Cannonball lung metastases as a presenting feature of ectopic hCG expression

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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, cT0N3M1b, stage III), 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.

Keywords:
Cannonball metastases
Choriocarcinoma
Endometrial cancer
Human chorionic gonadotropin

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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 metastases 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 FIGO III C13 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>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Reasons for metastatic workup</th>
<th>Serum β-hCG</th>
<th>Pathologic result of lung biopsy</th>
<th>Metastatic locations</th>
<th>Treatment regimen</th>
<th>From lung presentation to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 yrs</td>
<td>Male</td>
<td>Coughing, Cannonball nodules</td>
<td>507483 mIU/ml</td>
<td>Metastatic choriocarcinoma, immunoactive for β-hCG</td>
<td>Lung, retroperitoneum,</td>
<td>Bleomycin, etoposide, cisplatin, ifosfamide, etc</td>
<td>26 months</td>
</tr>
<tr>
<td>2</td>
<td>18 yrs</td>
<td>Male</td>
<td>Coughing, Cannonball nodules</td>
<td>7335 mIU/ml</td>
<td>Metastatic choriocarcinoma, immunoactive for β-hCG</td>
<td>Lung, anterior mediastinum, brain, gingiva</td>
<td>Bleomycin, etoposide, cisplatin, ifosfamide, etc</td>
<td>16 months</td>
</tr>
<tr>
<td>3*</td>
<td>72 yrs</td>
<td>Female</td>
<td>Cannonball nodules</td>
<td>2901 mIU/ml</td>
<td>Metastatic endometrial carcinoma</td>
<td>Pelvic lymph nodes, lung</td>
<td>Etoposide, cisplatin, ifosfamide</td>
<td>10 months</td>
</tr>
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β-hCG: beta-human chorionic gonadotropin.
* Patient with past history of endometrial cancer.
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, β-subunit (β-hCG) and hyperglycosylated β-hCG. The last three variants, made by most advanced malignancies, all behave similarly to block apoptosis in cancer cells and drive tumorigenesis. It is inferred that ectopic β-hCG effect is modulated via the transforming growth factor β (TGF-β) receptor, which brings about the coordinated processes of oncogenesis. Variants of hCG have long been detected in patients with various malignancies by highly sensitive methods. 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. Since choriocarcinomas include syncytiotrophoblasts (β-hCG producing cells), they cause high serum levels of β-hCG. It has also been known that most non-trophoblastic malignancies in advanced stages produce free β-hCG. The list of hCG expressing tumors is quite long, including gynecologic carcinomas (endometrium, cervix, vagina, ovary and vulva), gastrointestinal carcinomas (pancreas, biliary tract, liver, esophagus, stomach and intestine), and carcinomas of the prostate, kidney, breast, and lung, and neuroendocrine tissue. More generally, the overall incidence of hCG-β expression in epithelial cancer is approximately to be one-third of all cases, and in bladder, pancreatic and colorectal cancers, per se, it may be as high as 50%. The mechanism of hCG
production by non trophoblastic tumors is poorly understood. Most authors favor the concept of a trophoblastic metaplasia within the carcinomatous tissue.25

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.26 In a prospective study of 67 patients with endometrial cancer, elevation of the urine β-subunit core fragment (a degraded hCG product) were detected in 52% of the patients.26 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.27 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.28

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,2,3 choriocarcinomas,4 and endometrial cancers.5,6 It is noteworthy that these cancers are frequently described as hCG expressing tumors,2,3 choriocarcinomas,4 and endometrial cancers.5,6 It is important to note 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 and of gastrointestinal3,4,5 origins. Cannonball metastases imply the aggressiveness of the malignancy although a few cases with favorable outcome have been reported.3,29,32 A broader analysis would be needed to recognize ectopic hCG expression in the scarcity of objectivity in recognizing ectopic hCG expression in workup at most institutions, a noted limitation of our observation is abrupt lung metastases with cannonballs pattern at the time of initial diagnosis as shown in our cases have been reported in germ cell tumors,2,3 choriocarcinomas,4 and endometrial cancers.5,6 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 tumor genesis and angiogenesis.715 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 fulminating behaviors of the tumors.16

4. Conclusions

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

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

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<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
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<td>β-hCG</td>
<td>beta-subunit of human chorionic gonadotropin</td>
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<tr>
<td>CA-125</td>
<td>carbohydrate antigen-125</td>
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<tr>
<td>CD56</td>
<td>neural cell adhesion molecule, classification determinant</td>
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<tr>
<td>CK</td>
<td>cytokeratin</td>
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<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>FIGO</td>
<td>Fédération Internationale de Gynécologie et d’Obstétrique</td>
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<tr>
<td>hCG</td>
<td>human chorionic gonadotropin</td>
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<tr>
<td>LH</td>
<td>luteinizing hormone</td>
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<tr>
<td>TGF-β</td>
<td>transforming growth factor β</td>
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<tr>
<td>TTF-1</td>
<td>thyroid transcription factor 1</td>
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References


