Open Journal of
Clinical & Medical
Case Reports

Volume 4 (2018)
*Issue 9*

ISSN 2379-1039

# Serum beta-human chorionic gonadotropin secreting lung adenocarcinoma revealed by gynecomastia

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## Abstract

Gynecomastiais reported as a paraneoplasic syndrome. It is well known to be attributable to the ectopic Beta-Human Chorionic Gonadotropin (β HCG) secretionby gonadal and extragonadal originated cancer types. To our knowledge, only a few reports of gynecomastia as an earlier symptom of a lung cancercan be found in the literature. We report a rare case of 45 years–old man with a history of smoking, presented with bilateral tender breast enlargement and elevated β-hCG 74 mUI/l. Investigations revealed a lung adenocarcinoma with numerous metastases (bone, adrenals…). Our patient underwent radio and chemotherapy. Serum β HCG level decreased significantly to 17 mUI/l and gynecomastia regressed completely after 4 months. But our patient died 7 months later due to brain metastasis. Many authors have suggested the aggressive nature of βHCG positive tumors; thus, this atypical marker could be useful to predict prognosis and recurrence.

## Keywords

beta-human Chorionic gonadotropin; lung adenocarcinoma, gynecomastia; paraneoplastic syndrome

## Introduction

Gynecomastia is defined as the presence of palpable breast tissue in males unior bilaterally. The causes are benign in most cases but a careful diagnostic evaluation should be done since tumoralcauses exist (breast, testicular cancer). Gynecomastia as a paraneoplastic syndrome results from a paraneoplastic syndromes involving production of Human chorionic gonadotropin (HCG). This syndrome have been reported arising from tumors of multiple tissues, including bone, breast and stomach [1]. βHCG secretion is nowadays considered as paraneoplasic syndrome in numerous pulmonary carcinomas and was reported in 12% of NSCLC; elevated beta-human chorionic gonadotropin in such cases is not rare, however gynecomastia is uncommon [2] and may be the initial presenting complaint.

We report here a rare case of non-small cell lungcancer (NSCLC) secreting β -HCG in a male patient Thus, the awareness of paraneoplastic syndromes associated with lung cancer may lead to earlier diagnosis of malignancy.

## Case Presentation

A 45 years–old man, who was a sports teacher and father of three children, was referred to endocrinologists because of recent breast enlargement. He had a history of smoking and he noticed this gynecomastia since two months. He didn't reported any alcohol intake or home medication, weight loss or decreasing libido.

Physical examination showed bilateral moderate breast enlargement, firm and symmetric. All features of virilization (voice, facial and body hair, skeletal muscle bulk) were present and there was no goiter or lymphadenopathy. Biochemical testing for thyroid, liver, and kidney functions was normal.

There was a bilateral adrenal masses of two centimeters with a spontaneous radiographic density at 37 UH and low washout.

A fibrobronchoscopy revealed a mass and histopathological exam of biopsy material was consistent with poorly differentiated adenocarcinoma. In addition, β HCG expression was present in approximately 25 % of cells **Figure 2.**

Our case was β-HCG secreting non small cell lung carcinoma. Since the lesion was inoperable, a chemotherapy and palliative radiotherapy protocol was started. Four months later, our patient obtaineda total regression for his gynecomastia, and a markedly decreased in β HCGlevelat 17.5 UI/l.

The aggressive tumor continue to progress with development of brain metastasis. Our patient died 7 months later.

## Discussion

The main etiology of gynecomastia is an imbalance between androgens and estrogens with a relative estrogen excess. It is a common and benign symptom frequently seen during puberty and late adulthood. The elevated serum estrogens may be the results of excess of hCG commonly caused by gonadal and extragonadal cancer. Thus, the recognition of paraneoplastic gynecomastia should be the main target of physicians in these cases.

Secretion of HCG without clinical signs may occur in 10 to 15 per cent in all malignant neoplasms [3,4]. To our knowledge the number of case reports on β-hCG secreting lung cancer, remain rare [5-7]. Furthermore, clinically evident gynecomastia as a first sign of ectopic secreting β-hCG by lung tumors is uncommon.

The gynecomastia attributable to high level of hCG can be explained by the ability of the hCG to induce high level testosterone due to the homology between HCG and LH,and then higher level of estradiol resulting from the aromatization of testosterone [8].

Mechanism underlying the secretion of β-hCG by non-trophoblastic tumors remain poorly understood. Some authors explain this by a morphological and functional transformation (metaplasia) into a cell functionally similar to the trophoblastof the carcinomatous tissue [1]. Earlier data showed that fetal lung contain only trace to undetectable levels of hCG-beta mRNA [9]. However, in lung cancer tissues mRNA transcripts of the beta gene were detected resulting in a b-hCG production in malignantly transformed lung cells [10]. This suggested the possibility of reactivation of β-hCG gene transcription in the malignant transformed cells, leading to ectopic β-hCG protein expression [1].

To date many published reports describe the aggressive clinical course, chemo resistance and increased recurrence and in hCG secreting tumors. In fact free β-subunit and hyperglycosylated hCG were found to play a major role in the tumorigenesis of non-trophoblastic tumors. They would act as an autocrine anti-apoptotic (it reversesthe apoptosis-inducing effects of TGFβ due to the homology of structure) [11] and angiogenic growth factor (HCGitself has been suggested to be an angiogenic factor) [12]. Moreover, there it is suggested that there is a structural homology between HCGβ and the cystine knot growth factors in particular vascular endothelial growth factors (VEGFs) which are involved in metastasis and immune escape in cancers [13]. This molecular mechanism explain the poor prognosis and aggressive nature of such secreting tumors [14].

The findings supported the potential use of serum β-hCG to predict patients who are at risk of developing metastatic disease. Furthermore, it can be useful to evaluate the therapy response and predict the recurrence [1]. Gynecomastia is usually considered as an index of tumor activity and β-hCG expressing tumors are more commonly seen in patients with metastatic disease [8,9] and this is the case of our patient [15,16].

At present, many therapeutic approaches for such rare tumors continue to be the subject of investigation. Stewart A. observed a markedly delayed increase in pituitary gonadotropins after administration of 100 μg of gonadotropin-releasing hormone (LHRH) in a man with lung cancer. This chemotherapy restored to normal the HCG levels and the response to LHRH and resulted in an unusual 30-month complete remission [17]. HCG has been proposed as a ligand vehicle for toxic drugs, targeting the LH/hCG receptor reported to be expressed by malignant breast tissue.

- Inhibitory effects of anti-hCG antibodies in vivo in mice and of anti-sense oligonucleotides in vitro have been demonstrated [18-20].

-An anti-hCGcarboxy terminal peptide (CTP) vaccine has completed a phase II clinical trial in patients with colorectal cancer, which could be considered as a great step [21,22].

The study was hopeful for positive results especially because of the vaccine was administered to patients irrespective “of whether they were 'hCG positive' or not.

## Conclusion

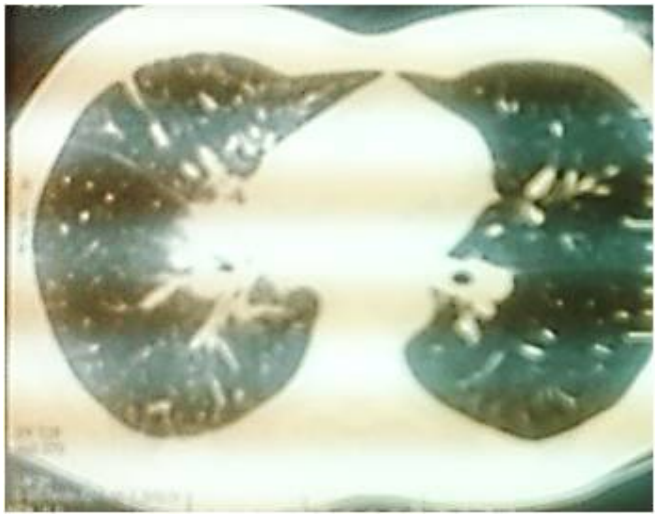
The report of this case of gynecomastia as a first sign of lung cancer is important to add data to the literature regarding this rare condition, to better understand its histopathogenesis, to help others in its diagnosis and management, and eventually to improve patient treatment and prognosis.

A large systematic evaluation of serum β-hCG levels and hormonal profiles is needed in oncology to further establish the concept of ectopic secretion especially in the lung cancer. Elevated βhCG levels seem to be associated with aggressive clinical course and it could be of useful role for evaluation of recurrence and therapy response.

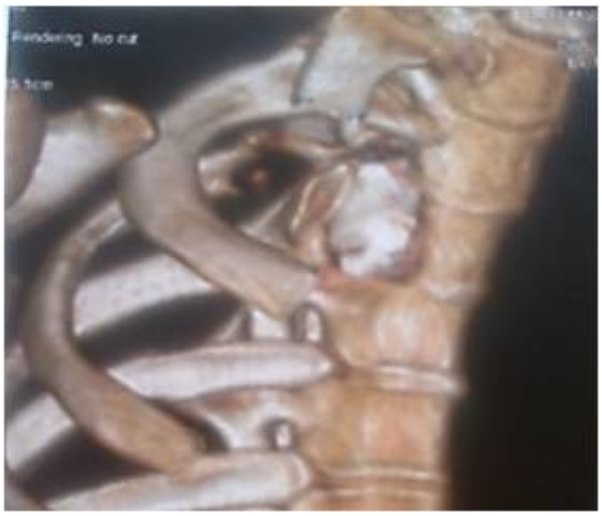
**Learning points :**

- Gynaecomastia is a very rare para neoplastic manifestation of lung cancer which is related to raised β-HCG
- Lung cancer secreting β-HCG are of poor prognosis and should be treated aggressively.
- β-HCG can be a biomarker for evaluation of recurrence and therapy response.

## Figures



A) ComputedTomographychestshows a pulmonary tumor mass on the apical region of right lung



B)Vertebral metastasis at the 3D computed tomography

**Figure 1:** Computed tomography at the initial diagnosis

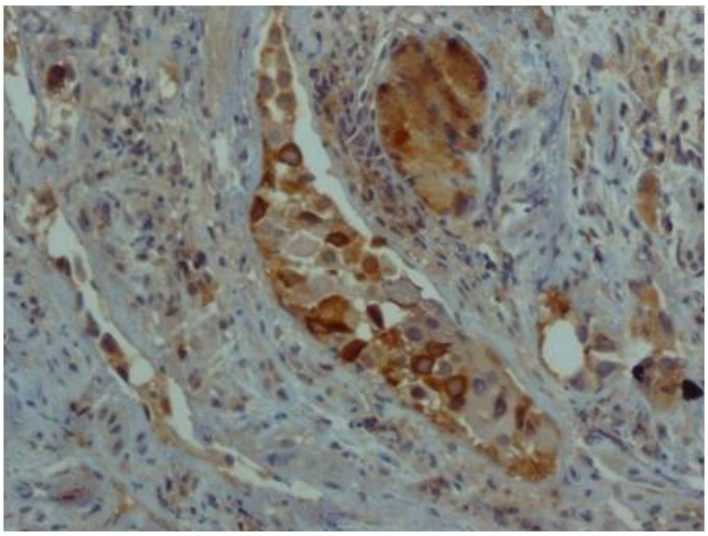


**Figure 2:** Endobronchial biopsy specimen showing β-HCG positive cytoplasm of tumour cells on immunohistochemistry (β-HCG immunostaining 400 X).

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**Manuscript Information:** Received: January 29, 2018; Accepted: May 11, 2018; Published: May 15, 2018

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**Citation:** Hadiji M, Sayadi H, Moussa A, Khochatali I. Serum beta-human chorionic gonadotropin secreting lung adenocarcinoma revealed by gynecomastia. Open J Clin Med Case Rep. 2018; 1413.



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