



# Cannonball lung metastases as a presenting feature of ectopic hCG expression

Rong-Hsin Yang<sup>a</sup>, Chien-Hsin Ting<sup>b</sup>, Yum-Kung Chu<sup>b,\*</sup>

<sup>a</sup> Division of Nuclear Medicine, MacKay Memorial Hospital Taitung Branch, No. 1, Lane 303, Changsha Street, Taitung 950, Taiwan

<sup>b</sup> Department of Nuclear Medicine, Taipei Veterans General Hospital, No. 201, Shipai Road Sec. 2, Beitou District, Taipei 112, Taiwan

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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.<sup>1</sup> 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,<sup>2,3</sup> choriocarcinoma<sup>3,4</sup> and endometrial cancer.<sup>5,6</sup> It is noteworthy that these cancers are sometimes described as human chorionic gonadotropin (hCG) expressing tumors as well.<sup>7</sup> Other than pregnancy, hCG may also be secreted abnormally by certain tumors,<sup>8</sup> particularly in gestational trophoblastic diseases, germ cell tumors, pathological growths of the bladder, uterus, testicular and epithelial cancers.<sup>7,9</sup> Research now shows that hCG variants inhibit apoptosis in cancer cells,<sup>7,10</sup> promote angiogenesis,<sup>11</sup> contributes to chemo-resistance and therefore poor prognosis.<sup>7</sup> This is a potential explanation for the notorious behavior and treatment resistance of hCG expressing tumors.

## 2. Case presentation

### 2.1. Case 1

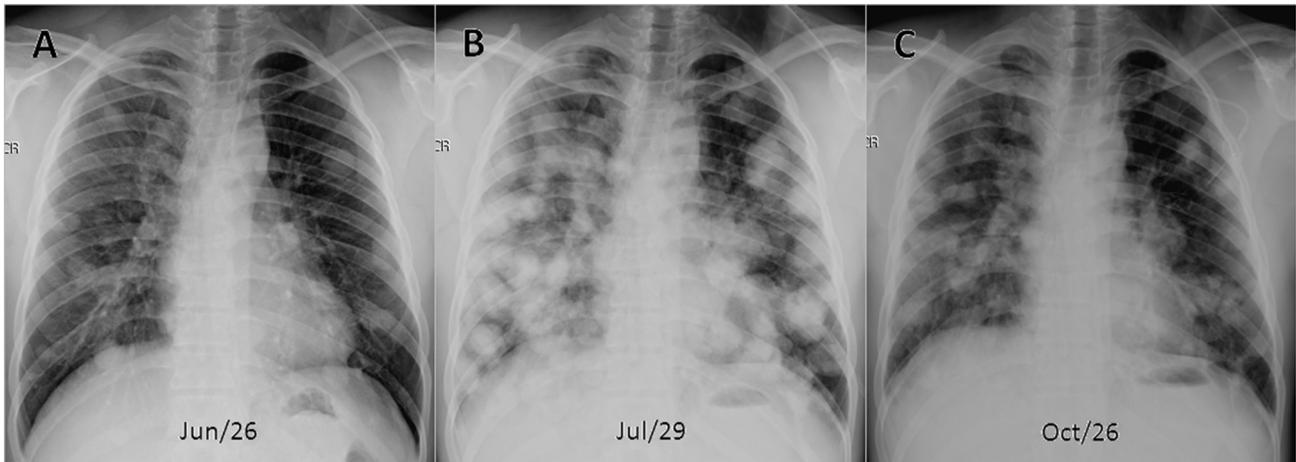
A 30-year old Taiwanese male who smoked two packs a day presented with blood-streaked mucus coughing and vague abdominal pain for 2 weeks. The patient had no previous medical comorbidities. His physical examination did not reveal any abnormality. On the basis of numerous well-defined nodules seen on 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  $\beta$ -hCG and cytokeratin (CK), and negative for AFP and TTF-1 on immunohistochemistry. His serum  $\beta$ -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),<sup>12</sup> 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.

\* Corresponding author. Fax: +886 2 28715849.

E-mail addresses: [ronghsin.yang@gmail.com](mailto:ronghsin.yang@gmail.com) (R.-H. Yang), [chting@vghtpe.gov.tw](mailto:chting@vghtpe.gov.tw) (C.-H. Ting), [ykchu@vghtpe.gov.tw](mailto:ykchu@vghtpe.gov.tw) (Y.-K. Chu).

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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  $\beta$ -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  $\beta$ -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 FIGOIIIC<sup>13</sup> 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.

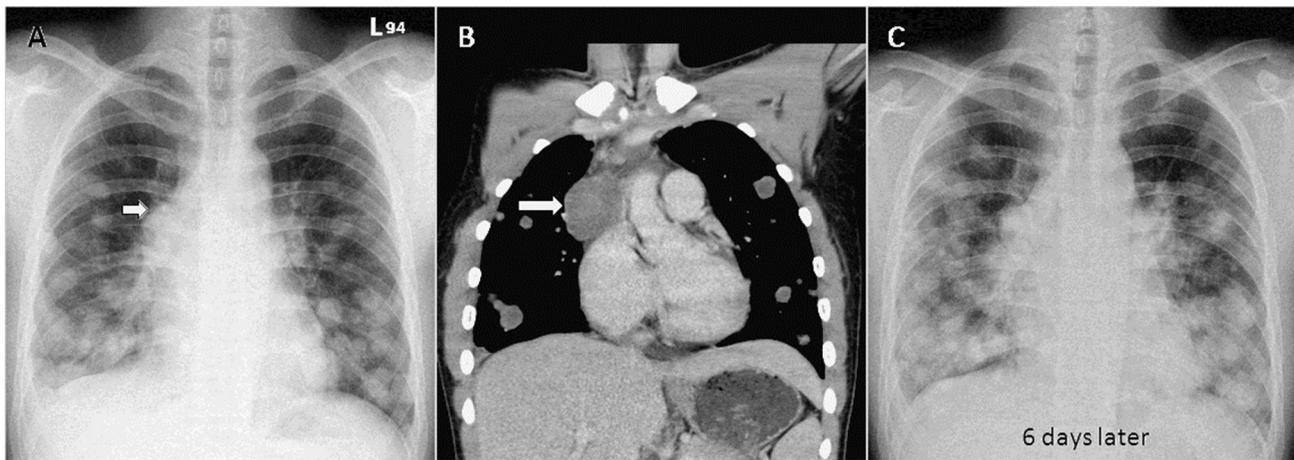
At 2-year follow-up, chest radiography demonstrated numerous round nodules that were not identified on previous imaging, with the classic appearance of cannonball metastases (Fig. 3A). The patient had no associated symptoms such as fever, productive cough, or chest pain. Serum CA-125 was 13.6 U/ml (normal <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 $\beta$ -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 $\beta$ -hCG	Lung, retroperitoneum	Bleomycin, etoposide, cisplatin, ifosfamide, etc	26 months
2	18 yrs	Male	Coughing, Cannonball nodules	7335 mIU/ml	Metastatic choriocarcinoma, immunoactive for $\beta$ -hCG	Lung, anterior mediastinum, brain, gingiva	Bleomycin, etoposide, cisplatin, ifosfamide, etc	16 months
3 <sup>a</sup>	72 yrs	Female	Cannonball nodules	2901 mIU/ml	Metastatic endometrial carcinoma	Pelvic lymph nodes, lung	Etoposide, cisplatin, ifosfamide	10 months

$\beta$ -hCG: beta-human chorionic gonadotropin.

<sup>a</sup> Patient with past history of endometrial cancer.



**Fig. 2.** An 18-year-old boy presented with progressive chest pain and episodic cough for 2 days. Radiograph and CT of the chest at presentation (A & B) revealed multiple bilateral cannon-ball opacities in both lungs and a 6-cm mass in the anterior mediastinum (white arrow). A fulminant behavior of the metastatic lesions was striking on the follow-up radiograph (C). More notably, a metastatic growth could rapidly occur in an exceedingly rare site of the body, his gingival



**Fig. 3.** This 72-year-old woman, with a history of endometrial cancer, was operated along with chemotherapy rendering a disease-free for last 18 months. However, an abrupt dissemination of cannonball metastases was presented in the lungs at a regular follow-up (A). During the course of salvage chemotherapy, merely a minimal response was noted by 2 months (B). Follow-up radiograph taken 1 month later demonstrated an ongoing disease (C)

neuroendocrine differentiation, in keeping with those seen on her original endometrial specimen. Tumor cells were immunoreactive for cytokeratins, CD56, and synaptophysin.

A further salvage chemotherapy with cisplatin, ifosfamide and etoposide was administered. Despite a transient response (Fig. 3B), she was found to have an ongoing metastasis, manifested as progressive dyspnea, hemoptysis, drowsiness, along with radiographic progression (Fig. 3C). After completing the ninth cycle of chemotherapy, the patient elected to go into hospice. She succumbed to her illness 10 months after pulmonary metastases diagnosis (Table 1).

### 3. Discussion

The term human chorionic gonadotropin (hCG) refers to five active variants of hCG, each produced by different cells with separate functions. Molecular variants differ in posttranslational modifications, compared with standard hCG in pregnancy. The five independent molecules are standard-hCG, pituitary or sulfated hCG, hyperglycosylated hCG,  $\beta$ -subunit ( $\beta$ -hCG) and hyperglycosylated  $\beta$ -hCG.<sup>14</sup> The last three variants, made by most advanced malignancies, all behave similarly to block apoptosis in

cancer cells and drive tumorigenesis.<sup>7,15</sup> It is inferred that ectopic  $\beta$ -hCG effect is modulated via the transforming growth factor  $\beta$  (TGF- $\beta$ ) receptor, which brings about the coordinated processes of oncogenesis.<sup>15</sup> Variants of hCG have long been detected in patients with various malignancies by highly sensitive methods.<sup>16,17</sup> Generally hCG is not found in normal men. Normal hCG levels are less than 5.0 mIU/ml in non-pregnant women, being less than 9.5 mIU/ml in postmenopausal women.

Ectopic expression of hCG and its beta subunit is now a widespread phenomenon described in many cancer subtypes.<sup>7,14,16,17</sup> Since choriocarcinomas include syncytiotrophoblasts ( $\beta$ -hCG producing cells), they cause high serum levels of  $\beta$ -hCG. It has also been known that most non-trophoblastic malignancies in advanced stages produce free  $\beta$ -hCG.<sup>17,18</sup> The list of hCG expressing tumors is quite long, including gynecologic carcinomas<sup>19–21</sup> (endometrium, cervix, vagina, ovary and vulva), gastrointestinal carcinomas<sup>22</sup> (pancreas, biliary tract, liver, esophagus, stomach and intestine), and carcinomas of the prostate, kidney, breast, and lung, and neuroendocrine tissue.<sup>18,23–25</sup> More generally, the overall incidence of hCG- $\beta$  expression in epithelial cancer is approximately to be one-third of all cases,<sup>16</sup> and in bladder, pancreatic and colorectal cancers, per se, it may be as high as 50%.<sup>15</sup> The mechanism of hCG

production by nontrophoblastic tumors is poorly understood. Most authors favor the concept of a trophoblastic metaplasia within the carcinomatous tissue.<sup>25</sup>

Grossmann and co-workers studied 39 cases of endometrial cancer for the expression of hCG and found 13 (33%) were positive, with the highest concentrations associated with histological grade III adenocarcinoma.<sup>19</sup> In a prospective study of 67 patients with endometrial cancer, elevation of the urine  $\beta$ -subunit core fragment (a degraded hCG product) were detected in 52% of the patients.<sup>26</sup> Increasing evidence suggests that the action of luteinizing hormone (LH) and hCG might also contribute to the malignant transformation of human cells, by promoting either promitogenic or antiapoptotic effects.<sup>27</sup> In fact, the common receptors for luteinizing hormone and gonadotropin (LH/hCG) have been detected in a high percentage of endometrial carcinomas, and their expression is apparently related to the cancer grading.<sup>28</sup>

Cannonball metastases refer to well circumscribed, round lung metastases that appear like cannonballs. Neoplasms with rich venous return directly into the systemic system often present in this fashion. Such a presentation, is classically seen in germ cell tumors,<sup>2–4,29</sup> and tumors of renal,<sup>30,31</sup> endometrial,<sup>6</sup> prostate,<sup>32</sup> and of gastrointestinal<sup>33,34</sup> origins. Cannonball metastases imply the aggressiveness of the malignancy although a few cases with favorable outcome have been reported.<sup>3,29,32</sup>

Abrupt lung metastases with cannonballs pattern at the time of initial diagnosis as shown in our cases have been reported in germ cell tumors,<sup>2,3</sup> choriocarcinomas,<sup>4</sup> and endometrial cancers.<sup>5,6</sup> It is noteworthy that these cancers are frequently described as hCG expressing tumors, as already indicated. hCG is an autocrine, acting directly on the cells which produce it, and as an invasion promoter for tumorigenesis and angiogenesis.<sup>7,15</sup> Ectopic hCG expression would seemingly go some way accounting for rapid disease progression and poor prognosis in most patients, as is the present series. This observation is in agreement with prior documented cases in which the ectopic hCG expression was associated with fulminant behaviors of the tumors.<sup>16</sup>

#### 4. Conclusions

Cannonball metastases on initial presentation or during regular cancer follow-up as seen in our series are not usual.<sup>34</sup> Such a radiological presentation is highly prevalent among patients with hCG expressing tumors,<sup>2–6</sup> a hitherto unproved association. Fulminant disease course and treatment resistance characterize the behaviors of hCG producing tumors.<sup>16</sup>

As hCG measurement is not routinely included in the metastatic workup at most institutions, a noted limitation of our observation is the scarcity of objectivity in recognizing ectopic hCG expression in most cases with cannonball metastases. A broader analysis would be of clinical interest.

#### Conflicts of interest

The authors have declared no conflicts of interest.

#### Abbreviations

AFP	alpha-fetoprotein
$\beta$ -hCG	beta-subunit of human chorionic gonadotropin
CA-125	carbohydrate antigen-125
CD56	neural cell adhesion molecule, classification determinant-56
CK	cytokeratin
CT	computed tomography

FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
hCG	human chorionic gonadotropin
LH	luteinizing hormone
TGF- $\beta$	transforming growth factor $\beta$
TTF-1	thyroid transcription factor 1

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