

Pleomorphic Carcinoma of the Lung with High Serum Beta-human Chorionic Gonadotropin Level and Gynecomastia

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Although gynecomastia is a well-defined paraneoplastic syndrome in patients with non-small cell lung cancer, the association with pleomorphic carcinoma has not been reported. A 50-yr-old man presented with bilateral gynecomastia and elevated serum beta-human chorionic gonadotropin (β hCG) level. Chest tomography showed a mass in the right middle lobe. Right middle lobectomy and mediastinal lymph node dissection were performed. β hCG levels decreased rapidly after surgery. Histological examination revealed pleomorphic carcinoma with positive immunostaining for β hCG. Serum β hCG levels began to increase gradually on postoperatively 4th month. Computed tomography detected recurrence and chemotherapy was started. After second cycle of chemotherapy, β hCG levels decreased dramatically again and tomography showed regression in mass. Patient died 6 months later due to brain metastasis. β hCG expression may be associated with aggressive clinical course and increased risk of recurrence, also β hCG levels may be used to evaluate therapy response in patients with pleomorphic carcinoma.

Key Words: Pleomorphic Carcinoma; Lung Neoplasms; Chorionic Gonadotropin, Gynecomastia

INTRODUCTION

Pleomorphic carcinoma of the lung is defined as a group of poorly differentiated non-small cell carcinoma that contains a component of sarcoma or sarcoma-like elements and shows carcinomatous as well as spindle and/or giant cell components [1]. Pleomorphic component should comprise at least 10% of neoplasm. It's a rare tumor that makes up only 0.1% to 0.4% of all malignant lung tumors, and its clinical prognosis is highly unpredictable [2-4].

Elevated serum beta-human chorionic gonadotropin (β hCG) levels have been reported in 12% of NSCLC patients [5]. When immunohistochemical methods are used, β hCG positivity have been detected in 28% of the resected specimens [5]. Although β hCG production is not seen rarely in NSCLC, clinically significant symptoms, e.g. gynecomastia are uncommon.

Here we describe a 50-yr-old male patient with pulmonary pleomorphic carcinoma producing high levels of β hCG and presenting with gynecomastia.

CASE REPORT

A 50-yr-old man with a history of smoking presented with bilat-

eral gynecomastia and weight loss on December 4, 2008. Physical examination showed bilateral slightly enlarged breasts. Although his serum AFP level was in normal range, his serum β hCG level was found to be elevated (6,500 MIU/mL). Physical examination of the testes and testicular ultrasonography did not detect any mass formation. Chest radiography revealed a right paracardiac opacity. Computed tomography (CT) showed a solitary mass in the right middle lobe (Fig. 1). In PET scan, a solitary hypermetabolic lesion (SUV: 12), 6 cm in size, was identified in the right middle lobe. The brain MRI detected no abnormalities. After excluding the presence of any middle zone tumors and lymph node involvement, excision of right lung lesion was planned.

The pleural cavity was entered through a right thoracotomy at the fifth intercostal space. The mass was explored in right middle lobe. Well-shaped mass located in the right middle lobe was seen; frozen section performed during operation identified malignancy, therefore a decision for right middle lobectomy was made. Major and minor fissures were divided free. Middle lobe arterial branches were explored and freed circumferentially by sharp and gentle blunt dissection and tied with 2-0 silk sutures and divided between ligatures. Middle lobe vein was isolated, ligated and divided between ligatures. Middle lobe bronchus

was dissected free and a TA 30 stapler was used to close the bronchus. After the staple line had been placed, a bronchus clamp was placed distal to the staples. Right middle lobectomy and mediastinal lymph node dissection were performed. Operation was finished without complication.

Pathological examination of lobectomy material revealed a peripherally located, 5 cm-in diameter, cavitary tumoral lesion. Microscopically, the tumor consisted mostly of polygonal pleomorphic cells, intermingled with few inflammatory cells (Fig. 2A). There were limited number of carcinoma foci with squamoid differentiation. Some non-cohesive multinuclear giant tumoral cells (giant cell component without syncytiotrophoblast) were seen in a few areas. The diagnosis of pleomorphic carcinoma was made due to cyokeratin immunopositivity in most of the tumor cells. β hCG and PLAP expression was present in approximately 40% of the multinuclear giant and polygonal cells on immunohistology, but the tumor cells were negative for TTF-1 (Fig. 2B, C). There was no tumoral involvement in the mediastinal and hilus lymph nodes.

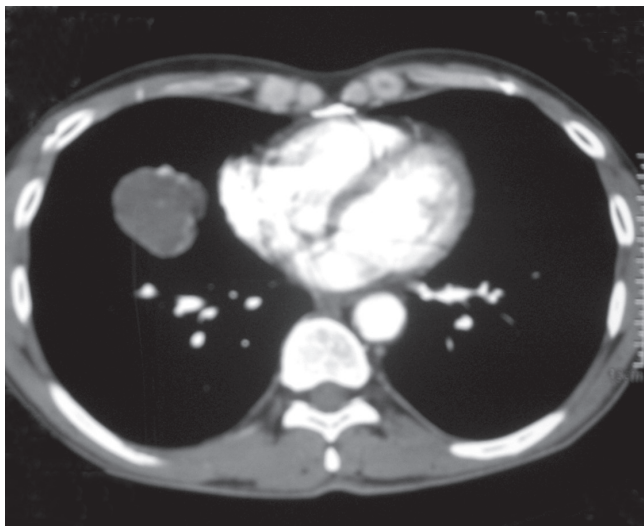


Fig. 1. Thorax CT scanning show solitary mass with 5.5×4.5 cm in size in the right middle lobe.

After surgery, serum β hCG level decreased gradually. At third day after operation, sudden loss of consciousness and respiratory distress occurred; urgent cranial CT scan was done. Right cerebellar infarction, closure of fourth ventricles and hydrocephalus were observed. In emergency conditions suboccipital craniotomy, right cerebellar infarctectomy and ventricular drainage were performed, pathology of resected material diagnosed cerebellar subacute infarction. Anticoagulant therapy was started. Tracheostomy and gastrostomy were applied.

Serum β hCG levels increased gradually in time during the patient's follow-up suggesting relapse or metastasis (Fig. 3) and subsequently a positron emission tomography scan was obtained which revealed a 3×4 cm in size, pleura-based lesion with a SUV of 6.2 located in the superior-posterior segment of the right hemithorax and FDG positive enlarged mediastinal lymph nodes. Histopathological verification of transthoracic fine needle aspiration biopsy material was consistent with pleomorphic carcinoma. Therefore chemotherapy was started with the indication of recurrent lung cancer. After two cycles of cispl-

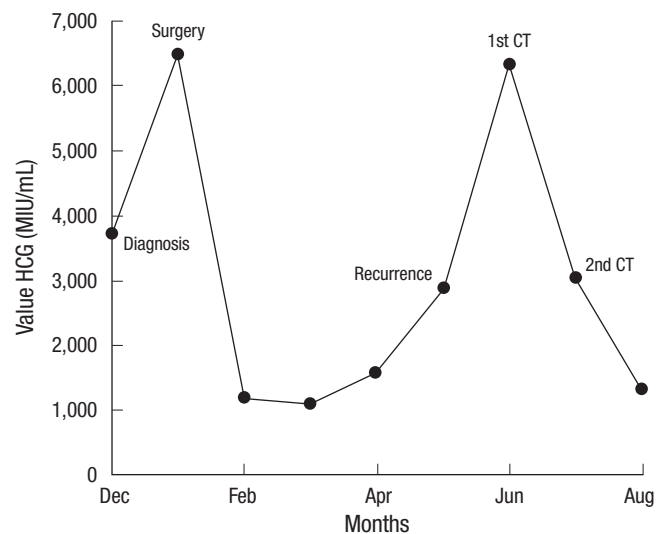


Fig. 3. β hCG level and its relation with treatment procedures.

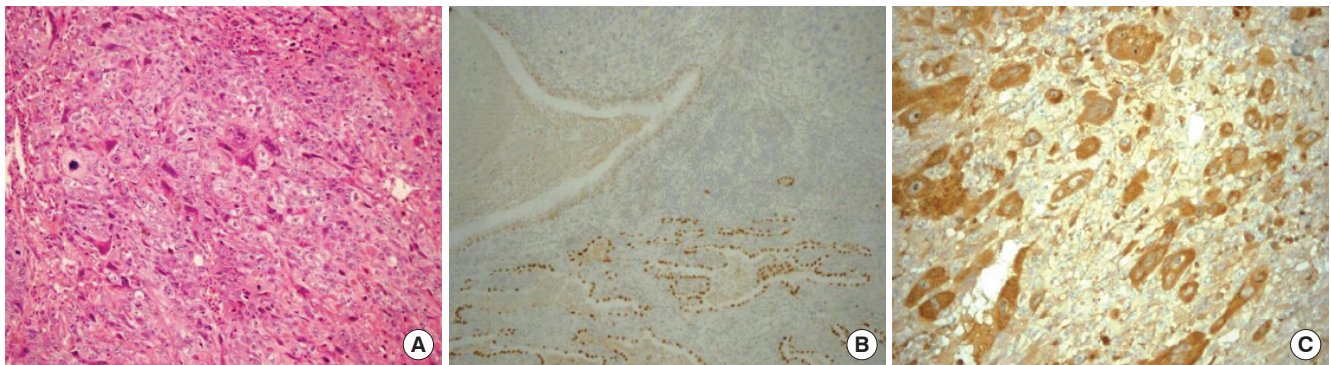


Fig. 2. Histopathological pictures of the tumor which represents of the pleomorphic carcinoma. (A) The tumor consists of polygonal tumor cells (H&E), (B) TTF-1 negativity of the tumor (upper part of the picture) while non-tumoral lung parenchyma showed TTF-1 positivity, (C) β hCG positivity in the giant multinuclear tumor cells.

atin-etoposid based chemotherapy, the levels of serum β hCG decreased dramatically (Fig. 3) and regression in the size of the lesion was observed through CT scan. Four months after the start of chemotherapy, the patient presented with headache and somnolence. Brain MRI showed multiple metastatic lesions with the largest one being 3 cm in diameter and accompanying perilesional edema. Antiedema treatment was started and palliative whole brain radiotherapy was performed. The patient died 2 months later from respiratory failure due to progression of brain metastases and cerebral edema resulting herniation.

DISCUSSION

In the 1999 WHO/International Association for the Study of Lung Cancer Histological Classification of Lung and Pleural Tumors, primary pulmonary choriocarcinoma is described as a miscellaneous tumor [1]. Primary extragonadal choriocarcinoma is very rare and when it occurs, it is usually located in the mid-line structures, mainly the retroperitoneum, mediastinum, or cranial cavity, although other sites have been reported. One of the least common sites is the lung [6]. Large cell carcinoma and pleomorphic carcinoma may occasionally include pleomorphic multi- and/or mononucleated tumor giant cells, which are similar to syncytiotrophoblastic cells and cytotrophoblastic cells of choriocarcinoma. This pathological image is sometimes confusing. In our case's histopathological investigation syncytiotrophoblastic and cytotrophoblastic cells were not seen. Giant cells suggesting choriocarcinoma stained positive for germ cell markers such as β hCG, HPL and PLAP, but were negative for TTF-1; so that tumor was not exactly derived from the lung. In the light of these findings this tumor was diagnosed as pleomorphic carcinoma of the lung with a giant cell component and expressing β hCG.

β 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 [7]. β hCG is usually produced in the human placenta. Although β hCG synthesis in NSCLC is well-known, β hCG producing pleomorphic carcinoma is very rare [8, 12]. Thus, to our knowledge this is the third case of pleomorphic carcinoma of the lung producing β hCG in the literature. Another important issue in our case is, elevated serum β hCG levels were associated with clinically significant gynecomastia. Gynecomastia is reported in some gonadal and extragonadal originated cancer types as a paraneoplastic syndrome [9, 10]. But again to our knowledge our case is also the first case with gynecomastia in pleomorphic carcinoma of the lung. As expected, with decreasing levels of β hCG after treatment gynecomastia gradually regressed.

The association between serum β hCG levels and recurrence

in patients with lung cancer were previously reported in the literature [5, 11]. In our patient, β hCG levels decreased after surgery, elevated with recurrence, and decreased again with chemotherapy. Hirano et al. had suggested that pleomorphic carcinoma patients with immunohistochemical positivity for β hCG have an elevated risk of local recurrence and metastasis [12]. Although our patient initially presented with a stage IB tumor, recurrence occurred in the postoperative 4th month. Therefore elevated β hCG levels may be associated with aggressive clinical course and increased risk of recurrence in patients with pleomorphic carcinoma expressing β hCG. Furthermore it may have an useful role for evaluation of recurrence and therapy response.

In patients with lung carcinoma, cases about development of cerebral infarct during or after surgical approaches (pneumonectomy or lobectomy) for primary tumor have been reported rarely in the literature. In these cases tumor embolies originating from tumor cells disseminating to systemic circulation through pulmonary vein in the course of surgical procedures are held responsible [13, 14]. Risk factors associated with arterial thromboembolism in patients with lung carcinoma are chemotherapy (especially cisplatin based) [15], targeted therapy (bevacizumab) [16], tumor induced nonbacterial thrombotic endocarditis [17] and disseminated intravascular coagulation [18]. Acute cerebral infarction due to tumor emboly developing after lobectomy for brain metastases was described in a case report [14]. However in our case, there were no tumor cells in histopathological examination of resected cerebral infarct material. Furthermore any of the risk factors related with arterial thromboembolism were absent in our case. In the light of these findings, we hypothesize that cerebral thromboembolism may have occurred due to hypercoagulability state associated with the primary tumor.

In conclusion, pleomorphic carcinoma is one of the rare tumors of the lung with clinically unpredictable course. Our patient is the first case of pleomorphic carcinoma of the lung presenting with gynecomastia reported in the literature. Elevated β hCG levels may be associated with early recurrence and poor prognosis in patients with pulmonary pleomorphic carcinoma.

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