Radiologic Features and Treatment Outcomes of Pulmonary Metastasis in Gestational Trophoblastic Neoplasia

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Objective: *To evaluate the radiologic patterns and treatment outcome of pulmonary metastasis in patients with gestational trophoblastic tumor (GTT).*
Material and Method: *The medical records and chest films of GTT patients treated at Chiang Mai University Hospital between January 1998 and June 2003 were reviewed.*
Results: *There were 85 GTT-patients in the study period. 32 cases (37.6%) had pulmonary metastasis diagnosed with chest X-rays. The most common radiologic pattern was well defined nodule. The radiologic features of patients who had lung metastases alone were not significantly different from those who had associated metastases in other organs. 27 patients (84.3%) received multiple chemotherapy and 6 required more than one regimen. The mean number of chemotherapy was 7 cycles (range 3-23). Adjuvant surgery consisted of hysterectomy (11), salpingo-oophorectomy (1), thoracotomy (2), and craniotomy (1). Four patients received whole brain irradiation for brain metastases. Among 10 patients with lung metastasis alone, 8 (80%) attained complete remission, the remaining 2 patients were lost to follow-up. Among 22 patients with associated multiple organ metastases, 16 (72.7%) had complete remission, 2 died from diseases, 4 were lost to follow-up.*
Conclusion: *The most common radiologic pattern of pulmonary metastasis in GTT patients was well-defined multiple lung nodules. The radiologic features of patients who had lung metastases alone were not significantly different from those who developed metastases in other organs.*

Keywords: *Trophoblastic disease, Pulmonary metastasis, Treatment, prognosis*

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Pulmonary parenchyma is the most common extrauterine site of metastasis in patients with gestational trophoblastic tumor (GTT)[1]. Various radiologic patterns of lung metastasis have been described, i.e. pleural effusion, alveolar, embolic and discrete round density[2-4]. The clinical presentations and patterns of pulmonary involvement in GTT patient are different among centers. In Saudi Arabia, Brakri et al[5] reported that their GTT patients with lung metastasis had greater than 50% opacification of the lungs, pleural effusion and more than 10 pulmonary metastasis sites in 33%, 48% and 43% respectively. In contrast, in the United states, GTT patients with pulmonary metastasis generally have small nodules on chest roentgenogram and infrequently present with prominent respiratory symptoms[6]. Thus far, the clinical features of pulmonary metastases has not been studied in Thailand. The present study was accordingly conducted to evaluate the radiologic features and clinical outcome of pulmonary metastases in patients with GTT.

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Material and Method

From January 1998 through June 2003, the medical records of GTT patients with pulmonary metastasis receiving treatment at Chiang Mai University Hospital were reviewed for clinical characteristics and treatment outcome. Diagnosis of

postmolar GTT was primarily based on 2 consecutive rising (> 10%) or 3 consecutive plateau level (< 10%) of weekly beta-human chorionic gonadotropin (β-hCG) titers after termination of molar pregnancy. After any type of pregnancy, GTT was also diagnosed when there was elevated β-hCG titer with clinical symptoms or radiographic evidence of metastatic disease, or histologic evidence of choriocarcinoma.

After diagnosis of GTT, a thorough metastatic work up was carried out which included clinical examination, hematologic studies, chest film, pelvic and abdominal ultrasonography. Other imaging studies, i.e. MRI or CT scan of the abdomen, chest and brain were performed when indicated. Pulmonary metastasis were diagnosed when there was radiologic evidence on the chest film. All chest roentgenograms were reviewed by one of the authors (JE). The number, the largest site, the main location, the laterality and radiological features of the metastatic lesions were recorded. Comparison of pulmonary features in patients who pulmonary metastasis alone with patients who had multiple metastasis organ were performed by using Chi-square and Fisher-exact test. CT-scan of the brain was performed in patients who had pulmonary metastases.

Patients with GTT were classified into 3 categories, i.e. non-metastatic, low- risk metastatic and high- risk metastatic based on the prognostic factors devised by Hammond[6]. Patients in the low- risk group were treated with either single agent methotrexate or actinomycin D, while those in the high-risk group were treated with combined chemotherapy of etoposide, methotrexate, and actinomycin D (EMA). The interval of chemotherapy was 2-3 weeks depending on the patients compliance and toxicity. Whole brain irradiation of 30 Gray was administered in patients with brain metastases. Surgical intervention including hysterectomy, thoracotomy and craniotomy were performed when indicated i.e. removal of chemotherapy resistant foci or control hemorrhage in emergency cases.

Serum β-hCG and hematologic profile were determined before each course of chemotherapy. Remission was diagnosed after 3 consecutive weekly β-hCG levels were within normal range. Additional 2 and 3 courses of chemotherapy were given after the first normal β-hCG level in low and high- risk groups respectively. After remission, β-hCG levels were evaluated every 2 weeks for 3 months, every month for 3 months, every other month for 6 months and every 6 months thereafter. Chest-X-ray was determined every 6 months when deemed necessary in patients with lung metastasis. Temporary contraceptions, usually with birth-control pills were advised for one year after completion of chemotherapy. Data were collected and analyzed by frequency table with number and percentage.

Results

During the study period, 85 patients were diagnosed as GTT, in which 32 cases (37.6%) had associated pulmonary metastasis. The mean age of these 32 patients was 30 with a range of 21-55 years. The median interval from antecedent pregnancy to diagnosis of GTT was 24 months with a range of 1-288 months. The median β-hCG level was 106,537 IU/L with a range of 140-2,557,500 IU/L. The clinical features are shown in Table 1. The most common antecedent pregnancy was molar pregnancy accounting for 43.8% followed by term pregnancy (31.3%) and abortion (25%). Only 9 patients (28.1%) presented with pulmonary symptoms, i.e. hemoptysis (4), chest pain (3), and dyspnea (2). Although the symptoms of hemoptysis and dyspnea were severe, the clinical condition improved after treatment with chemotherapy. No respirator support was needed. Two patients had no symptoms at diagnosis. The remaining 21 (65.6%) patients presented with signs and symptoms of other

Table 1. Clinical characteristics of 32 GTT patients with pulmonary metastasis

Characteristics	Number (%)
Antecedent pregnancy	
Molar pregnancy	14 (43.8)
Term pregnancy	10 (31.3)
Abortion	8 (25.0)
Presenting signs & symptoms	
Pulmonary symptoms	9 (28.1)
Hemoptysis	4 (12.5)
Chest pain	3 (9.4)
Dyspnea	2 (6.2)
Uterine bleeding	10 (31.3)
Pelvic pain	5 (15.6)
Peritonitis	3 (9.4)
Weakness	1 (3.1)
Hematuria	1 (3.1)
Vaginal discharge	1 (3.1)
No symptom	2 (6.3)
Histology	
Choriocarcinoma	15 (46.9)
Unknown	17 (53.1)

systems. Thoracotomy was performed to resect lung nodule in one patient without prior test of for serum hCG. Metastasis GTT was diagnosed when the pathological report revealed choriocarcinoma. Histologic evidence of choriocarcinoma was identified in 15 (46.9%) patients. Of the 30 patients undergoing brain CT scanning, 4 (13.3%) had associated brain metastasis. Ten (31.3%) patients developed lung metastasis alone. Eleven patients also had associated persistent GTT in the uterus. The remaining 7 patients had metastasis in the vagina (2), ovary (1), liver (2), spleen (1), pelvis (1), kidney (1), bladder (1), and ureter (1). One and 2 patients had 4 and 3 metastatic sites respectively.

Radiologic features of pulmonary metastases are shown in Table 2. Fifteen (46.9%) patients had more than 10 metastatis foci in both lungs, and the largest size was 8 cm. The main location was the lower lung. Nearly two-thirds of lung metastasis were bilateral. The most common feature of metastasis was well-defined multiple nodules accounting for 75%. There were no statistically significant differences in terms of number, maximum size, main location, laterality and pattern of metastasis between patients who had pulmonary metastasis alone and who had multiple organ involvement.

Five patients were treated with single agent methotrexate (3), actinomycin D (1), and etoposide (1). The remaining 27 patients were treated with a combination of chemotherapy of etoposide, methotrexate and actinomycin D (EMA regimen). Of these 27 patients, 6 (22%) developed drug resistance and required salvage regimen. The mean number of chemotherapy was 7 cycles with a range of 3-23 cycles.

Sixteen patients underwent surgical intervention including endometrial curettage (2), hysterectomy (11), salpingo-oophorectomy (1), thoracotomy (2) and craniotomy (1). One patient underwent thoracotomy after hysterectomy.

Four patients with associated brain metastasis were additionally treated with whole brain irradiation. Of these 4 patients, 2 died of disease. The first one underwent thoracotomy to resect chemoresistant lung nodule followed by chest irradiation and multiple chemotherapy regimens but failed. She subsequently developed brain metastases 3 years after

Table 2. Radiological features of pulmonary metastasis related to the number sites of spreading (n = 32)

Radiological Features	Pulmonary metastasis alone (n = 10)	Pulmonary metastasis plus other site (n = 22)
Number of metastases		
1	3	4
2-5	-	5
6-10	2	3
> 10	5	10
Maximum size of metastases (mm)		
< 10	1	8
10-20	3	9
21-40	2	2
> 40	10	22
Main locations		
Upper	1	3
Middle	1	5
Lower	4	5
Generalized diffusion	4	9
Bilateral lesion	8	12
Unilateral lesion	2	9
Pattern of metastases		
Well-defined nodule	9	16
Ill-defined nodule	1	1
Pleural effusion	-	3
Mediastinal node	-	1
Atelectasis	-	1

the diagnosis of GTT or 1 year after thoracotomy. Overall, she received 6 regimens of chemotherapy for 23 cycles and survived for 31 months after diagnosis. The second case received 7 regimens of chemotherapy for 20 cycles. She underwent adjuvant hysterectomy and craniotomy and survived for 21 months after diagnosis.

Among 10 patients with only lung metastasis, 8 (80%) attained complete remission, the remaining 2 had partial response and were lost to follow up. Of 22 patients with associated metastases in other organs, 16 (72.7%) achieved complete remission, 4 had partial response and were lost to follow up, and 2 died of wide spread metastatic disease including brain metastasis as mentioned above.

Discussion

The prevalence of pulmonary metastasis (37.6%) in the present study was much lower than those in the previous studies which ranged from 45-87%[3,7,8]. This difference may result from various factors including early referral of patients, severity and duration of disease and diagnostic method. In the authors' center, chest X-ray is the diagnostic method used to detect lung metastasis although the sensitivity is much lower than that of the CT-scan in identifying micrometastasis. Mutch et al[9] reported that CT-scan could detect pulmonary metastasis in 41% of GTT patients who had a negative finding on the chest X-ray, and all of these patients had increased risk of methotrexate failure. However, Ngan et al[10] found that the prognosis of GTT patients who had lung metastasis detected only by CT-scan did not differ from that of patients who had no metastasis. They concluded that CT-scan of lung was not essential in the staging of GTT.

Among 32 GTT patients with lung metastasis in the present study, only 9 patients (28.1%) had pulmonary symptoms including dyspnea, chest pain and hemoptysis. The clinical symptoms of patients who presented with severe hemoptysis or dyspnea improved when treated with chemotherapy. In Singapore, only 4% of 97 GTT patients had pulmonary symptoms[11]. while such symptoms in a report from Saudi Arabia were higher at 57.3% in 75 patients with GTT[5]. Kelly et al[12] noted that GTT patients who had opacification of chest X-ray, more than 50% had initial hCG titer of more than 100,000 IU/L. Chest pain and anemia had an increased risk of developing early respiratory death. However, in the present study, patients who presented with pulmonary symptoms responded well to chemotherapy. No patient died from respiratory failure.

The most common radiologic pattern of pulmonary metastasis in the present study was well-defined nodules accounting for 75% of GTT patients with lung metastasis. This pattern was also the most common in the previous reports[2,3]. The pattern of metastasis was not statistically different between patients who had multiple organ or only pulmonary involvement. Pleural effusion occurred in 3 patients in the present study. This pattern resulted from rupture of superficial lung nodule with bleeding into the pleural space[3]. Mediastinal involvement occurred in only one patient in the present study, much lower than 25 reported (33.3% cases) reported by Bakri et al [5]. GTT patients in the present study might be less advance than those in Saudi Arabia.

The histology in the present study could be identified in 15 patients (46.9%) who had surgical intervention. However, there was one surgical case that the histology was unknown because her specimen was not sent to the pathologist. This patients underwent right salpingo-oophorectomy performed in another hospital due to intraabdominal bleeding and was diagnosed with GTT from the rising of β-hCG..

The response rate to EMA regimen in these patients was 77% similar to the previous reports of about 67%-75%[13-15]. About the surgical involvement, two patients in the present study underwent thoracotomy. The first one was aimed to resect lung mass with no prior diagnosis of GTT, the pathology revealed choriocarcinoma later. The second one was operated on to remove persistent lung nodule after failure of multiple chemotherapy regimens. Tomada et al[16] suggested that the following criteria should be met in patients who planned to undergo lung resection, i.e. a good surgical candidate, primary malignancy controlled, no evidence of other metastatic site, a solitary lung lesion and persistent hCG level < 1,000 mIU/ml. Besides these, it is recommended that lung resection should only be performed after chemotherapy failure. However, this operation must be carefully considered because some residual lung nodules may be benign[17,18].

Patients who had only lung metastasis had a better prognosis than those who had associated metastases in other organs especially the brain. Two of 4 patients with brain metastasis died of disease in the presented series. However, no recurrence was found in the study period in patients who attained primary remission. When compared with other reports.

Kumar et al[11] noted a 2-year overall survival of 64.9%. The prognosis was also worse in patients who had associated brain metastasis.

In conclusion, the most common radiological pattern of pulmonary metastasis in GTT patients was well-defined multiple lung nodules followed by ill-defined nodules and pleural effusion. GTT patients with only lung metastasis seemed to have a better prognosis than those with lung and other organ metastasis.

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ลักษณะทางภาพรังสีและผลการรักษามะเร็งเนื้อรกที่มีการกระจายไปยังปอด

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วัตถุประสงค์: *เพื่อประเมินลักษณะภาพเอกซเรย์ปอดและอาการทางคลินิกของผู้ป่วยมะเร็งของเนื้อรกที่มีการกระจายไปยังปอด*

วัสดุและวิธีการ: *ทบทวนเวชระเบียนและภาพเอกซเรย์ปอดของผู้ป่วยมะเร็งของเนื้อรกที่มารับการรักษาที่ ร.พ. มหาราชนครเชียงใหม่ ตั้งแต่ มกราคม พ.ศ. 2541 ถึง มิถุนายน พ.ศ. 2546*

ผลการศึกษา: *มีผู้ป่วยมะเร็งของเนื้อรกในช่วงที่ศึกษา 85 ราย ในจำนวนนี้มีผู้ป่วย 32 ราย ที่พบการกระจายของโรคไปยังปอดจากภาพเอกซเรย์ โดยลักษณะที่พบบ่อยที่สุดคือ well defined nodule และไม่พบความแตกต่างของภาพเอกซเรย์ปอดในผู้ป่วยที่มีการกระจายของโรคไปที่ปอดอย่างเดียว เมื่อเปรียบเทียบกับผู้ป่วยที่มีการกระจายของโรคไปที่อวัยวะอื่นร่วมด้วย ในส่วนของยาเคมีบำบัดที่ใช้ พบว่าผู้ป่วย 29 รายได้รับยาเคมีบำบัดหลายตัว และมี 15 ราย ที่ได้รับยามากกว่า 1 ขนาน โดยมีค่าเฉลี่ยของจำนวนรอบยาเป็น 7 รอบ (3-23 รอบ) มีผู้ป่วย 11 ราย ที่ได้รับการตัดมดลูก, 1 ราย ผ่าตัดรังไข่, 2 ราย ผ่าตัดปอด และ1 ราย ผ่าตัดสมอง ผู้ป่วย 4 ราย ได้รับรังสีรักษาบริเวณสมอง สำหรับผู้ป่วย 10 ราย ที่มีการกระจายของโรคไปที่ปอดอย่างเดียว มี 8 ราย (ร้อยละ 80) ที่มี complete remission อีก 2 ราย ขาดการติดต่อ และในส่วนผู้ป่วย 22 ราย ที่มีการกระจายไปยังอวัยวะอื่นนอกจากปอด มี 16 ราย (ร้อยละ 69.5) มี complete remission, 2 ราย เสียชีวิต และ 4 ราย ขาดการติดต่อ*

สรุป: *ลักษณะเอกซเรย์ปอดของผู้ป่วยมะเร็งเนื้อรกที่กระจายไปปอดที่พบบ่อยที่สุดคือ well defined multiple nodules โดยที่ไม่พบความแตกต่างอย่างมีนัยสำคัญของลักษณะภาพเอกซเรย์ปอดในผู้ป่วยที่มีการกระจายของโรคไปที่ปอดแห่งเดียว กับผู้ป่วยที่มีการกระจายของโรคไปยังอวัยวะอื่นร่วมด้วย*