Clinical Oncology: Case Reports

Case Report

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What's the Odds: Beta-Human Chorionic Gonadotropin in Lung Cancer and Complete Response to Third Line Nivolumab

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Abstract

Ectopic secretion of β-hCG by lung cancer is rare, particularly regarding male patients. Here we describe a clinical case of a β-hCG-secreting lung squamous cell carcinoma who had an exceptional response to 3rd line therapy nivolumab.

A 52-year-old man, KPS score of 90, presented a 12-month history of intermittent right-sided testicular pain. No other positive findings were issued in the anamnesis and/or at physical examination. Despite β-hCG serum elevation, no other changes were observed on analytical studies. No abnormalities were described on scrotal ultrasonography. CT showed thoracic lymphadenopathies and a right adrenal gland mass. PET/CT showed abnormal FDG uptake in the referred lymphadenopathies and mass. EBUS-TBNA biopsy and pathology examination revealed a poor-differentiated squamous cell carcinoma positive for CK7 and p65. The patient was diagnosed with a stage IV NSCLC and initiated chemotherapy with cisplatin-gemcitabine. After two cycles a partial response was achieved at CT and there was a β-hCG decrease. Because of headache complaints a head MRI was performed, demonstrating a single metastatic lesion, which was surgically removed. The histopathologic results confirmed the primary pulmonary origin revealing that it was a poor-differentiated lung squamous cell carcinoma with positive p63 and β-hCG immunostaining. After holocranial RT, patient restarted the same chemotherapy scheme. Response assessment exams showed new multiple irregular cavities with thickened walls in the lung parenchyma, compatible with progressive lung disease. A retrospective assessment was carried out leading to the suspicion that the primary lung tumor was probably present since the first CT. At this time, patient KPS score was 70 and 2nd line treatment with docetaxel was started. After four cycles, the lung disease was still progressing. PD-L1 IHC 22C3 was quantified, obtaining a >50% value. Nivolumab was started in 3rd line and after six months of treatment a complete metabolic response was achieved. Currently, the patient continues under nivolumab, having completed 17 months of therapy, with no signs of clinical, analytical or imaging progression.

Keywords

Beta-human chorionic gonadotropin; Lung cancer; Non-small cell lung cancer; Lung squamous cell carcinoma; Complete response; Nivolumab

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Abbreviations

β-hCG: Beta-human Chorionic Gonadotropin; CT: Computed Tomography; CHT: Chemotherapy; EBUS-TBNA: Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration; FDG: 18-F-Fluoro-2-Deoxyglucose; ICI: Immune Checkpoint Inhibitors; KPS: Karnofsky Performance Status; SCC: Squamous Cell Carcinoma; MRI: Magnetic Resonance Imaging; NSCLC: Non-Small Cell Lung Cancer; PD-1: Programmed Death Receptor-1; PD-L1: Programmed Death-Ligand 1; PET: Positron Emission Tomography; PET/CT: Positron Emission Computed Tomography; RT: Radiotherapy; US: Ultrasonography

Introduction

There are a limited number of case reports of Human Chorionic Gonadotropin (hCG)-secreting Non-Small-Cell Lung Cancers (NSCLCs) described in literature, particularly regarding male patients. These tumors follow an unusually aggressive behavior with poor clinical outcome [1,2].

Over the past few years, the use of Immune Checkpoint Inhibitors (ICI) has revolutionized the field of oncology and has underlined the critical role of the immune system in fighting cancer [3]. Here we describe a rare clinical case of a β-hCG-secreting lung Squamous Cell Carcinoma (SCC) who had an exceptional response to third line therapy nivolumab, a human Programmed Death Receptor-1 (PD-1) blocking antibody.

Case Report

A 52-year-old male was referred to an urologist evaluation because of a 12-month history of intermittent right-sided testicular pain. He reported no trauma, hematuria, dysuria nor urethral discharge. He had no constitutional symptoms, such as fever, night sweats, weight loss, fatigue, malaise, chest pain, cough, hemoptysis, new masses, headache or other neurological complaints. The patient was an electrical technician, active smoker (480 pack years), and denied the use of illicit drugs. He drank up to 48 grams of alcohol per day. His past medical history included hydrocele and lumbar disks herniations. At physical examination no abnormalities were observed. Analytical studies revealed a serum β-hCG elevation of 80 mUI/mL (reference value <1.2 mUI/ml) and no relevant changes were observed at blood count and differential, renal and liver-function, electrolytes, glucose and/or lactate dehydrogenase levels. The scrotal ultrasonography demonstrated normal echotexture in both testes and normal Doppler flow, with no focal lesions. Urine cultures were negative. Computed Tomography (CT) showed thoracic lymphadenopathies (one on the right hilus measuring 16 mm in the short axis and two lower paratracheal lymphadenopathies with 29 mm and 24 mm, respectively on the right and left) and a right adrenal gland mass with 80 mm in the long axis. The patient, with a Karnofsky Performance Status (KPS) score of 90, was evaluated in the Oncology Department for further investigation. The 18-F-Fluoro-2-Deoxyglucose (FDG) Positron Emission Computed Tomography (PET/CT) showed abnormal FDG uptake on those lesions (Figure 1). A Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) biopsy was performed and the pathology examination revealed a poor-

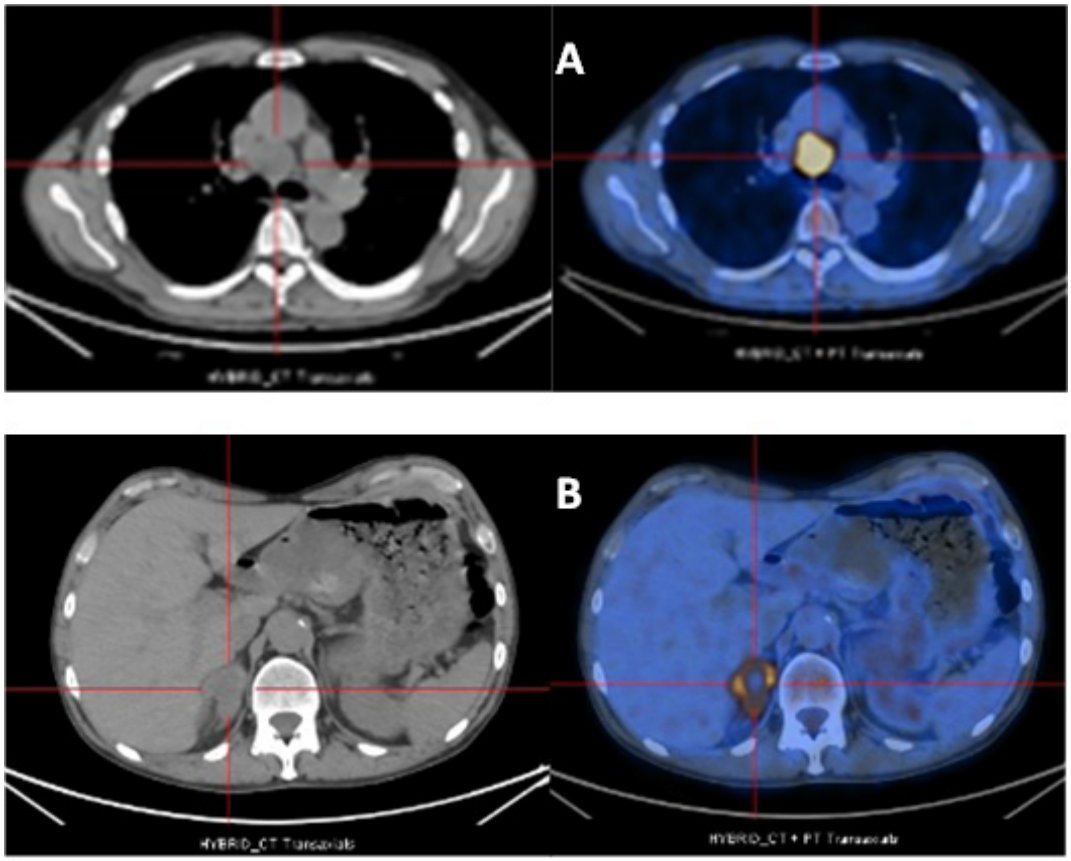

Figure 1: PET/CT images showing increased metabolic activity in the mediastinum (A) and in right adrenal gland; (B) before starting chemotherapy.

differentiated SCC of probable origin from the lung (Figure 2), which was positive for CK7 and p65, and negative for CK20, TTF1, CD56 and 34BE12 immunostaining. At this time the serum β-hCG was of 329 mUI/mL (Figure 3, point A). The diagnosis of an stage IV NSCLC was assumed and patient initiated a cisplatin 75 mg/m^2-gemcitabine 1250 mg/m^2 Chemotherapy (CHT) scheme q3w. After two cycles a partial response was achieved at CT with a β-hCG decrease to 22 mUI/mL (Figure 3, point B). At this point, a head Magnetic Resonance Imaging (MRI) was performed due to headache complaints and demonstrated a single right parietal metastatic lesion measuring 40 mm. The brain lesion was surgically removed and the histology revealed a poor-differentiated lung SCC with positive p63 and β-hCG immunostaining (Figure 4). The patient received whole-brain radiotherapy (30 Gy/10 fractions) and two additional cycles of the same CHT scheme. A progressive lung disease was observed in PET/CT despite the β-hCG value being within the normal range (Figure 3, point C). Multiple irregular cavities with thickened walls appeared in the lung parenchyma (Figure 5). Secondary spontaneous pneumothorax led to patient hospitalization (Figure 6). Additional investigation excluded both acute and opportunistic infections. After evaluating the morphology of the metastatic lung lesions in all the performed CT's, it was suspected (retrospectively) that primary lung tumor was probably present since the first CT: this would be a multicystic lesion with thin walls in the right apex (Figure 4, Nov/2017), which became progressively unilocular with wall thickening during the course of the disease, alongside with new cystic bilateral lung

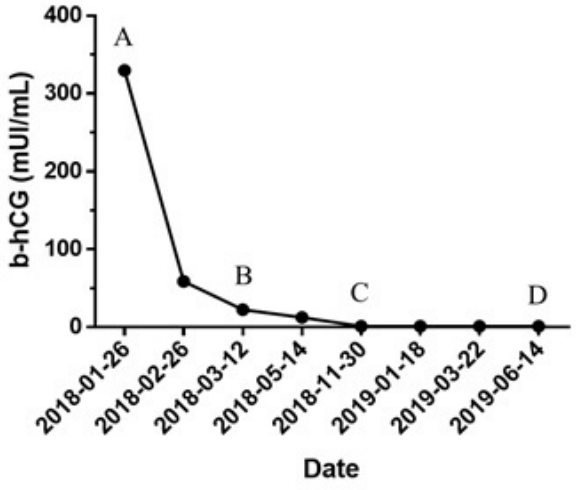

Figure 2: Evolution of β-hCG serum levels over the time and its relation with treatment procedures. Point A: β-hCG serum level before chemotherapy (329 mUI/mL); Point B: β-hCG serum level after two cycles of cisplatin-gemcitabine; Point C: β-hCG serum level after whole-brain radiotherapy and two additional cycles of cisplatin-gemcitabine; Point D: β-hCG serum level after six months of nivolumab therapy, 3 mg/Kg every two weeks.

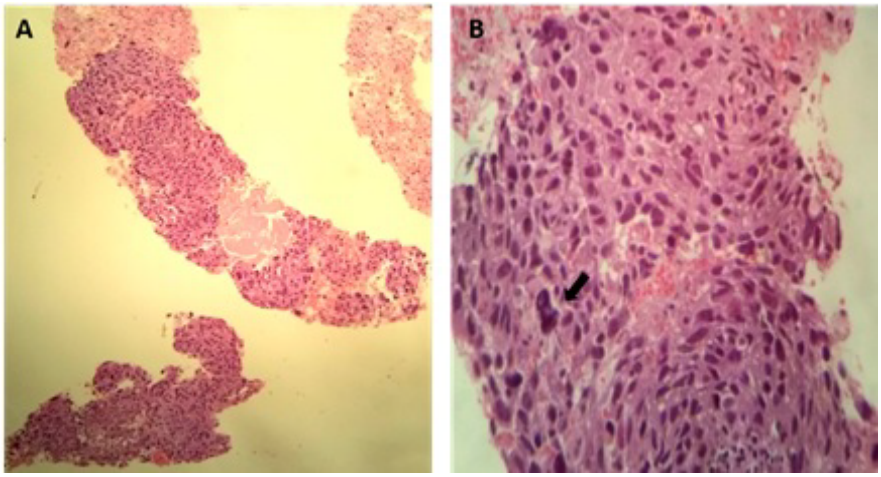

Figure 3: EBUS-TBNA biopsy of poor-differentiated squamous cell carcinoma (Hematoxylin and Eosin staining), 40x (A) and 600x (B). Note the presence of syncytiotrophoblast-like cells (black arrow B).

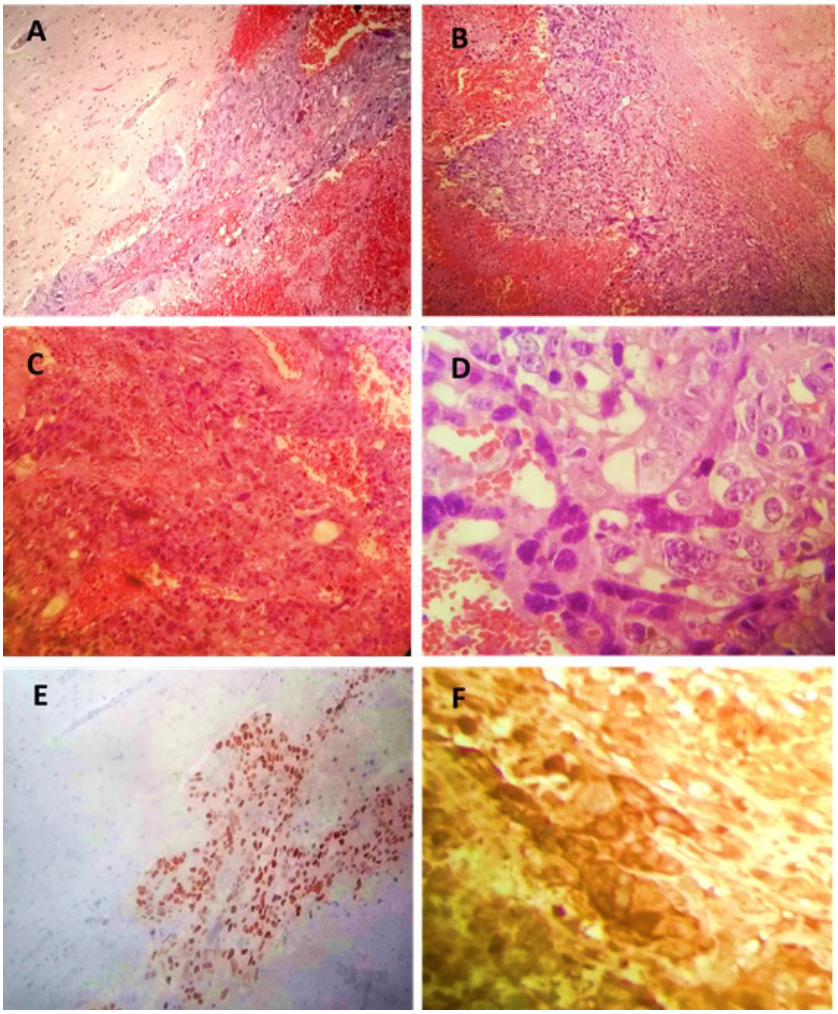

Figure 4: Brain metastasis of poor-differentiated lung squamous cell carcinoma: brain-tumor transition areas (40x) (A and B); tumor metastasis 100x (C) and 600x (D) (Hematoxylin & Eosin staining in A-D). Note the presence of syncytiotrophoblast and cytotrophoblast-like cells (D). Positive immunostaining for p63 (E) and β-hCG (F).

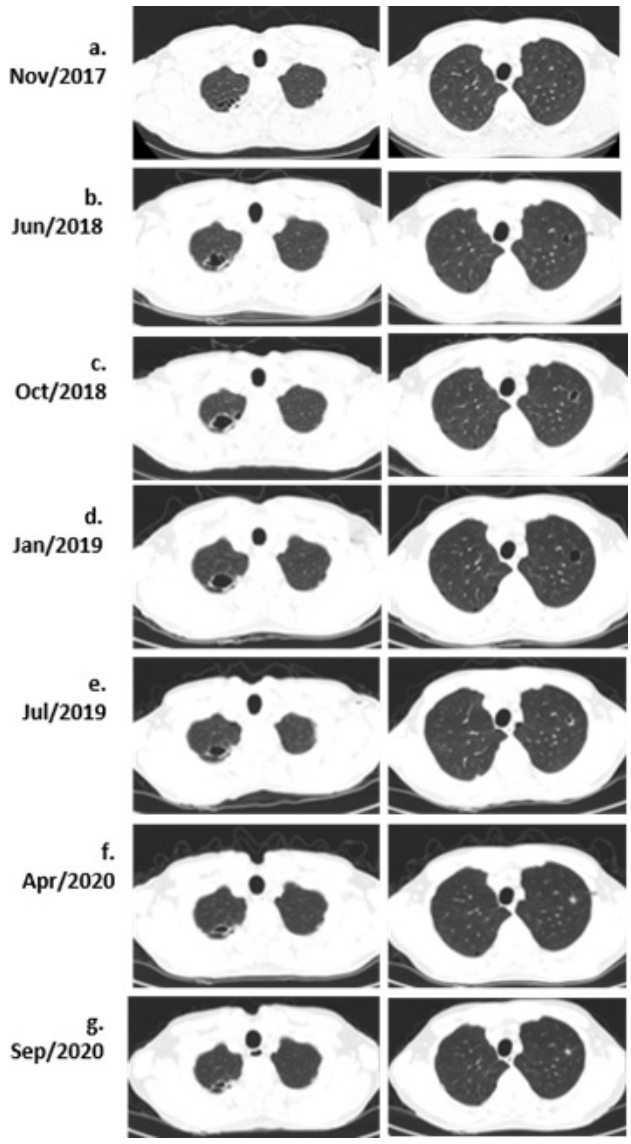

Figure 5: Initial presentation and evolution of cystic lung lesions on chest CT's at various points of the follow-up period, showing the progressive irregular thickening of cystic wall, the one on the left evolving to a solid nodule (a-e) and the onward reduction after starting the immunotherapy (f, g).

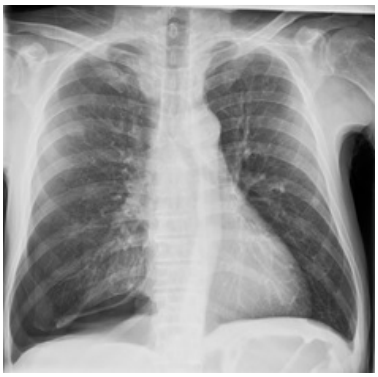

Figure 6: Chest X-ray showing right pneumothorax (absence of lung marks in the periphery of right hemithorax and a linear shadow of visceral pleura); multicystic airspace lesion is also seen on the left upper lung.

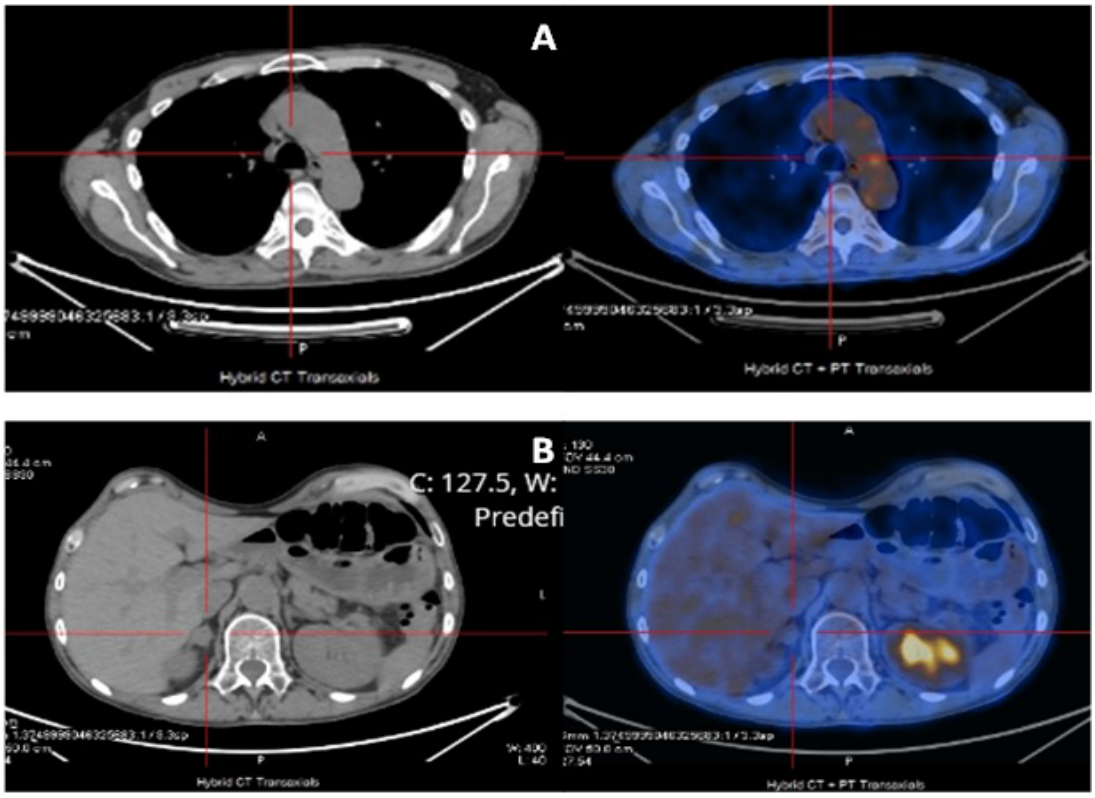

Figure 7: PET/CT images showing complete metabolic response both at the (A) mediastinum and (B) in right adrenal gland with nivolumab therapy.

Table 1: Clinical cases of stage IV lung cancer β-hCG producers described in the literature from the year 2000 onwards.

Gender	Age (years)	Smoker status	Clinical presentation	Lung cancer location	Histology	Metastasis pattern	β-hCG concentration (mUI/mL)	Treatment	Outcome
F	43	Current smoker	Amenorrhea +Positive pregnancy test +Chest pain	Right lung	Adenocarcinoma	Multiple pulmonary lesion+Paravertebral mass	436	Cisplatin +Vinorelbine (3c) Followed by Docetaxel (4c) Followed by Erlotinib	Deceased with evidence of oncological disease
M	43	Current smoker	Chest pain +Dyspnea +Gynecomastia	Right lung	Large cell carcinoma	Bilateral involvement+Pleural effusion+Mediastinal lymph nodes	4261	CHT not specify	Not reported
F	48	Current smoker	Bilateral cervical and supraclavicular adenopathy	Right lung	Adenocarcinoma	Bilateral involvement +Pericardial effusion+Brain metastasis	1161	Carboplatin +Pemetrexed (4c) Followed by Docetaxel (3c)	Deceased with evidence of oncological disease
F	62	Non-smoker	Dyspnea +Anorexia +Weight loss	Right lung	Adenocarcinoma	Adrenal metastasis	11212	Cisplatin +Etoposide (1c)	Deceased with evidence of oncological disease
M	50	Current smoker	Gynecomastia +Weight loss	Right lung	Pleomorphic carcinoma	Bilateral involvement+Brain metastasis +Ganglionar metastasis	6500	Cisplatin +Etoposide (4c)	Deceased with evidence of oncological disease
F	37	Current smoker	Pneumonia	Left lung	Large cell carcinoma	Bilateral involvement +Pericardial effusion	206	Best supportive care	Deceased with evidence of oncological disease
F	31	Current smoker	Metrorrhagias +Chest pain	Right lung	Squamous cell carcinoma	No	12238	Lobectomy	Not reported
M	68	Ex-smoker	Constitutional symptoms	Left lung	Squamous cell carcinoma	Bilateral involvement +Abdominal masses +Retroperitoneal	11286	Best supportive care	Not reported

Legend: β-hCG: Beta-human Chorionic Gonadotropin; c: cycles; CHT: Chemotherapy; F: Female; M: Male.

metastases. At that moment, the patient KPS score was 70. Treatment with second line docetaxel 75 mg/m^2 q3w was initiated but, after four cycles, lung disease was progressing. Programmed Death-Ligand 1 (PD-L1) IHC 22C3 was quantified, obtaining a >50% value and third line nivolumab 3 mg/Kg q^{2}w was initiated. After six months of therapy, the patient achieved metabolic complete response in PET/CT (Figure 7) and β-hCG remained within the reference values (Graphic 1, point D). Six months later the supposed primary lesion on the right apex and the metastatic cystic lesion became smaller, one of them on the left lobe full solid (Figure 5, Apr/2020).

At the present moment, the patient completed seventeen months of therapy and presents no signs of clinical, analytical or imaging progression.

Discussion

In this report we present the rare case of a man diagnosed with a stage IV β-hCG-secreting lung SCC. To the best of our knowledge, this is the first clinical case reporting a complete response to third line treatment nivolumab for this condition. We will now discuss the initial clinical presentation of this case; and analyze the difficulty of identifying lung cancers associated with cystic airspaces at early stages.

The patient presented with a chronic testicular pain for several months. The differential diagnosis for chronic orchialgia can include varicoceles, tumors, chronic epididymitis and low back strain. High levels of β-hCG initially prompted the medical team to investigate germinative tumors. The final diagnosis was made on the basis of imaging and histopathology studies. These were consistent with a poorly differentiated NSCLC (squamous type) with trophoblastic components (syncytiotrophoblast and cytotrophoblast) and strongly positive for β-hCG by immunostaining. As a concurrent illness the testicular pain was caused by degenerative spinal injuries with root compression.

Lung cancers associated with cystic airspaces are increasingly recognized as a cause of missed or delayed diagnosis. Paraseptal emphysema in the lung apices is common in smokers, often with apical scarring, which is difficult to differentiate from pericystic thickening, as it was in this case. The patient had also a few thin-walled lung cysts, from which some evolved to wall nodularity or diffuse wall thickening with disease progression (Figure 5). PET-CT is not useful to identify thin-walled cysts as malignant lesions, as the overall density of metabolically active cells is reduced. One of the complications that can occur with cystic lung metastases is the development of pneumothorax, as it occurred in the present case.

Some case reports have described stage IV β-hCG-secreting lung cancers, most with unusually rapid and progressive clinical course with widespread dissemination and chemo-resistant disease [4] (Table 1). The mechanism is not well understood but it has been suggested to be ectopic secretion by tumor cells that may act as a growth factor blocking apoptosis. Boucher et al. studied the expression of trophoblastic cell markers in lung carcinomas and concluded that theses markers were expressed in squamous cell carcinoma, adenocarcinoma and large cell carcinomas [5].

It must be highlighted that the initial good tumor response to cisplatin-gemcitabine with a decrease of the β-hCG level was not correlated with a clinical improvement as described in previous case reports (Table 1). The brain surgery was indicated for removal of the single brain metastasis in the setting of controlled systemic disease. However, dedifferentiation of the tumor and a stopping of β-hCG production occurred. As the patient did not respond to second line CHT with docetaxel, a complete response to nivolumab in monotherapy was unexpected.

Importantly, high β-hCG levels may be an exclusion criteria in clinical trials, particularly in women because of pregnancy suspected, leading to a delay in the appropriate management of these patients and also potentially preventing the participation in innovative therapeutic strategies [6,7]. Therefore, this clinical case may contribute to the development of new research hypotheses. Further studies are needed to explore the importance of the immune checkpoint inhibitors in this condition treatment [8-13].

Conclusion

To the best of our knowledge, this is the first report of a β-hCG-secreting lung SCC with brain metastasis with complete metabolic response to nivolumab in latter lines. It raises awareness on the possibility of lung cancers associated with cystic airspaces being missed on CT, leading to delayed diagnosis and, it may also help to guide treatment decisions in similar clinical scenarios.

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