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Cannonball lung metastases as a presenting feature of ectopic hCG expression

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ABSTRACT

Cannonball metastases refer to well-defined spherical nodules scattered over both lungs, being a classical presentation of hematogenous tumor spreading. Striking progression of lung metastases without established primary malignancy can raise a diagnostic challenge. We herein report three cases with cannonball metastases at initial presentation. Two patients ended up having a choriocarcinoma but no awareness of the presence of primary tumors, and the third had abrupt lung metastases of endometrial cancer while she was being asymptomatic. Relentless progression was illustrated by clinical and radiographic changes. Ectopic expression of human chorionic gonadotropin (hCG) would seemingly go some way responsible for fulminant cancer spreading associated with poor prognosis in our patients. The goal of this presentation is to raise awareness of ectopic hCG expression in patients presenting with similar astonishing scenarios.

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1. Introduction

Multiple well-defined lesions in both lungs are called cannonball metastases due to their large, round appearance. This pattern is the common manifestation of metastatic disease. The rich vascular bed of the lungs is hospitable to tumor emboli. Most patients with disseminated disease have a history of malignancy.¹ In some patient, however, a history of a primary cancer is lacking at initial presentation. Such a sole presentation of cannonball metastases is classically seen in germ cell tumor,^{2,3} choriocarcinoma^{3,4} and endometrial cancer.^{5,6} It is noteworthy that these cancers are sometimes described as human chorionic gonadotropin (hCG) expressing tumors as well.⁷ Other than pregnancy, hCG may also be secreted abnormally by certain tumors,⁸ particularly in gestational trophoblastic diseases, germ cell tumors, pathological growths of the bladder, uterus, testicular and epithelial cancers.^{7,9} Research now shows that hCG variants inhibit apoptosis in cancer cells,^{7,10} promote angiogenesis,¹¹ contributes to chemo-resistance and therefore poor prognosis.⁷ This is a potential explanation for the notorious behavior and treatment resistance of hCG expressing tumors.

2. Case presentation

2.1. Case 1

A 30-year old Taiwanese male who smoked two packs a day presented with blood-streaked mucus coughing and vague abdominal pain for 2 weeks. The patient had no previous medical comorbidities. His physical examination did not reveal any abnormality. On the basis of numerous well-defined nodules seen on chest radiograph (Fig. 1, A & B) and computed tomography (CT), the possibility of metastatic disease was thought. Pathology specimen from the CT-guided lung biopsy was suggestive of choriocarcinoma metastasis, showing positive staining for β -hCG and cytokeratin (CK), and negative for AFP and TTF-1 on immunohistochemistry. His serum β -hCG level was 507483 mIU/ml (reference <5 mIU/ml). Another mass of 6-cm in size in aortocaval space involving the inferior vena cava was noticed on abdomen CT. Histologically the biopsy of the retroperitoneal tumor was identical to that of the lung specimen, showing characteristics of a choriocarcinoma.

With a diagnosis of non-seminomatous germ cell tumor (choriocarcinoma, cTON3M1b, stage III),¹² the patient was commenced on the BEP regimen (bleomycin, etoposide and cisplatin, every 3 weeks) for 4 courses. However, only a transient partial response occurred (Fig. 1C). Chemotherapy was switched to 5 courses of VIP regimen (vinblastine, ifosfamide and cisplatin) but did not result in any measurable benefit in the following 5 months. The patient subsequently underwent autologous PBSCT.

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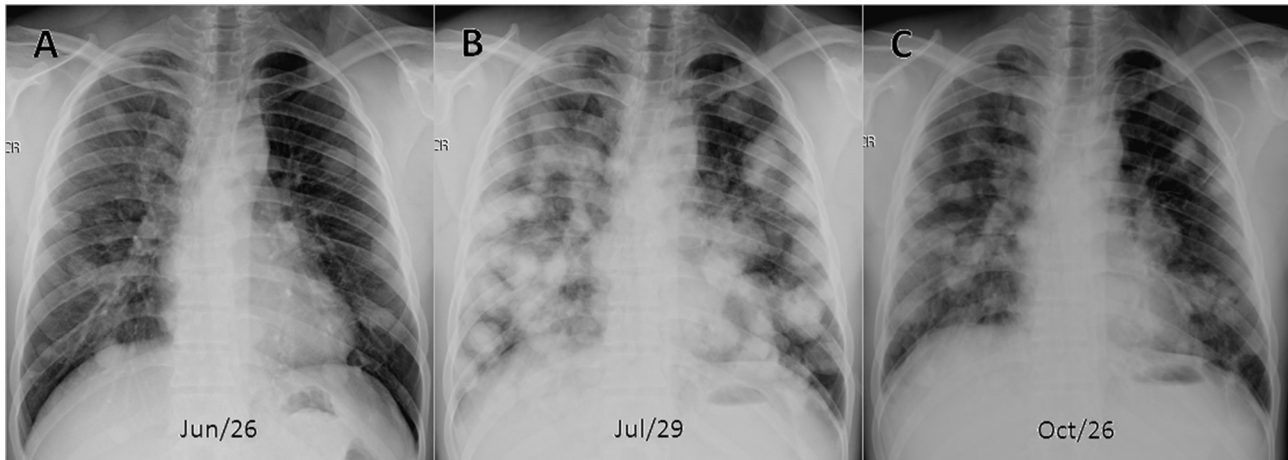


Fig. 1. Chest radiographs of a 30-year-old man showed multiple round nodules with “cannonball” morphology, highly suggestive of pulmonary metastases (A & B). The patient completed four courses of BEP regimen (bleomycin, etoposide and cisplatin) for his choriocarcinoma confirmed histologically. Only a transient partial response occurred (C). Elevated left scapula (Sprengel's deformity) was also noted

Chemotherapy with etoposide, dacarbazine and ifosfamide was maintained for further 10 months. Clinical improvement never happened after the autologous transplantation. The patient decided to cease treatment, and was discharged voluntarily. He only lasted 2 years after diagnosis (Table 1).

2.2. Case 2

An 18-year-old Taiwanese boy presented to our emergency department on April 30, 2012 with progressive chest pain and episodic cough of about 2-day. His medical history was unremarkable. A chest radiograph and CT demonstrated a 6-cm mass in the anterior mediastinum, and multiple cannonball lesions throughout both lungs (Fig. 2, A & B). Ultrasound findings of the abdomen and scrotum ultrasound were interpreted as normal. Serum β -hCG was elevated (7335 mIU/ml). Ultrasound-guided biopsy of the mediastinal mass was performed and histologically established the diagnosis of choriocarcinoma. An immunohistochemical stain showed positive for hCG and CK, and negative for TTF-1. The patient was started on BEP chemotherapy regimen (bleomycin, etoposide and cisplatin). His respiratory status deteriorated rapidly, with the development of hemoptysis and acute respiratory failure, requiring mechanical ventilation for 2-week duration. Just 2 months after extubation, the patient developed epileptic seizures related brain metastases, and underwent whole-brain radiation in July 2012.

During a 6-cycle BEP treatment, his β -hCG level transiently declined to 1271 mIU/ml, but continued to rise despite ongoing chemotherapy. Judging this as a worsening of clinical condition, chemotherapy was shifted to ICE regimen (ifosfamide, cisplatin and

etoposide) in October 2012. However, the treatment did not produce any response over the ensuing 2 months. Salvage chemotherapy comprising paclitaxel and ifosfamide was given, with gamma-knife surgery for recurrent brain metastasis in January and April 2013. Pleural effusion, syncope, episodes of melena, and a rapidly growing gingival mass in the maxilla were noted afterward, and clinical condition continued to deteriorate. His hospital course was later complicated by gingivostomatitis, oral candidiasis and uncontrolled *Klebsiella pneumoniae* bacteremia. The patient passed away 16 months after his initial presentation (Table 1).

2.3. Case 3

A 72-year-old Taiwanese woman presented with abrupt and asymptomatic tumor dissemination in the lungs noticed at regular follow-up. Originally she was diagnosed with endometrioid endometrial adenocarcinoma FIGOIIIC¹³ involving right pelvic lymph nodes previously. She had been treated with total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection followed by 6 cycles of adjuvant cisplatin and paclitaxel. After completing chemotherapy she remained disease-free in following 18 months. Intensive surveillance included chest X-ray and serum cancer antigen (CA-125) measurement every 3 months.

At 2-year follow-up, chest radiography demonstrated numerous round nodules that were not identified on previous imaging, with the classic appearance of cannonball metastases (Fig. 3A). The patient had no associated symptoms such as fever, productive cough, or chest pain. Serum CA-125 was 13.6 U/ml (normal <35 U/ml), and hCG 2901 mIU/ml (postmenopausal females: <9.5 mIU/ml). Morphology of lung biopsy revealed an adenocarcinoma with

Table 1
Clinical features of three patients with cannonball pulmonary metastases at presentation

Case	Age	Sex	Reasons for metastatic workup	Serum β -hCG	Pathologic result of lung biopsy	Metastatic locations	Treatment regimen	From lung presentation to death
1	30 yrs	Male	Coughing, Cannonball nodules	507483 mIU/ml	Metastatic choriocarcinoma, immunoactive for β -hCG	Lung, retroperitoneum	Bleomycin, etoposide, cisplatin, ifosfamide, etc	26 months
2	18 yrs	Male	Coughing, Cannonball nodules	7335 mIU/ml	Metastatic choriocarcinoma, immunoactive for β -hCG	Lung, anterior mediastinum, brain, gingiva	Bleomycin, etoposide, cisplatin, ifosfamide, etc	16 months
3 ^a	72 yrs	Female	Cannonball nodules	2901 mIU/ml	Metastatic endometrial carcinoma	Pelvic lymph nodes, lung	Etoposide, cisplatin, ifosfamide	10 months

β -hCG: beta-human chorionic gonadotropin.

^a Patient with past history of endometrial cancer.

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