ECTOPIC ACTH SECRETION WITH CONCOMITANT HYPERAMYLASEMIA IN A PATIENT WITH SMALL CELL LUNG CARCINOMA: CASE REPORT

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SUMMARY – Histologically confirmed small cell lung cancer associated with Cushing's syndrome and elevated amylase is rarely described in the literature. We present a case of a 63-year-old patient admitted to cardiology department due to shortness of breath, exhaustion, palpitations and nausea. Elevated values of troponin and electrocardiography suggested that he could have acute coronary syndrome. According to the radiologist's opinion, plane lung radiography was normal. Elevated level of amylase was found in both serum (3802 U/L, normal range 28-100) and urine (12012 U/L, normal range 0-450 U/L), as well as elevated sodium (156 mmol/L, normal range 137-147 mmol/L), hyperglycemia (12 mmol/L, normal range 3.8-6.1 mmol/L) and lowered serum potassium (1.7 mmol/L, normal range 3.5-5.3 mmol/L). Computerized tomography (CT) of the abdomen revealed a tumor of the left adrenal gland and enlargement of the right adrenal gland with normal structure of the pancreas. During hospitalization, the patient had blood while coughing and CT scan of the lungs showed a tumor 48x38x51 mm in size localized in the laterobasal segment of the left lung with mediastinal lymphadenopathy. He also had bilateral pleural effusions with signs of pulmonary embolism, which explained elevated troponin values. Biopsy confirmed microcellular lung carcinoma and tumor cells were diffusely positive for TTF-1 and focally for CK7, expressing markers of neuroendocrine differentiation (chromogranin +++, synaptophysin +++, NSE ++). Since neuroendocrine tumor was confirmed and the patient had low potassium and high glucose, hypercortisolism was suspected. High morning cortisol (1784 mmol/L, normal range 171-536) and unsuppressed ACTH (214 pg/L, <60), as well as a high level of chromogranin (1339 μg/L, <65) were determined. During hospital stay, the patient developed heart and respiratory failure and died in the second week of hospitalization.

Key words: *Small cell lung carcinoma; Adrenocorticotropic hormone; Hyperamylasemia; Case reports*

Introduction

Small cell lung cancer (SCLC) is a neuroendocrine carcinoma that exhibits aggressive behavior, rapid growth, early spread to distant sites, exquisite sensitivity to chemotherapy and radiation, and frequent association with distinct paraneoplastic syndromes, including hypercalcemia, Eaton-Lambert syndrome, syndrome of inappropriate diuretic hormone, and many others.

Ectopic adrenocorticotropic hormone (ACTH) secretion was the first paraneoplastic endocrine syndrome described in the literature. The most common tumors associated with ectopic ACTH production are small cell lung cancer and atypical carcinoids[1]. The

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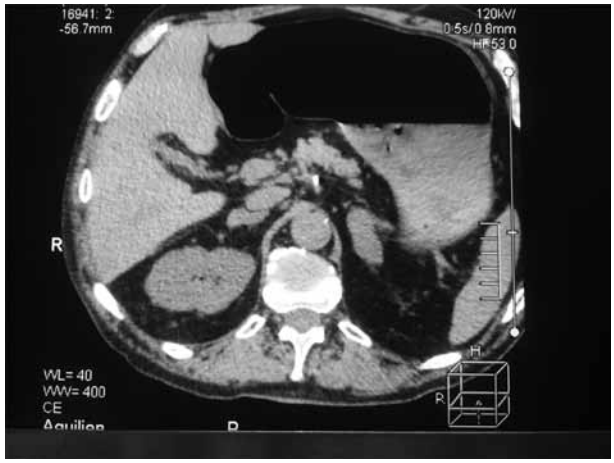

Fig. 1. Abdominal CT scan showing tumor of the left adrenal gland and enlargement of the right adrenal gland. Liver and pancreas appeared normal.

first case report of elevated serum amylase caused by lung carcinoma was published in 1951[2]. Since then, mostly cases of amylase producing tumors described in the literature have been ovarian cancer, pheochromocytoma and multiple myeloma[3]. Elevated serum and urine amylase associated with lung cancer is a rare condition occurring in 1% to 3% of all lung cancer cases[4]. The highest incidence of lung cancer is in male population aged over 65 years. However, amylase producing lung carcinomas are often seen in younger population aged 53 to 58 years[5]. More than 80% of cases are adenocarcinoma associated and very rarely hyperamylasemia is seen in microcellular carcinoma[5].

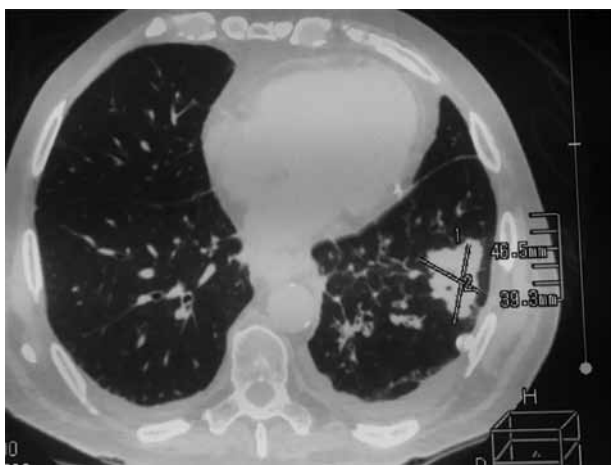

Fig. 2. CT scan of the thorax showing tumor in the left lung.

The occurrence of elevated serum amylase is more frequent in males (60%) and is associated with worse prognosis and more disseminated metastases[6].

Case Report

A 63-year-old patient was admitted to cardiology department due to shortness of breath, exhaustion, palpitations and nausea. He had a history of arterial hypertension, alcohol consumption and smoking 20 cigarettes a day for the last 40 years. Clinical examination showed plethoric facies and lowered respiratory sound with elongated expirium on auscultation. Elevated values of troponin and electrocardiography suggested that he could have acute coronary syndrome. Elevated level of amylase was found in both serum (3802 U/L, normal range 28-100 U/L) and urine (12012 U/L, normal range 0-450 U/L), along with elevated sodium (156 mmol/L, normal range 137-147 mmol/L), hyperglycemia (12 mmol/L, normal range 3.8-6.1 mmol/L) and lowered serum potassium (1.7 mmol/L, normal range 3.5-5.3 mmol/L). Serum lipase was normal (35 U/L, normal range 18-180 U/L). Initial plane lung radiography was normal. Abdominal ultrasound examination revealed enlarged head of the pancreas. Computerized tomography (CT) of the abdomen showed a tumor of the left adrenal gland and enlargement of the right adrenal gland. The liver

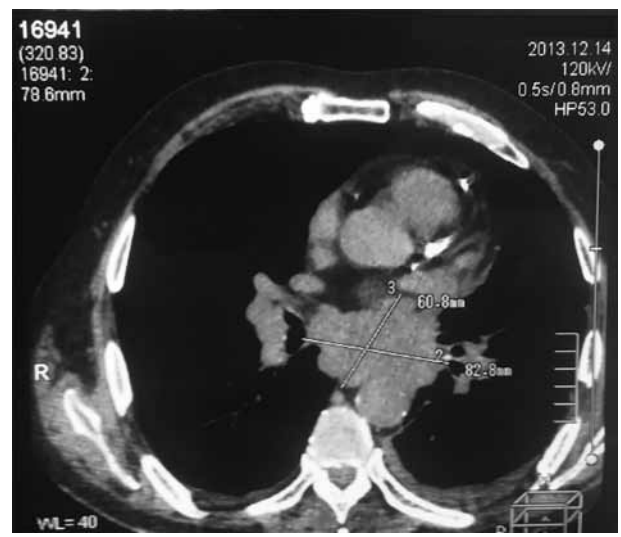

Fig. 3. CT scan of the thorax: mediastinal lymphadenopathy.

and pancreas appeared normal (Fig. 1). He had blood while coughing during hospitalization. CT scan of the lungs revealed a tumor 48x38x51 mm in size in the laterobasal segment of the left lung (Fig. 2), with lymphadenopathy of the mediastinum (conglomerate of lymph nodes in posterior mediastinum, 82x60x52 mm in diameter). In addition, bilateral pleural effusions (Fig. 3) were found. Elevated values of the following tumor markers were found: NSE=77.43 ng/mL (<16.3), CYFRA21.1=7.20 ng/mL (<3.0), and CA19-9=210.8 U/mL (<35.4).

Bronchoscopic examination was conducted and biopsy from the left laterobasal segment was obtained. Biopsy confirmed microcellular lung carcinoma; tumor tissue consisted of oval tumor cells about twice of the size of lymphocytes, with deficient cytoplasm and big hyperchromatic nuclei. Tumor stroma was scarce and there were a number of large necrosis foci. Tumor cells were diffusely positive for TTF-1 and focally for CK7, and expressed markers of neuroendocrine differentiation (chromogranin +++, synaptophysin +++, NSE ++), while being negative for CK20. Proliferation index was high and 90% of cell nuclei expressed Ki-67 antigen (Fig. 4). A high value of morning cortisol (1784 mmol/L, normal range 171-536 mmol/L), unsuppressed ACTH (214 pg/L, <60) and high level of chromogranin (1339 μg/L, <65) were found. During hospital stay, the patient developed heart and respiratory failure and died in the second week of hospitalization.

Discussion

We present a very rare clinical case of elevated amylase without signs of acute pancreatitis and with normal CT scan of the pancreas. The source of ectopic elevated amylase secretion was small cell lung cancer confirmed by immunohistology.

Expression of neuroendocrine markers including synaptophysin, chromogranin A, and neuron-specific enolase indicates the presence of neuroendocrine differentiation of carcinoma, i.e. small cell carcinoma or neuroendocrine large cell carcinoma of the lung. Subtype identification of lung carcinoma is sometimes

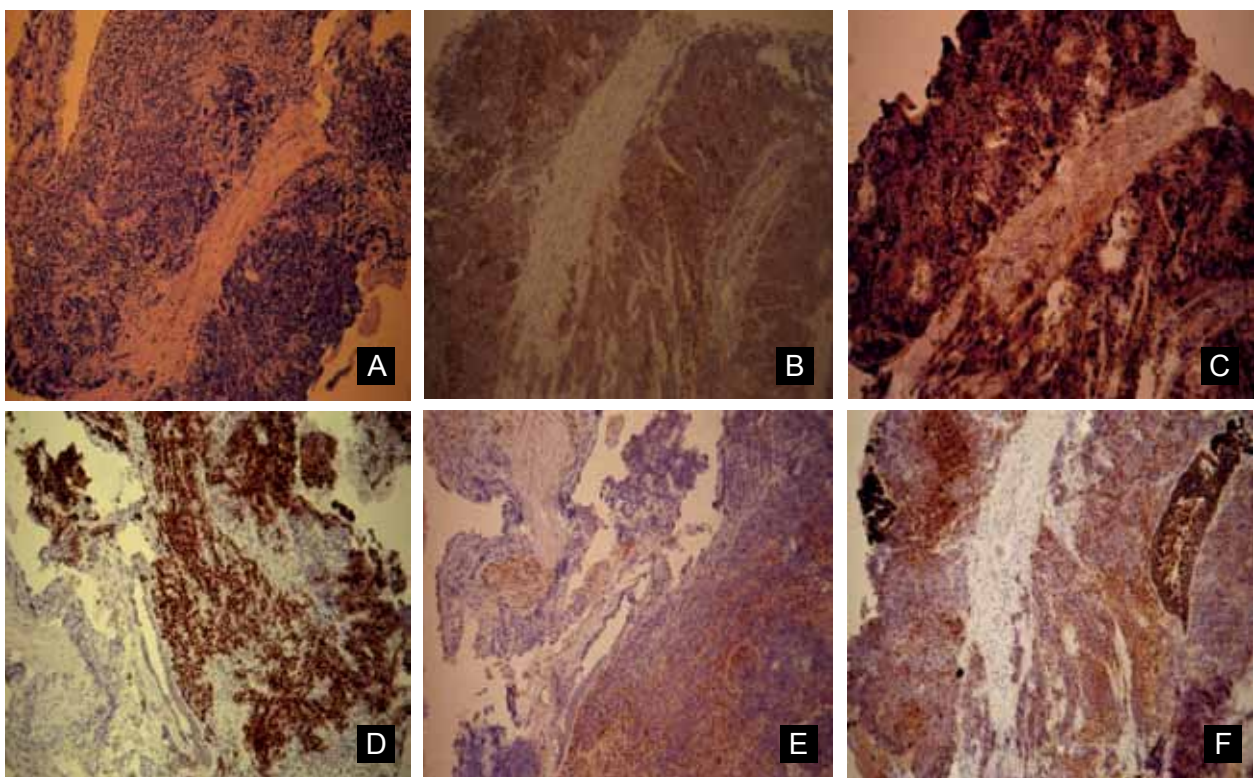

Fig. 4. Histologic samples dyed in: hematoxylin-eosin (HE) x100 (A), synaptophysin LSAB x200 (B), chromogranin A LSAB x200 (C), CK7 LSAB x 00 (D), TTF1 LSAB x100 (E), and NSE x200 (F).

hard based only on cellular morphology, but a high nucleo-cytoplasmic ratio, uniformity of cellular shape and size, and immunohistochemical phenotype confirmed it to be a small cell carcinoma.

The pathophysiology of amylase production in lung cancer is still unclear. Amylase activity is noticed in normal epithelial ciliated cells of the bronchus and normal cells of bronchial glands[3]. Direct invasion of tumor cells in submucosa of bronchial glands can be the cause of amylase activity. This can be the reason for elevated amylase in adenocarcinoma. In small cell carcinoma, elevated amylase is considered to be connected to carcinogenesis of this tumor type. In embryonal period, these cells have multidirectional differentiation, which can be directed towards endocrine, but also to exocrine function. Therefore, some studies suggest that elevated amylase can be considered as one of the manifestations of paraneoplastic syndrome in microcellular carcinoma of the lung[7]. Although amylase is not associated with carcinogenesis, in our case it could be used as a tumor marker.

Prolonged elevated levels of sodium and hyperglycemia, accompanied with decreased potassium, bilateral adrenal hyperplasia and hypercortisolemia with high ACTH pointed to ACTH dependent Cushing's syndrome. This indicated that ACTH originated from lung cancer.

Ectopic Cushing's syndrome is common in patients with neuroendocrine tumors such as small cell lung cancer, medullary carcinoma of thyroid gland, and pancreatic neuroendocrine tumor[8,9]. This syndrome is connected with decreased survival rates, shortened life expectancy and more severe clinical manifestations[10]. Ectopic Cushing's syndrome occurs in 8% to 20% of patients with microcellular lung carcinoma[11].

In patients with small cell lung cancer, paraneoplastic syndrome including Cushing's syndrome is often seen. High levels of amylase sometimes do not point to the pathology of the pancreas. Neuroendocrine tumor (especially small cell carcinoma of the lung) should be suspected in patients without significant clinical abdominal symptoms, and with normal ultrasonography and CT of the pancreas.

Acknowledgment

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Sažetak

EKTOPIČNO LUČENJE ACTH UDRUŽENO S HIPERAMILAZEMIJOM U BOLESNIKA S KARCINOMOM PLUĆA MALIH STANICA: PRIKAZ SLUČAJA

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Histološki potvrđeni slučajevi karcinoma malih stanica udruženi s Cushingovim sindromom i povišenim vrijednostima amilaze u serumu su jako rijetko opisani u literaturi. Prikazujemo slučaj 63-godišnjeg bolesnika primljenog na odjel kardiologije zbog kratkoće daha, iscrpljenosti, lupanja srca i mučnine. Povišene vrijednosti troponina i elektrokardiogram ukazivali su na mogući akutni koronarni sindrom. Prema mišljenju radiologa i snimaka pluća radiografija je bila normalna. Povišena razina amilaze pronađena je u serumu (3802 U/L, normalni raspon 28-100 U/L) i mokraći (12012 U/L, normalni raspon 0-450 U/L), kao i povišenje natrija (156 mmol/L, normalni raspon 137-147 mmol/L), hiperglikemija (12 mmol/L, normalni raspon 3,8-6,1 mmol/L) i nizak serumski kalij (1,7 mmol/L, normalni raspon 3,5 do 5,3 mmol/L). Kompjutorizirana tomografija (CT) trbuha pokazuje tumor lijeve nadbubrežne žlijezde i proširenja desne nadbubrežne žlijezde s normalnom strukturom gušterače. Tijekom hospitalizacije bolesnik je izbacivao krv dok kašlje i CT pluća pokazuje tumorsku masu veličine 48x38x51 mm, lokaliziranu u laterobazalnom segmentu lijevog pluća s medijastinalnom limfadenopatijom. On je također imao bilateralne pleuralne izljeve sa znakovima plućne embolije, što je bio razlog povišene vrijednosti troponina. Biopsija je potvrdila da se radi o karcinomu pluća malih stanica i tumorske stanice su bile difuzno pozitivne na TTF-1 i fokalno na CK7, izražavajući biljege neuroendokrine diferencijacije (kromogranin +++, sinaptofizin +++, NSE ++). Kako je potrvđen neuroendokrini tumor te kako je bolesnik imao nizak kalij i visoku razinu glukoze, postavljena je sumnja na hiperkortizolizam. To je potvrdio nalaz visoke razine jutarnjeg kortizola (1,784 mmol/L, normalni raspon 171-536) i nesuprimiranog ACTH (214 pg/L, <60), kao i visoka razina kromogranina (1339 μg/L, <65). Tijekom boravka u bolnici u bolesnika se razvila srčana i respiracijska insuficijencija te je preminuo u drugom tjednu hospitalizacije.

Ključne riječi: *Karcinom pluća malih stanica; Adrenokortikotropni hormon; Hiperamilazemija; Prikazi slučaja*