.5	11.4	S	1	49
18	28	–	483,498	C	27.0	R	≤0.5	15.7	S	1	49
19	34	8.6	270,000	C	7.6	L	≤0.5	13.9	S	1	23
20	28	–	–	C	14.3	R	≤0.5	24.0	S	3	17

\* A plateau of β-hCG level lasted for two weekly measurements and then declined to a normal level in this patient. † The patient started her first visit at PUMCH. ‡ PET-CT at PUMCH showed multiple nodule-like lesions in the bilateral lungs but no abnormal increase in FDG metabolism. § A slight increase in the β-hCG level lasted for two weekly measurements and then returned to normal. || The patient had already achieved β-hCG normalization, and the lung lesions on pulmonary CT showed a significant decrease before the first visit to PUMCH. PUMCH: Peking Union Medical College Hospital; β-hCG: β-human chorionic gonadotrophin; CT: Computed tomography; P: Partial; C: Complete; B: Bilateral; L: Left; R: Right; S: Shrinkage; PET: Positron emission tomography; FDG: Fluorodeoxyglucose; –: Not available.

**Table 2: The duration to achieve normal β-hCG levels in patients with pulmonary deportation of hydatidiform mole after the first evacuation according to different characteristics.**

Characteristics	n	Duration (weeks)	Z	P
Age			0.094	0.925
≥40 years	4	15.8 (12.2, 21.5)		
<40 years	16	15.5 (12.9, 23.0)		
Type of antecedent mole			0.165	0.869
Partial mole	6	15.2 (12.5, 27.4)		
Complete mole	14	15.9 (12.9,21.5)		
Distribution of pulmonary nodules			0.386	0.700
Bilateral lungs	12	15.2 (12.8, 22.5)		
Unilateral lung	8	15.9 (13.2, 22.2)		
Maximum size of pulmonary nodules			1.815	0.070
>0.5 cm	6	13.0 (11.3,17.2)		
≤0.5 cm	14	16.0 (14.5, 23.8)		
Times of evacuation			0.832	0.405
Once	7	15.0 (13.0, 16.3)		
Twice or three times	13	16.0 (12.8, 23.9)		

Duration data are shown as median (Q<sub>1</sub>, Q<sub>3</sub>). β-hCG: β-human chorionic gonadotrophin.

twice or three times: 15.0 [13.0, 16.3] weeks vs. 16.0 [12.8, 23.9] weeks, Z = 0.832, P = 0.405).

**Discussion**

Till now, limited cases of spontaneous regression of molar pregnancy with small lung nodules have been reported. The management of this condition is still posing a great challenge for professionals working on this rare issue. Obviously, the ultimate goal is the cure for the most

patients possible with least injury or toxicity. Our experience in treating the largest cohort of such patients might help in recognizing and managing this condition.

The most peculiar biologic characteristic of trophoblasts is their ability to erode maternal tissue. Even in normal pregnancies, trophoblasts have the potential for invasion and metastasis. The deportation of large numbers of detached syncytial cells to the maternal lung has been studied extensively ever since the first report by Schmorl,<sup>[3]</sup>

who described this phenomenon in women dying from eclampsia.

Although chest CT scans are recommended in the diagnosis of lung metastasis owing to its superior sensitivity for detecting lung lesions,<sup>[4]</sup> the clinical significance of so-called “micrometastases” on CT scans, which may be too small to be detected on chest X-rays, remains uncertain.<sup>[5]</sup> It has long been debated whether these are truly malignant pulmonary metastases or whether they represent only lung granulomata that are the results of deportation. The concept of benign metastases or the deportation of hydatidiform moles has been discussed for over 50 years, beginning in 1959 when Jacobson and Enzer reported the first case in the scientific literature.<sup>[6]</sup> Such cases often show simultaneous regression of suspected distant metastases (ie, lung, vagina) from a histologically proven benign hydatidiform mole after uterine evacuation along with delayed normalization of  $\beta$ -hCG levels. In 1963, Lin and Lian<sup>[2]</sup> from PUMCH reviewed nine cases with vaginal or pulmonary deportation of hydatidiform moles. In 1972, Ring<sup>[7]</sup> reported two cases with histologically proven pulmonary deportation of hydatidiform moles through pulmonary biopsy or wedge resection. In 2010, Knol *et al*<sup>[8]</sup> identified morphologic regression on pulmonary CT scans instead of on the previously used chest X-rays in a 49-year-old woman with complete hydatidiform mole after hysterectomy and suggested that a hysterectomy may be a curative option for such patients. Recently, Japanese researchers reported two cases of spontaneous regression of lung metastases without treatment, defining these occurrences as spontaneous regression of post-molar trophoblastic neoplasms possibly due to immune stimulation.<sup>[9]</sup> In this study, all 20 patients achieved complete hydatidiform mole remission without any chemotherapy or other invasive manipulation beyond uterine evacuation. In contrast to distant metastasis from an invasive mole, which is classified as GTN, that from an essentially benign hydatidiform mole does not possess unlimited growth or proliferation potential and therefore lacks the capacity to become lethal. The results from the positron emission tomography-computed tomography (PET-CT) scans of patient 16 in our study may support this notion. Although the patient’s pulmonary CT did show bilateral micrometastases, the PET-CT scans were negative for any hypermetabolic lesion, indicating that the micrometastases were actually lung granulomata with necrosis or bleeding.<sup>[10]</sup> From a clinical point of view, the term metastasis is used inappropriately for this unique group of patients, and deportation is a more precise description of this benign metastatic pattern, considering the fact that the discovery of placental elements in pulmonary tissue is not unique to molar pregnancies.<sup>[11]</sup> Our retrospective cohort study may add more evidence to support the concept of the deportation of benign hydatidiform mole rather than the spontaneous regression of certain kinds of malignancies.

Our cohort reported the greatest number of such patients and found that neither the location nor the size of pulmonary deportation nodules was significantly associated with the time for  $\beta$ -hCG declination. More research is needed to explain the clinical significance of pulmonary

lesions in this particular group of patients and to determine whether their prognosis might vary depending on the location or size of the lesions. The maximum measurable diameter on PUMCH pulmonary CT in this study was 0.6 to 1.2 cm, while the remaining visible lesions were usually no more than 0.5 cm. Only a few patients with molar pregnancy accepted chest X-ray at local hospitals and none of them reported abnormal chest X-ray results when transferred to PUMCH. A previous study reported that the maximum diameter of lung lesion was 2 cm on chest X-ray with pathologic evidence of hydatidiform mole after pulmonary wedge resection.<sup>[7]</sup> These lung lesions took longer to disappear than it took for the  $\beta$ -hCG level to normalize. The median interval from the time to achieve the first normal  $\beta$ -hCG measurement to the time to achieve elimination or shrinkage of the lung lesions on pulmonary CT was 11.5 (5.3, 35.4) weeks. Based on the fact that chest CT alone cannot determine the diagnosis of post-molar GTN,<sup>[12]</sup> it seems appropriate to maintain close hCG surveillance of these patients as long as they experience satisfactory normalization of their hCG levels even when they have residual pulmonary lesions.

The hCG is the most commonly used and non-comparable serum biochemical parameter in the diagnosis and monitoring of GTDs worldwide. In patients with pulmonary deportation of hydatidiform mole, the serum hCG level is an essential marker used to adjust the monitoring strategy for these patients at the risk of developing post-molar GTN. During post-molar surveillance, we found that in patient 2, the  $\beta$ -hCG level plateaued for 2 weeks and then normalized, while in patient 17, the  $\beta$ -hCG level slightly increased for 2 weeks and then normalized. Since they did not meet the diagnostic criteria of post-molar GTN or persistent trophoblastic disease based on 2000 International Federation of Gynecology and Obstetrics guideline, these patients were not treated with chemotherapy. Although the  $\beta$ -hCG levels failed to decrease to normal level within 6 months, the values of patients 1 and 4 were 17.2 and 24.2 mIU/mL at 6 months after evacuation respectively with the tendency of continuous falling. These two patients selected hCG surveillance only until hCG level declined to a normal level spontaneously. An average time of 18.5 weeks and a maximum time of 42.9 weeks were needed to achieve the first normal  $\beta$ -hCG measurement in our study, which were much longer than the intervals reported previously.<sup>[13]</sup> Therefore, close follow-up for a longer period was needed according to the reported increased risk of post-molar GTN that is associated with a slow decrease in the hCG level after molar evacuation; there is a greater than 120-fold increase in risk when the time to the normalization of the hCG level increases from 4 to 13 weeks.<sup>[14]</sup> Because delay in treatment until post-molar GTN defined based on hCG plateau over 3 weeks or hCG increase over 2 weeks did not affect outcomes of those with high risk of post-molar GTN regarding uterine perforations or treatment failures,<sup>[15]</sup> we found that informing these patients about their future risk of GTN and the necessity of a long follow-up period is essential for relieving their anxiety and improving their compliance.

Uterine evacuation and expectant management instead of hysterectomy, the excision of pulmonary lesions or

chemotherapy were implemented in our cohort, and no patients experienced relapse during the follow-up period (until May 2019). Although variables such as maternal age over 40 years and a longer interval to achieve an undetectable  $\beta$ -hCG level are associated with an increased risk of GTN, the benefits of prophylactic chemotherapy and hysterectomy are controversial.<sup>[16,17]</sup> In contrast to Knol's point of view,<sup>[8]</sup> we believe that hysterectomy is not a necessary treatment for patients over 40 years of age (patients 5, 10, 15, and 16), as it showed no obvious benefits in patients with pulmonary deportation. The results of our study favored reducing the use of unnecessary toxic therapies or invasive manipulation after balancing the future risk of GTN with patient safety.

A limitation of the current study is that this particular type of patients is exceedingly rare in the clinical setting. Moreover, pre-treatment serum hCG and enlarged uterus may have a potential influence on the risk of GTN or the time interval to  $\beta$ -hCG regression, but the information is partially missing because most patients are transferred from other hospitals.

In conclusion, the ultimate goal of our retrospective cohort study, which had the largest number of hydatidiform molar pregnancy patients with pulmonary deportation to date, was to improve the patient outcomes by improving the clinical identification of this extremely rare entity, reducing the use of unnecessary toxic and invasive therapies, and developing appropriate treatment and follow-up strategies. We encourage more collaborative international studies on this rare condition, which will enable us to draw more meaningful conclusions regarding the optimal management of these patients.

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### Conflicts of interest

None.

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