



Case Report

Postmolar Metastatic Choriocarcinoma Mimicking Primary Lung Cancer

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Abstract

Postmolar choriocarcinoma with delayed recurrence can be aggressive and has only been published in a few reports. We describe a postmenopausal woman with a molar pregnancy 10 years previously who presented with respiratory and neurological symptoms. Metastatic choriocarcinoma of the lungs with extensive metastases to various sites mimicking primary lung cancer was noted. She was successfully treated with systemic chemotherapy and had stable disease status 8 months after the diagnosis. Metastatic choriocarcinoma originating from an antecedent molar pregnancy can be overlooked given a prolonged latency. We review the published literature of postmolar choriocarcinoma and discuss the diagnosis and updates on treatment.

Keywords: Gestational trophoblastic disease, hydatidiform mole, postmolar choriocarcinoma, β -human chorionic gonadotropin

INTRODUCTION

Choriocarcinoma is a malignant trophoblastic neoplasm composed of cytotrophoblasts and syncytiotrophoblasts secreting β -human chorionic gonadotropin (β -hCG). It is characterized by a distribution in midline structures and frequent metastases to various organs, notably the lungs and liver. Antecedent molar pregnancy, ethnicity, and older maternal age contribute to the development of choriocarcinoma.^[1] A 1000-fold increased risk has been reported after a complete mole compared with a normal pregnancy in patients with choriocarcinoma.^[2] However, delayed recurrence of the disease over many years of β -hCG normalization is rare and has only been reported in a few studies.^[3,4] The clinical scenario can be

confounded by the fact that the disease can occur as either a primary nongestational tumor or as secondary postgestational recurrence.

Although choriocarcinoma can be treated with modern multimodality strategies, patients with high-risk advanced disease are still associated with a high mortality rate.^[5] Herein, we describe a case of a postmenopausal woman with an antecedent molar pregnancy 10 years previously who developed advanced choriocarcinoma mimicking

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primary lung cancer. The disease presented with extensive metastases to various sites, and she was successfully managed with systemic chemotherapy. We also performed a literature review of published reports concerning postmolar choriocarcinoma.

CASE REPORT

A 50-year-old postmenopausal gravida 1 para 1 Asian woman presented with headache, dyspnea, and hemoptysis for 1 week. Chest roentgenography and computed tomography (CT) revealed a 6.5 cm × 5.5 cm heterogeneous right upper lung mass [Figure 1a and b]. Magnetic resonance imaging (MRI) of the brain identified multiple metastatic tumors with hemorrhagic transformation [Figure 1c]. The brain tumor was removed, and a lung mass biopsy was performed under the suspicion of a primary lung cancer. Further imaging studies indicated extensive metastasis to the liver, kidneys, duodenum, and urinary bladder. She had received total abdominal hysterectomy at the age of 40 due to an antecedent molar pregnancy, and she had been followed after β -hCG normalization for 1 year. A pelvic examination and CT did not confirm an identifiable origin in the vaginal stump and adnexa. Pathological results revealed β -hCG-positive tumor cells mixed with syncytiotrophoblasts and cytotrophoblasts. Additional immunohistochemical staining suggested that the tumor was less likely to be of pulmonary origin [Figure 2a-c]. Her serum β -hCG level was markedly elevated (β -hCG, 352,338 mIU/mL; reference range in postmenopausal women <7 mIU/mL), whereas α -fetal protein, carcinoembryonic antigen, and cancer antigen-125 levels were within normal limits. The risk score according to the International Federation of Obstetrics and Gynecology 2000 gestational neoplasm scoring system was 17, indicating high risk.^[6]

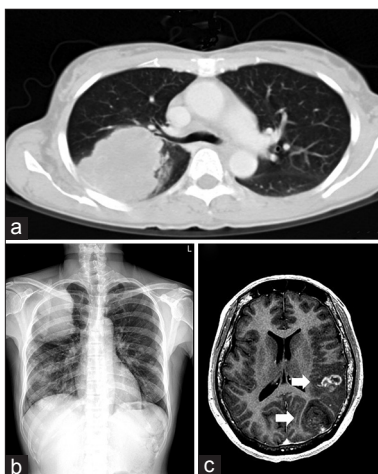


Figure 1: A huge pulmonary tumor with an extensive metastasis to various sites. Chest roentgenography and computed tomography revealed a 6.5 cm × 5.5 cm solitary mass at the right upper lobe with some satellite nodules in the periphery (a and b). Magnetic resonance imaging of the brain with gadolinium enhancement identified multiple enhancing metastatic cerebral lesions (arrowhead) with hemorrhagic transformation (c)

She received one cycle of bleomycin 30,000 IU on D1, D8, and D15; cisplatin 20 mg/m² on D1–D5; and etoposide 100 mg/m² on D1–D5 (bleomycin/etoposide/cisplatin [BEP] protocol) as definitive systemic chemotherapy. We omitted bleomycin in the subsequent cycle due to poor pulmonary function, and she completed three cycles of cisplatin and etoposide. Her condition improved with regression of the tumors. Her serum β -hCG also decreased after treatment (β -hCG: 13,779 mIU/mL). Due to persistent residual tumors and high serum β -hCG, we initiated salvage chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine as per the etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA/CO) protocol.^[7] Despite the presence of residual disease and detectable serum β -hCG, her disease status was stable without active neurological sequelae or respiratory symptoms 8 months after the initial diagnosis and was subsequently followed up at our outpatient clinic.

DISCUSSION

Choriocarcinoma due to a prior molar pregnancy has been reported to occur in only 2%–3% of women with a complete hydatidiform mole, and less than 0.1% of those with a partial mole.^[8,9] It typically presents several months after the causal pregnancy event and may be complicated with obstruction, hemorrhage, sepsis, or embolism.^[10] Owing to the nature of early hematogenous spreading, multiple metastases are common even after a hysterectomy. The most commonly involved sites include the lungs, liver, and brain. Pulmonary involvement is associated with life-threatening complications, and simultaneous cerebral and pulmonary metastases predict a worse survival.^[11] In our case, pulmonary and cerebral manifestations presented initially, and extensive bulky metastases with rapid progression in various organs were observed, compatible with previous published reports.

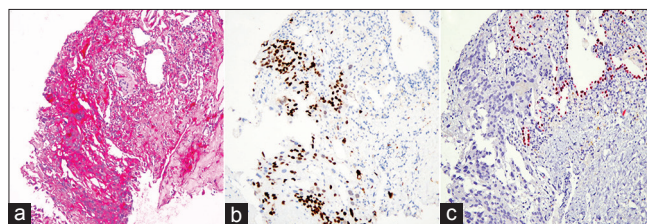


Figure 2: Pathological identification of metastatic choriocarcinoma. Lung mass biopsy revealed the tumor cells presenting features of multinucleated giant syncytiotrophoblasts and mononuclear nucleoli-prominent cytotrophoblasts in the pulmonary parenchyma. Immunohistochemistry analysis indicated that the malignant cells were strongly positive on β -hCG (a) and SALL-4 (b) and negative on Napsin-A (figure not shown). TTF-1 staining was negative on the tumor cells as compared with positive control on normal alveolar epithelium TTF-1 (c). In summary, given the history of antecedent molar pregnancy, choriocarcinoma with metastasis to the lungs is impressed rather than β -hCG-secreting large cell carcinoma or primary choriocarcinoma of the lungs (panel a, β -hCG; panel b, SALL-4; panel c, TTF-1; all sections in ×200). β -hCG: Beta-human chorionic gonadotropin, TTF-1: Thyroid transcription factor-1, SALL-4: Sal-like protein-4

The well-established hypothesis for the origin of choriocarcinoma includes: (1) tumor cells originating from primordial germ cells that migrated to midline structures during embryogenesis, such as the mediastinum, retroperitoneum, and pineal gland; (2) primary gonadal choriocarcinoma with spontaneous regression at the original site; (3) metastasized tumor from an antecedent molar pregnancy after a long period of latency; and (4) primary lung cancer with trophoblastic differentiation. In the present case, considering her age, pattern of involved organs, history of previous molar pregnancy, and no identifiable origin, we consider an undetected dormant gestational trophoblastic tumor *in utero* that subsequently disseminated to the lungs with a prolonged latency of 10 years posthysterectomy to be most likely. Although the pulmonary lesion presented with a solitary mass and some satellite nodules in the periphery mimicking a primary lung tumor with multiple metastases, primary pulmonary choriocarcinoma is still an extremely rare disease with limited reports.^[12-15] In addition, the immunohistochemistry of the tumor was positive for β -hCG and Sal-like protein-4 and negative for thyroid transcription factor-1 and Napsin-A, indicating a trophoblastic tumor in nature rather than a β -hCG-producing large cell carcinoma of the lung. Further, cytogenetics, DNA ploidy determination, and maternal DNA content detection may have provided clues to delineate the disease entity. A review of the published reports concerning choriocarcinoma originating from an antecedent molar pregnancy is presented in Table 1.

Owing to the relatively few number of cases of choriocarcinoma, therapeutic options remain unchanged with no major breakthroughs in the latest decade. In general, the treatment incorporates systemic chemotherapy, radiotherapy, and surgical resection as a multimodality approach. Systemic chemotherapy is the mainstay of treatment for high-risk

gestational trophoblastic neoplasms and metastatic diseases. A therapeutic protocol incorporating EMA/CO remains the standard first-line treatment.^[7] Alternatives such as paclitaxel/cisplatin or paclitaxel/etoposide (TP or TE), BEP, and 5-fluorouracil/actinomycin D have been reported to be effective regimens with less toxic effects.^[16-19] Multidrug refractory disease, liver/brain metastases, and disease development of more than 4 years after an antecedent pregnancy event are associated with adverse survival outcomes.^[20-22] In the absence of novel therapies against chemotherapy-resistant disease, Veras *et al.* indicated the strong immunoreactivity of programmed death-ligand 1 (PD-L1) in the neoplastic syncytiotrophoblasts of choriocarcinoma rather than intermediate trophoblastic tumors.^[23] In addition, Ghorani *et al.* reported four patients with resistant disease who successfully salvaged the PD-1 inhibitor pembrolizumab monotherapy.^[24] However, there are currently no validated novel agents aiming at resistant/refractory choriocarcinoma in the published literature.

CONCLUSION

We present the case of a female patient who developed postmolar metastatic choriocarcinoma of the lung mimicking primary lung cancer with a prolonged latency of 10 years. She was successfully managed with systemic chemotherapy and had stable disease status 8 months after the diagnosis. Metastatic choriocarcinoma originating from an antecedent molar pregnancy can be overlooked given a prolonged latency. Chemotherapy-resistant/refractory disease remains a medical challenge in the absence of potential novel therapies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

Table 1: List of published cases of postmolar pregnancy choriocarcinoma

References	Case number	Patient age	Antecedent molar pregnancy	Pathology diagnosis	Time interval (years) [#]	Treatment	Outcome
Looi and Sivanesaratnam 1981 ^[25]	1	28	PHM	Chorio	1.1	NA	Death
Ito <i>et al.</i> , 1985 ^[26]	8	NA	HM	NA	>2.0	NA	NA
Bagshawe <i>et al.</i> , 1990 ^[27]	2	41	PHM	Chorio	2.2	NA	NA
		23	PHM	Chorio	0.2	NA	NA
Thanikasalam 1991 ^[3]	1	56	HM	Chorio	5.0	Etoposide/actinomycin D	Alive
Gardner and Lage 1992 ^[28]	1	37	PHM	Chorio	0.8	Etoposide/actinomycin D/methotrexate	Alive
Fisher <i>et al.</i> , 1995 ^[29]	1	30	CHM	Chorio	4.0	EMA/CO	Alive
Seckl <i>et al.</i> , 2000 ^[9]	1	27	PHM	Chorio	0.6	EMA/CO; hysterectomy	Alive
Maestá <i>et al.</i> , 2010 ^[4]	2	28	HM	Chorio	4.2	C/T; pulmonary and liver resection	Death
		22	HM	Chorio	2.5	C/T; pulmonary resection	Alive
Joneborg <i>et al.</i> , 2011 ^[30]	1	49	HM	Chorio	3.0	C/T	Alive
Ma <i>et al.</i> , 2016 ^[31]	1	36	PHM	Chorio	0.5	EMA/CO	Alive
Present case	1	50	HM	Chorio	10.0	BEP; EMA/CO	Alive

[#]Determined by the time interval between the antecedent molar pregnancy and diagnosis of subsequent gestational trophoblastic neoplasm. HM: Hydatidiform mole, PHM: Partial hydatidiform mole, CHM: Complete hydatidiform mole, Chorio: Choriocarcinoma, C/T: Chemotherapy, EMA/CO: Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine, BEP: Bleomycin, cisplatin, and etoposide, NA: Not available

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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