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Beta-HCG secretion by a pulmonary pleomorphic carcinoma: A case report

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ABSTRACT

Ectopic secretion of beta-subunit of human chorionic gonadotropin (β-HCG) in pulmonary pleomorphic carcinoma is remarkably rare. Such unusual ectopic hormone production by lung cancer may be initially misinterpreted as extragonadal choriocarcinoma or germ cell tumor.

We report a 56-year-old postmenopausal female, smoker, who presented a 5-month history of progressive dyspnea, dry paroxysmal cough, and significant weight loss. She was referred by a local hospital with the preliminary diagnosis of gestational trophoblastic neoplasia due to a rapidly growing thoracic tumor with persistently elevated serum β-HCG. Computed tomography of the chest showed a lung mass in the right upper lobe associated with homolateral pleural effusion. Positron emission tomography showed pathological 2-[^{18}F]FDG uptake at the mass lesion. Biopsies were performed. Histological examination described pleomorphic carcinoma with positive immunostaining for β-HCG. The serum levels of β-HCG were also elevated indicating ectopic secretion. The patient had rapid clinical deterioration and deceased before chemotherapy initiation.

Only a few cases of paraneoplastic β-HCG secretion have been reported in the literature. Previous studies suggested that the ability to secrete β-hCG in tumors may correlate to some extent to chemoresistance; thus, it might be useful as a prognosis marker.

1. Introduction

Pulmonary pleomorphic carcinoma (PPC) is a rare tumor comprising 0,14% to 0,3% of all malignant lung tumors [1–3]. It has a more aggressive clinical course and a poorer prognosis compared to other histological types of non-small cell lung carcinoma (NSCLC) [3,4].

Human chorionic gonadotropin (HCG) is a hormone secreted by placental syncytiotrophoblasts. Measurable serum β-human chorionic gonadotropin (β-HCG) is usually consistent with pregnancy or pregnancy-related conditions such as gestational trophoblastic neoplasms. Ectopic secretion of this hormone by other non-trophoblastic malignancies, such as cervical cancer, breast, bladder, ovarian, brain, colorectal, uterine, brain, and lung malignant cell lines, has been described [5]. However, PPC producing β-HCG is very rare [6–8].

We report a case of a 56-year-old female with pleomorphic carcinoma of the lung associated with elevated serum levels of β-HCG.

2. Case report

A 56-year-old Caucasian woman with a five-month history of progressive dyspnea, dry paroxysmal cough, anorexia, and significant weight loss, was found to have a rapidly growing thoracic tumor with persistently elevated serum β-HCG. She was referred to our institution by a local hospital with the preliminary diagnosis of gestational trophoblastic neoplasia, likely choriocarcinoma.

The patient was a heavy smoker, with a history of a total hysterectomy 19 years ago. Her BRCA status was unknown. Regarding the family history of cancer, her father deceased due to a non-specified hepatic malignant neoplasm. The remaining family and social history were unremarkable.

On physical observation, she presented clinical signs of hypoxic respiratory failure, with marked dyspnea, fatigue, and pallor. Pulmonary auscultation revealed diminished vesicular murmur in the right hemithorax, and there was also a moderate tenderness in the right upper abdominal quadrant. There were no infectious contacts reported, and

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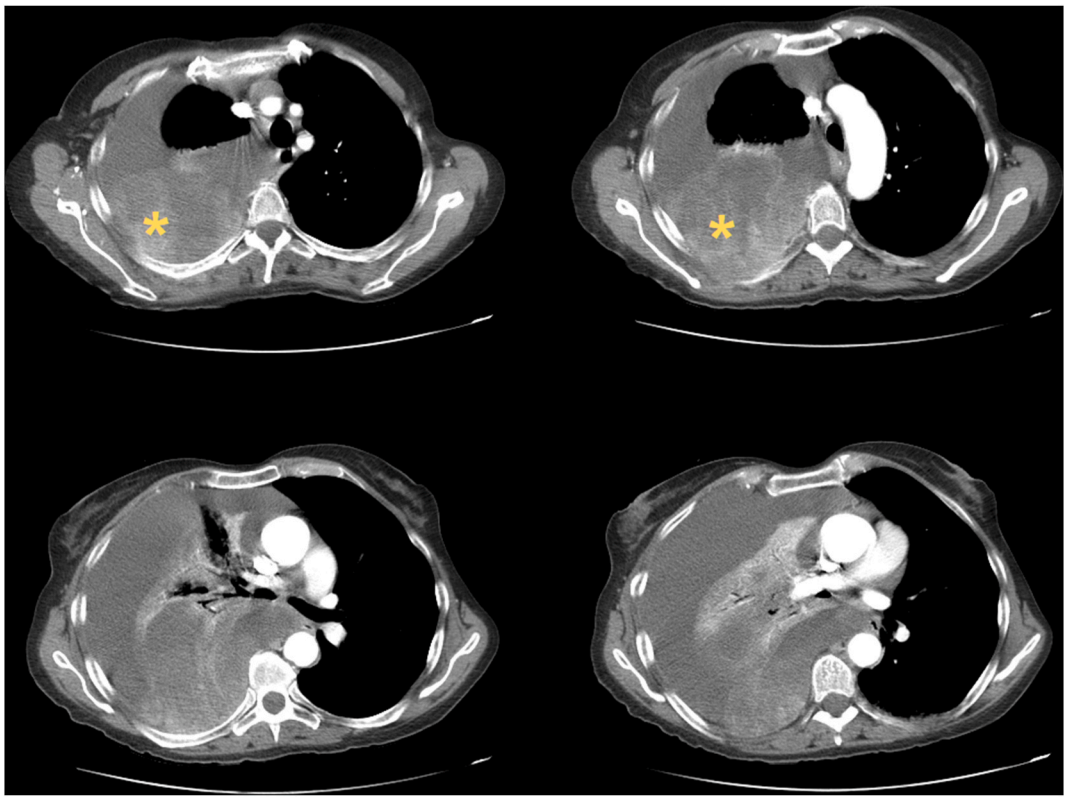

Fig. 1. Chest CT showing a lung mass in the right upper lobe associated with large homolateral pleural effusion.

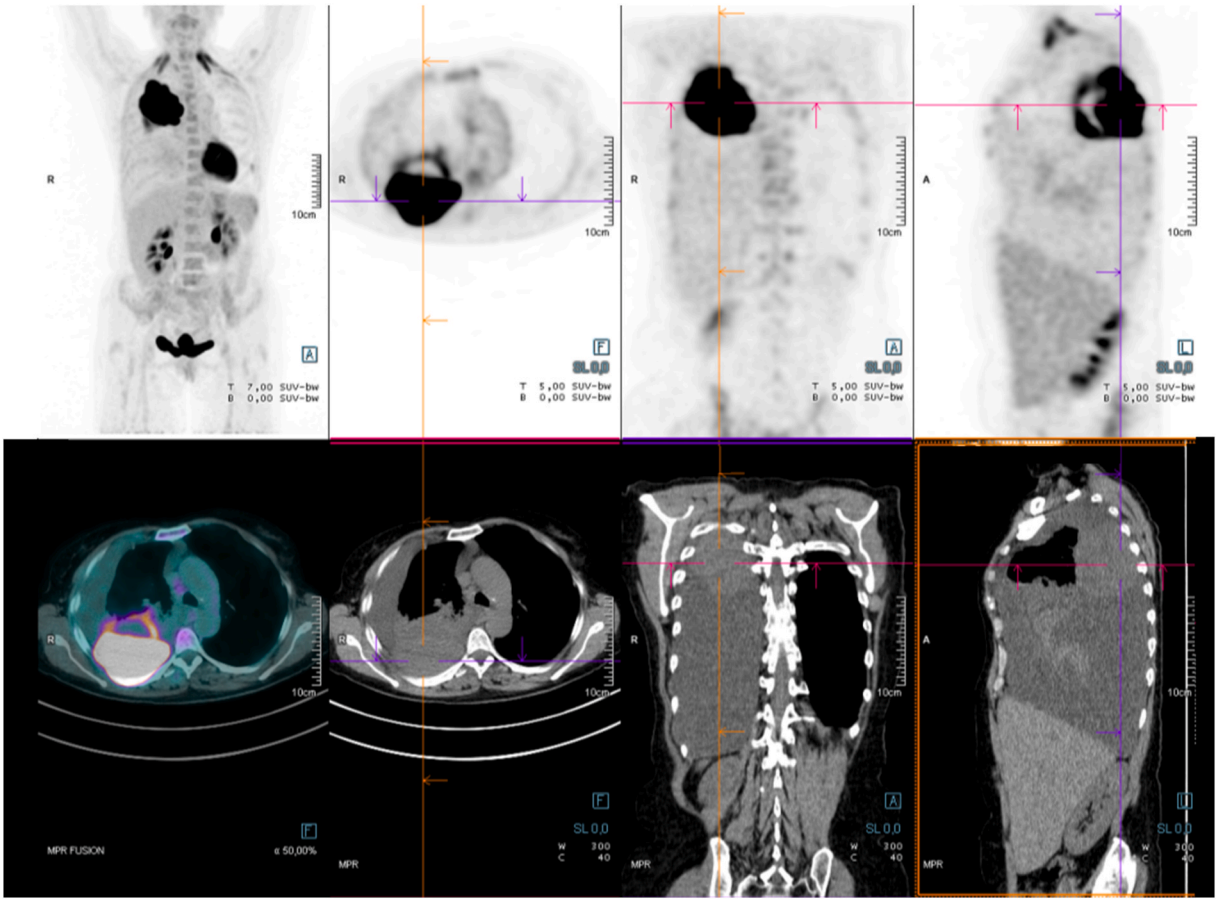

Fig. 2. PET/CT scan showing high FDG uptake at a lesion in the upper lobe of the right lung and a smaller lesion in the lower lobe of the left lung.

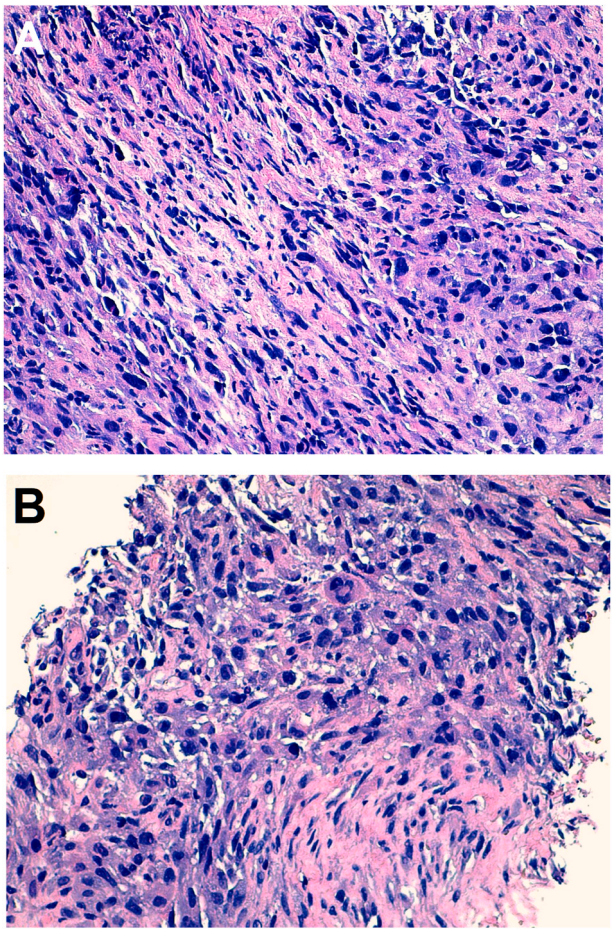

Fig. 3. Pleomorphic carcinoma comprising an undifferentiated non-small cell carcinoma component with large, pleomorphic cells (A and B) and rare giant multinucleated cells (B) admixed with a fusocelular component (H&E staining at 200x magnification).

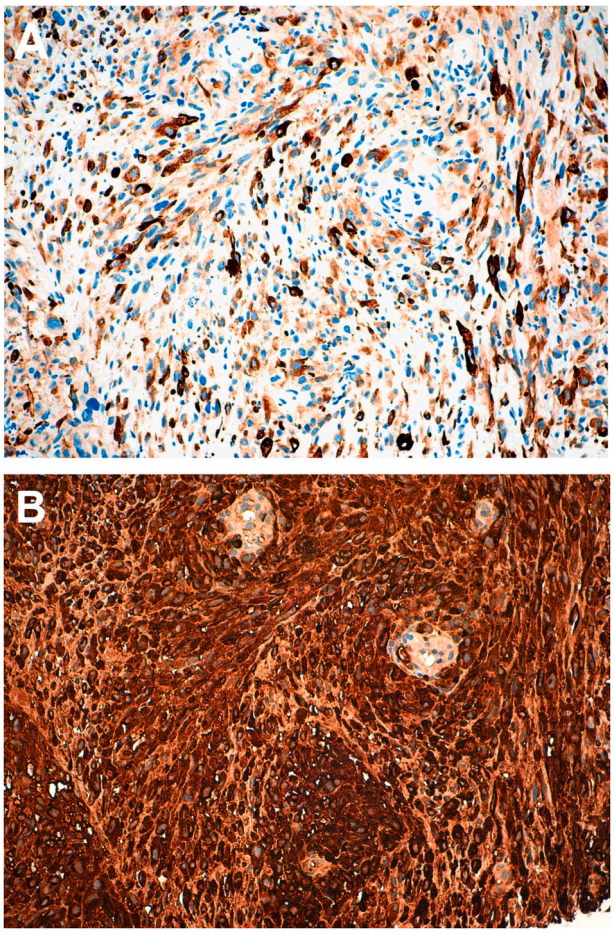

Fig. 4. Immunohistochemistry (IHC) images showing CKAE1AE3 expression (A) and β-HCG expression (IHC at 200x magnification).

the remainder of the physical examination showed no obvious abnormalities.

Chest radiography revealed complete opacification of the right hemithorax. Chest computed tomography (CT) showed a lung mass in the right upper lobe associated with large homolateral pleural effusion (Fig. 1). Whole-body positron emission tomography (PET/CT) scan detected a high 2-[^{18}F]FDG uptake lesion in the upper lobe of the right lung (SUVmax = 51,0) and a small lesion (SUVmax = 2,7) in the lower lobe of the left lung (Fig. 2).

Although we do not routinely examine β-HCG at the initial assessment of patients with suspected lung cancer, we proceeded with a serum reevaluation as an elevated β-HCG was reported in the referral information. Accordingly, of the serum tumor markers, her initial β-HCG at admission was 1 702,00 UI/l, increasing to 5 511,00 UI/l within a few days. Alpha-fetoprotein (AFP) levels were within the normal range.

The patient underwent thoracocenteses and percutaneous pleural biopsies. The microbiological study of pleural fluid and pleural biopsies were negative, to malignant cells. Bronchofibroscopy showed right upper segmental bronchi extrinsic compressions signs. Both bronchial aspirate and bronchoalveolar lavage fluid were negative for bacteriology and mycobacteriology testing, as well as for neoplastic cells.

Transthoracic needle biopsy (TTNB) of the right lung lesion was performed. Histopathological examination was consistent with pleomorphic carcinoma comprising an undifferentiated non-small cell carcinoma component, with large pleomorphic cells and rare giant multinucleated cells admixed with a spindle-shaped component (Fig. 3).

Immunohistochemically (IHC), both components displayed immunopositivity for cytokeratin (CK) AE1/AE3 (CKAE1/AE3), vimentin, and β-HCG. The epithelial cell component showed focal expression for CK7 and did not express TTF-1 or P40 (Fig. 4). Ki-67 was 50%. Additionally, tumor cells were also positive for programmed death-ligand 1 (PD-L1 IHC clone 22C3; 10%) and negative for anaplastic lymphoma kinase (ALK IHC clone D5F3), desmin, actin, S100 protein, P63, CK5/6 neural cell adhesion molecule (NCAM/CD56), napsin-A, cyclin-D1, AFP, and placental alkaline phosphatase (PLAP).

Initiation of chemotherapy was withheld due to rapid clinical deterioration and radiological progression. Best supportive care was the alternative option.

3. Discussion

Pulmonary pleomorphic carcinoma (PPC) is a rare aggressive tumor accounting for <1,0% of all malignant tumors. A retrospective analysis of 718 lung malignancies showed that PPC comprised 0.14% of all lung malignancies [2]. This entity has a male preponderance and a median age at diagnosis of 65 years. It is strongly associated with tobacco smoking. Studies also describe a predilection for peripheral locations, favoring upper lobes [1,3].

On histopathology and according to the WHO classification, PPC is a poorly differentiated non-small cell lung carcinoma containing at least 10% spindle and/or giant cells, or a carcinoma consisting only of spindle and giant cells [9]. Occasionally, PPC may include pleomorphic multi- and/or mononucleated giant cells, resembling syncytiotrophoblastic and cytotrophoblastic cells of choriocarcinoma. Those cells display immunopositivity for HCG, challenging the distinction between primary

choriocarcinoma of the lung, and β-HCG expressing pulmonary carcinoma [7]. Typically, primary choriocarcinoma of the lung (PCL) shows a mixed population of both multinucleated cells (syncytiotrophoblast) and medium-size cells, often with clear cytoplasm (cytotrophoblast) [10]. Reversely, PPC can exhibit a population of non-small cell carcinoma, comprising large pleomorphic cells, usually with eosinophilic cytoplasm, as in the present case. Furthermore, there is a relevant spindle-shaped component with rare multinucleated giant cells, which is not found in choriocarcinoma.

The immunohistochemical profile of PPC is also significantly heterogeneous. Nevertheless, it may highlight the different cell components. In our case, both components (non-small cell component and spindle-shaped component) displayed immunopositivity for CKAE1/AE3, vimentin, and β-HCG. There was also a focal expression for CK7 and no expression of TTF-1, P40, napsin-A, or PLAP. As mentioned, both PCL and PPC may express β-HCG, however, PPC does not express other germ cell tumor markers such as PLAP, as seen in our case.

Consequently, the histological and immunohistochemical findings of the patient described were consistent with the criteria for PPC of WHO classification, as the features of choriocarcinoma such as syncytiotrophoblastic and cytotrophoblastic cells were not seen, and there was no evidence of germ cell neoplasms.

Of note, and despite multiple biopsies of the lesion were made yielding the same pathological image, a definitive diagnosis may only be made on a resected tumor. Even though the features may be recognized and described [9]. This circumstance might be a potential limitation that should be addressed.

As mentioned, our case displayed immunopositivity for β-HCG. This hormone is usually produced by placental syncytiotrophoblasts. Although rare, some histological types of pulmonary carcinoma express β-HCG, such as adenocarcinomas, squamous cell carcinomas, or large cell carcinomas [11]. β-HCG expression in PPC has been rarely reported. A retrospective study of 2790 lobectomy specimens identified only six cases of pulmonary carcinoma expressing β-HCG. All six cases were diagnosed as PPC expressing β-HCG, as given by significant β-HCG positivity in the pleomorphic giant cell component. However, the authors could not follow the serum β-HCG level to establish the concept of β-HCG-producing lung cancer [12].

Serum β-HCG elevation in pulmonary carcinomas as the result of the tumor's ability to produce this hormone is a rare but important biologic feature of lung carcinomas. Comparably, in our case alongside tissue β-HCG expression, the serum levels of β-HCG were also elevated suggesting ectopic secretion. Both tissue β-HCG expression and serum β-HCG elevation in pulmonary carcinoma appear to be related to an extensive stage of the disease, chemoresistance, and poorer prognosis [11].

The incidence of PPC producing β-HCG is unknown. To the best of our knowledge, this is the fourth case of PPC producing β-HCG in the literature [6–8]. Therefore, although further study is required to identify the frequency of this association and its implications, tissue β-HCG expression, and serum β-HCG evaluation might be of interest as markers for diagnosis, clinical management, and prognosis in pleomorphic pulmonary carcinoma and other non-small cell lung carcinomas.

Author statement

Magno Dinis de Sousa, Margarida Barata and Ana Raquel Miranda contributed to this article as co-first authors.

Pedro Sequeira and Ana Oliveira contributed also to this article with pathology information on the case and related images.

All authors contributed to drafting the article and revising it critically for important intellectual content.

All authors have read the final manuscript and agree to the content.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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