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Case report

Galactorrhea, mastodynia and gynecomastia as the first manifestation of lung adenocarcinoma. A case report

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ABSTRACT

Gynecomastia with mastodynia and galactorrhea as a paraneoplastic syndrome due to lung cancer with complete response after surgical excision is rare.

A 62-year-old Caucasian male presented with mastodynia, galactorrhea and right breast enlargement. Chest x-ray revealed a left upper lobe tumor. The patient had high levels of serum beta-human chorionic gonadotropin (b-HCG) and prolactine. Complete staging was negative for metastases.

A typical left upper lobectomy with radical mediastinal lymph node dissection was performed. Pathology report was consistent with a poorly differentiated adenocarcinoma ($T_2N_1M_0$). Immunohistochemically, multinucleate cells and occasional mononucleate tumor cells showed positivity for human chorionic gonadotropin.

The patient received adjuvant chemotherapy with cisplatin – navelbine. One year later physical examination showed regression of both gynecomastia and mastodynia and there was no nipple discharge, while he is free from local or distant metastatic disease and the b-HCG level is normal (1,59 mIU/ml).

This case represents a very rare, first manifestation of lung cancer. Galactorrhea, mastodynia and gynecomastia were the initial symptoms, which totally resolved following the successful surgical resection and adjuvant chemotherapy. In this case, prolactin and b-HCG are useful biomarkers during follow up for checking local or distal recurrence of the disease.

1. Introduction

Gynecomastia is defined as the abnormal development of large mammary glands in males, resulting in breast enlargement, and appears to be associated with elevation of the human chorionic gonadotropin levels. Human chorionic gonadotropin (HCG) is a glycoprotein hormone, normally produced in the human placenta during pregnancy. From the two subunits that comprise HCG, only the β-subunit is assayed. However, there are numerous conditions related with higher levels of β-HCG, apart from pregnancy, including ectopic secretion of the hormone from tumours of different organs, including lung, leading sometimes to the appearance of a paraneoplastic syndrome. Although has been documented in cases with non–small-cell lung cancer (NSCLC) since 1967 [1], variably elevated b-HCG levels are detected in up to 50% of patients with NSCLC, in either serum or urine and may be a poor prognostic marker [2,3]. Since these initial observations, more than fifteen years ago, there has been an increasing number of reports in the literature supporting the use of b-HCG as a serum biomarker for NSCLC [4–6]. Subclinical elevations in prolactin have also been described in a minority of NSCLCs. Recently, Seder et al. reported that both b-HCG and prolactin might be useful serum biomarkers for identifying patients with higher probability of NSCLC recurrence after initial excision [7]. We present a rare case of a male patient with lung cancer, appearing with gynecomastia causing mastodynia and galactorrhea as initial symptoms. These findings were attributed to paraneoplastic syndrome due to lung cancer, as they were associated with high b-HCG and prolactin levels and went into complete remission after surgical excision.

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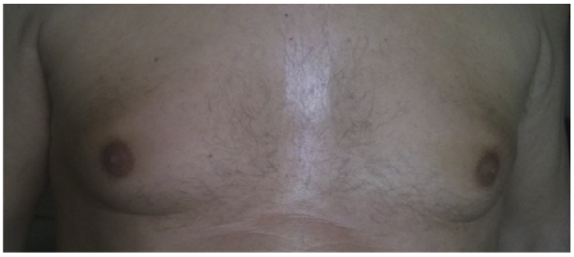

Fig. 1. Preoperative photo showing gynecomastia.

1.1. Case report

A 62-year-old Caucasian male presented with mastodynia, galactorrhea and right breast enlargement (Fig. 1). These symptoms were present for about 3 months before admission. He was a heavy smoker and he denied use of other medications, supplements or hormones. Physical examination showed a slightly enlarged right breast with a milky discharge from the nipple and sensitivity to palpation. Physical examination of the testes and testicular ultrasonography were normal. The performed mammogram revealed only bilateral hyperplasia of the mammary glands. Chest radiography revealed a left upper lobe tumor. Computed tomography (CT) of the chest was consistent with a solitary mass in the left upper lobe without mediastinal lymph node involvement (Figs. 2 and 3). Complete staging (abdominal and brain CTs and bone scanning) was negative for metastatic disease. In addition, PET/CT scan showed strong FDG uptake with a SUV of 6.4 in the left upper lobe tumor. The patient had a serum beta-human chorionic gonadotropin (b-HCG) level of 7660 mIU/ml (normally undetectable - normal values range: < 10 mIU/ml) and a prolactin level of 270 ng/ml (normal values range: 1,8–15,9 ng/ml). Alpha-fetoprotein value was within normal range.

A typical left upper lobectomy with radical mediastinal lymph node dissection was performed. The patient had a straightforward postoperative period. Pathology report was consistent with a poorly differentiated adenocarcinoma ($T_2N_1M_0$) (Fig. 4A). Immunohistochemically, the tumor cells were highly positive for cytokeratin (CK)7, CK AE1/AE3, CK CAM5.2, carcinoembryonic antigen (CEA) and TTF-1 (Fig. 4B). Neuroendocrine markers such as synaptophysin and chromogranin, vimentin and CK20 were negative. Moreover, the malignant cells were positive to human chorionic gonadotropin.

Fifteen days later, physical examination showed regression of both gynecomastia and mastodynia and there was no nipple discharge (Fig. 5). One month after surgery the bHCG level was 135 mIU/ml and the prolactin level was normal (14,40 ng/ml). The patient received adjuvant chemotherapy with cisplatin – navelbine. One year later he is free from local or distant metastatic disease and the b-HCG level is normal (1,59 mIU/ml).

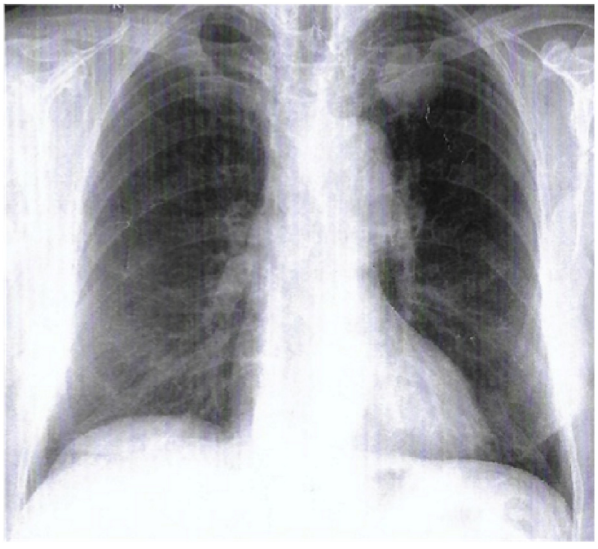

Fig. 2. Röntgen thorax showing a mass in the left upper lobe.

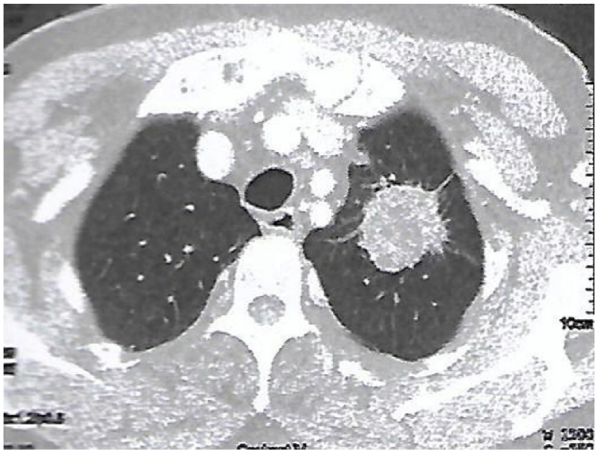

Fig. 3. Chest Computed Tomography with a solitary mass in the left upper lobe without mediastinal lymph node involvement.

2. Discussion

Gynecomastia is defined clinically by the presence of a rubbery or firm mass extending concentrically from the nipples. Gynecomastia results from an altered estrogen-androgen balance, in favor of estrogen, or from increased breast sensitivity to a normal circulating estrogen level [8]. The imbalance is between the stimulatory effect of estrogen and the inhibitory effect of androgen. Estrogens induce ductal epithelial hyperplasia, ductal elongation and branching, proliferation of the periductal fibroblasts and an increase in vascularity. The histologic picture is similar in male and female breast tissue after exposure to estrogen [9]. Estrogen production in males results mainly from the peripheral conversion of androgens (testosterone and androstenedione), through the action of the enzyme aromatase, mainly in muscle, skin, and adipose tissue, to estradiol and estrone. Gynecomastia is reported in some gonadal and extragonadal originating cancer types as a paraneoplastic syndrome [10,11]. The lung cancer with paraneoplastic syndrome as an initial symptom is difficult to diagnose because of its latent onset. Patients with lung cancer and gynecomastia as a paraneoplastic syndrome have a frequency of approximately 2.4% [12].

In our case an increased level of b-HCG and prolactin was noted. HCG is usually produced in the human placenta. b-HCG is used for detecting and managing gestational trophoblastic diseases, diagnosing quiescent gestational trophoblastic disease, diagnosing placental site trophoblastic tumor, managing testicular germ cell malignancies and monitoring other human malignancies [13]. b-HCG production is frequently detected in lung tumours, using immunohistochemical methods. Eventually, elevated serum levels of the b-subunit of b-HCG lead to paraneoplastic symptoms, like gynecomastia in male lung cancer patients [14].

Prolactin is a hormone with multiple biological actions, synthesized by the anterior pituitary gland and is best known for its roles in the mammary gland. However, it is now revealed that prolactin is able to exert its effects on additional cells and tissues (decidual cells of the placenta, bone, brain, lymphocytes and breast epithelial cells). Prolactin is secreted not only by lactotrophic cells of the pituitary gland but also by a variety of other normal tissues and human tumours including malignant tumours of the lung, kidney, uterine, ovary, and breast [15].

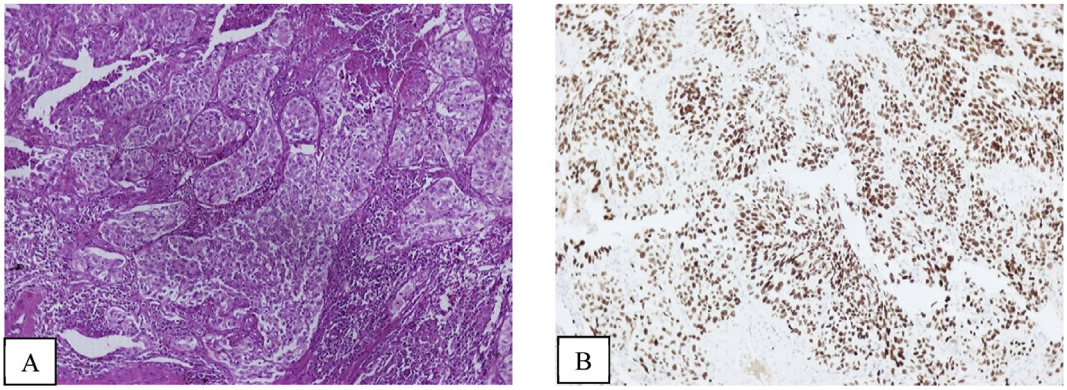

Fig. 4. A. Microscopic image of lung adenocarcinoma (H-E stain, x100), B. Microscopic image of the specimen depicting positivity for TTF-1 stain (x100).

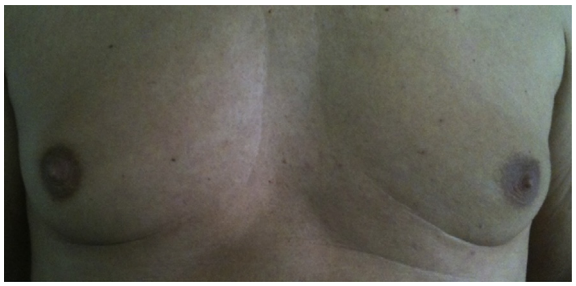

Fig. 5. Post treatment photo showing regression of gynecomastia.

Paraneoplastic syndromes (PNS) represent a clinical spectrum of manifestations of the indirect and remote effects produced by tumor metabolites or other products and exclude metastasis or any other normal events associated with tumor progression [16]. It is reported that 7.4% of all cancers have PNS associated with them. Although rare, it is important to be aware of these PNS as their clinical presentation could often be the first or most prominent clinical manifestation of cancer and they can raise suspicion of a deep-seated tumor [17]. The exact nature of the paraneoplastic phenomena associated with underlying malignancy is not fully understood. However, it was suggested that neoplastic cells utilize more than one way to produce components of PNS. Tumor cells can produce hormones, enzymes or fetal proteins, cytokines, stimulate antibody production and metabolize steroids [18]. Paraneoplastic syndromes occur in approximately 10% of all patients with lung cancer. Although gynecomastia has been documented in non–small-cell lung cancers (NSCLC), variably elevated b-HCG levels are detected in up to half of patients with NSCLC in either serum or urine using sensitive assays and may be a poor prognostic marker.

NSCLC secreting b-HCG hormone in men is rare, and to our knowledge, only five such cases have been reported in the international literature with variable outcomes [4, 13, 19–21]. Okutur et al. described a case of a 50-yr-old man with bilateral gynecomastia and elevated serum b-HCG levels due to a pleomorphic carcinoma of the lung. The b-HCG levels decreased after surgery, as happened in our case also. The authors correlated a sudden increase in b-HCG levels during the follow-up with early recurrence of the carcinoma, which was ascertained with positron emission tomography and fine needle biopsy [13]. Kocer et al. report another case of a 43-yr-old male with a b-HCG secreting NSCLC, with gynecomastia, although in their report they present no clues about the fluctuation of b-HCG levels after the initiation of chemotherapy [4].

Due to the tight correlation of b-HCG with pregnancy, some authors have described elevated levels of the hormone in female patients with NSCLC. After gynecological and biochemical examination ruled out an unknown pregnancy, the elevated b-HCG were attributed to the tumor, which was certified from the surgical specimen immunohistochemically [22]. As Khobta reports, the suspicion of this rare secretion from lung tumours is important in order to rule out pregnancy for female patients susceptible to chemotherapy who might appear with elevated levels of b-HCG [23].

3. Conclusion

This case represents a very rare first manifestation of lung cancer. Galactorrhea, mastodynia and gynecomastia were the initial symptoms which completely resolved following the successful surgical resection and adjuvant chemotherapy. Elevated levels of b-HCG due to lung cancer might manifest as gynecomastia in male patients or cause suspicion of pregnancy in female patients. In either case prolactin and b-HCG might be useful biomarkers during follow up for checking recurrence of the disease, alongside other examinations, provided that the neoplasm retains its secretory behaviour and histological subtype.

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