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Case report

Ectopic calcitonin secretion in a woman with large cell neuroendocrine lung carcinoma

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ABSTRACT

OBJECTIVE: Serum calcitonin (CT) is a sensitive but not specific marker for medullary thyroid carcinoma (MTC). There are a large number of conditions that may elevate CT levels. CASE REPORT: Herein we present the case of a 47-year old woman with Hashimoto thyroiditis, goiter, cervical lymphadenopathy and high CT and CEA levels. After surgical extirpation of the lymph node neuroendocrine cancer metastasis was suspected. Computed tomography of the chest showed a tumor mass on the right lung. Bronchoscopy was performed and pathological and immunohistochemical analysis revealed large cell neuroendocrine lung cancer (LCNEC). After chemotherapy, significant reduction of tumor mass was achieved with a moderate decrease in CT levels in parallel. CONCLUSIONS: We present a female with LCNEC, a condition which is usually observed in older men (7th decade) and is not associated with CT secretion. Hashimoto thyroiditis is associated with increased incidence of different types of cancers (e.g. thyroid, colon). No reports at present exist on the incidence of lung cancers in patients with thyroid disease.

Key words: Calcitonin, Ectopic Secretion, LCNEC

INTRODUCTION

Serum calcitonin (CT) is considered as a sensitive marker of medullary thyroid carcinoma (MTC), and consecutive determination of CT in all patients with thyroid nodules as a screening procedure for the diagnosis of MTC has been proposed.[1,2] However, CT is not an especially specific marker for MTC: only 10-40% of all patients with thyroid nodules and elevated basal CT levels had MTC,[3] with some patients being erroneously submitted to total thyroidectomy due to elevated CT levels.[4] There are numerous conditions that might be associated with elevated basal CT levels such as hypergastrinemia (gastrinoma, atrophic gastritis, chronic use of omeprazole),[5] hypercalcemia,[6,7] renal insufficiency,[8] thyroid carcinomas (follicular and papillary carcinomas),[3,7] neuroendocrine tumors (paragangliomas, pheochromocytomas, insulinomas,

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VIPomas, neuroendocrine larynx, lung and pancreas carcinomas),[9-12] other non-neuroendocrine carcinomas (breast, bronch, lungs)[13-15] and drugs (beta blockers, glucagon, glucocorticoids).[16]

Controversial results have been reported regarding CT levels in Hashimoto thyroiditis. Thus, while elevated CT levels due to C-cell hyperplasia were reported in up to 12.5% patients with Hashimoto thyroiditis,[17] other studies observed significantly lower basal and stimulated CT levels in patients with Hashimoto thyroiditis.[18,19] Low CT levels are thought to be a consequence of inflammatory processes characterized by progressive lymphocytic infiltration that leads to follicular and parafollicular cell damage and C-cell destruction.[20]

Most of the abovementioned conditions are associated with CT levels between 10-100 pg/ml. Constante et al suggested that basal CT levels higher than 100 pg/ml are 100% predictive of MTC.[21] In addition, basal CT levels much higher than 100 pg/ml (up to 9571 p/ml) were reported in patients with ectopic CT secretion.[12,14] Herein, we present a female with Hashimoto thyroiditis, goiter, cervical lymphadenopathy and very high basal CT levels secreted by large cell neuroendocrine lung cancer (LCNEC).

CASE REPORT

In a 47-year old female, Hashimoto thyroiditis with primary hypothyroidism (positive family history for Hashimoto thyroiditis) was diagnosed 20 months ago and therapy with L-thyroxine was initiated. After 6 months, ultrasound examination revealed multinodular goiter grade II-III and cervical lymphadenopathy (TSH was optimally suppressed on 150 mcg of L-thyroxine therapy, CT was normal). Fine needle aspiration biopsy (FNAB) of the thyroid nodules confirmed the diagnosis of chronic thyroiditis. After one year she was referred to a gastroenterologist due to weight loss (20 kg/3 months) and pain in the epigastrium. The findings on ultrasound examination of the abdomen, gastroscopy and colonoscopy were normal. A paracardial tumor mass on the basal parts of the right lung was observed on X-ray examination (the patient is a smoker: 20-30 cigarettes per day). Multi-sliced computed tomography (MSCT) showed a 32 mm peripheral mass on the right lung with paratracheal and jugular lymphadenopathy. FNAB of an enlarged lymph node (LGL) located on the left side of the neck was performed in a Regional Health Center and the cytology finding was adenocarcinoma. Hormonal testing revealed high levels of calcitonin (260 pg/ml) and CEA (31.7 ng/ml), while TSH, PTH and calcium levels were normal as was also the total of the routine biochemistry analysis. The patient was referred to our Clinic as a patient with a MTC diagnosis.

On examination, the patient had a BMI of 22.5 kg/m2 and was eumetabolic. She had multinodular goiter grade II, with a palpable firm and painless 20 mm lymph node located submandibular on the left side. The rest of the physical examination was unremarkable. Laboratory analysis revealed high basal CEA and CT levels without CT response during a calcium stimulation test (Tables 1 and 2). Procalcitonin levels were not determined. NSE and CYFRA 21 were slightly elevated. TSH (on 150 mcg L-thyroxine therapy), chromogranin A (CGA), calcium, PTH, α- feto protein (AFP) and β-hcg were normal, as well as all of the routine biochemical analysis. Urine catecholamines were normal. RET mutation analysis was not performed.

Ultrasound examination of the neck revealed a

Table 1. Hormonal results

Analysis	Before therapy	After 6 cycles of chemotherapy
Calcitonin (ng/l, 0-10)	303	152.3
CEA (ng/ml, 0-4)	31.7	10.1
CYFRA 21-1 (mcg/l, 0-3.3)	4.2	1.9
Chromogranin A (ng/ml, 19.4 – 98.1)	59.4	
NSE (ng/ml, 4.7 – 14.7)	23.4	
PTH (ng/l, 0-80)	50.2	
Calcium (mmol/l)	2.46	
AFP	3.93	
B Hcg	0.369	

Table 2. Calcitonin response during calcium stimulation test

H (min)	0	1	2	5
Calcitonin (pg/ml)	223.4	182.3	217.1	185.3

significantly enlarged thyroid (grade III), hypoechogenic, lobulated, with significant fibrosis and without separated nodules. There was an enlarged lymph node on the left side (under bifurcation of CCA) of the neck, suspicious for metastasis. DMSA scintigraphy of the whole body and mammography were normal. The enlarged lymph node was surgically excised and the histological report suggested metastasis of a neuroendocrine carcinoma (Figure 1A).

MSCT of the chest revealed an infiltrative tumor formation in the lower part of the right lung connected with a package of LGL consisting of paratracheal, hilar, subcarineal LGLs (Figure 2A). No other metastases were observed. Bronchoscopy examination revealed infiltration of both principal bronchi by malignant tissue. Biopsy was performed and cytological and imunohistological analysis findings revealed a large cell neuroendocrine cancer of the lung (LCNEC) positive for TTF, CGA, CT, CEA and negative for cytokeratin 20 (the finding was the same as it had been for the extirpated LGL from the neck) (Figure 1B). Ki 67 staining was 30%.

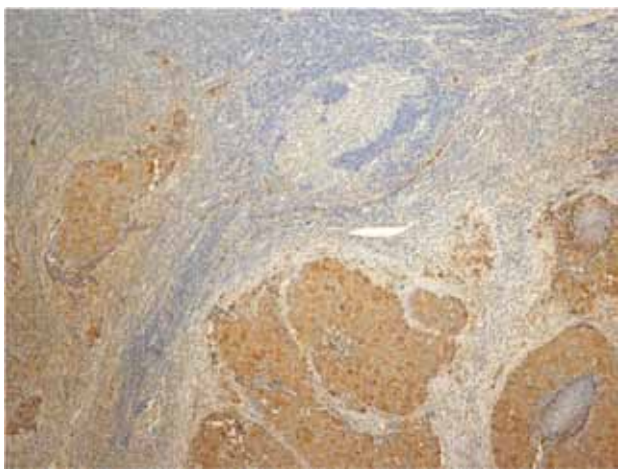

Figure 1A.

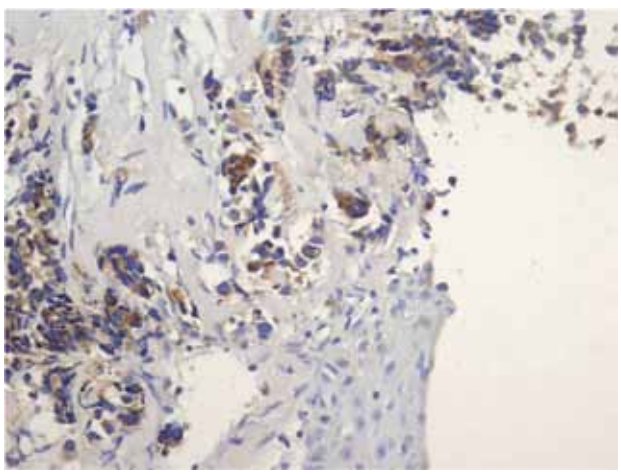

Figure 1B.

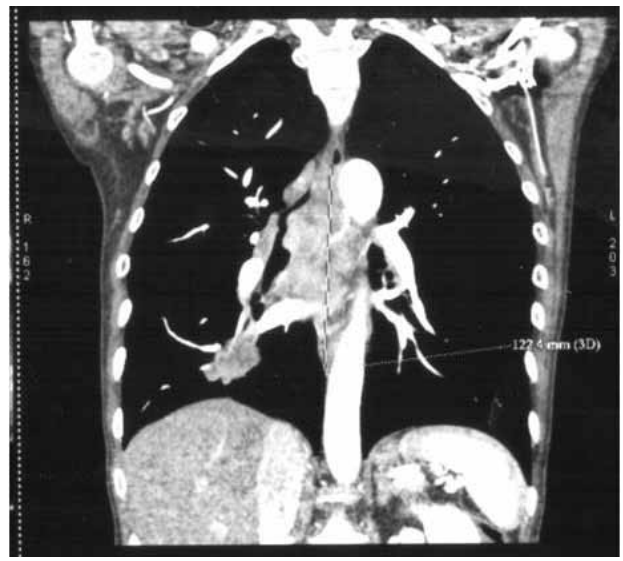

Figure 2A.

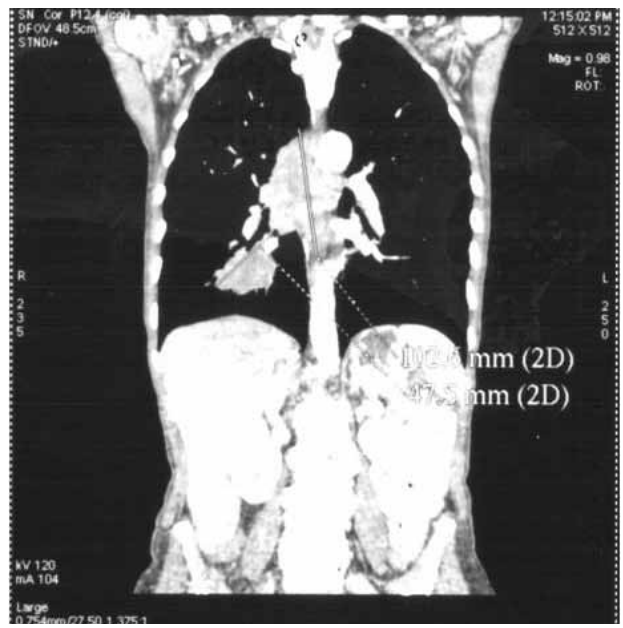

Figure 2B.

Cisplatin-Etoposide combination therapy was started and after 6 therapeutic cycles control MSCT visualization observed reduction of the tumor and the LGL mass by approximately 30% (Figure 2B), while CT and CEA levels were moderately decreased (Table 1). Since the octreoscan (*^{111}In-pentetreotid*) examination was positive in projection of tumor, the patient was sent for PRRT (Peptide Receptor Radionuclide Therapy) (Figure 3). After one course of PRRT the patient developed pneumonia and died.

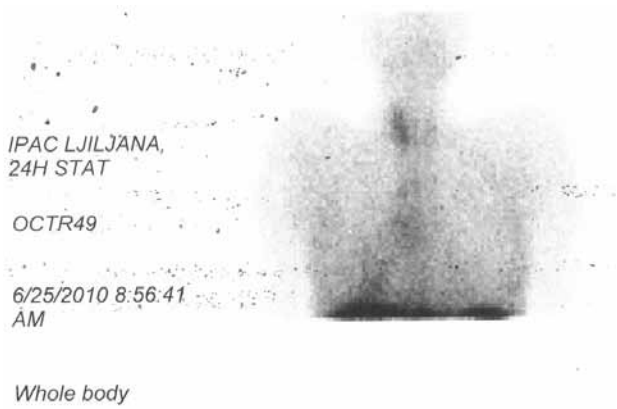

Figure 3.

DISCUSSION

We present a female patient with large multinodular goiter, neck lymphadenopathy and high CT and CEA levels suggesting the diagnosis of MTC. Careful and detailed evaluation of the patient led us to the diagnosis of ectopic CT secretion originating from LCNEC.

High basal CT levels in this case together with goiter and cervical lymphadenopathy suggested MTC. Some authors have proposed that basal CT levels above 100 pg/ml are 100% predictive for MTC,[7] but there have been several reported cases with basal CT levels much higher than 100 pg/ml in patients with ectopic secretion of CT,[12,14,22] as was our case. Moreover, in our case, during a calcium stimulation test there was no CT response, as was observed during other stimulation tests in patients with ectopic CT secretion.[10] High CT levels might be associated with secretory diarrhea and hypokalemia, as has been observed in patients with pancreatic and pulmonary tumors,[23,24] but in most of these cases with ectopic CT secretion and paraneoplastic syndrome, elevated CT levels were associated with ectopic secretion of other hormones (Vasoactive Intestinal peptide – VIP, insulin, somatostatin,...).[12,25,26] Our patient did not have diarrhea or any other paraneoplastic symptom/sign nor any ectopic secretion of other hormones (except tumor markers: NSE, CEA and CYFRA 21-1). Furthermore, CT levels in our patient's serum were not extremely high, which might be one of the reasons why she did not have diarrhea.

There are several reports of ectopic CT secretion in patients with pulmonary tumors. Most frequently these concern patients with small cell lung carcinoma (SCLC) and pulmonary carcinoids.[10,24,27] In approximately 20% of patients with non-small cell lung carcinoma (NSCLC) - adenocarcinoma, squamous cell carcinoma and large cell carcinoma, cancer may display neuroendocrine differentiation and clinically present with paraneoplastic endocrine syndromes. Pratz et al reported a 38-year old male patient with large cell lung carcinoma with neuroendocrine differentiation and ectopic secretion of CT and VIP. He had extremely high basal levels of CT (approximately 10,000 pg/ml) and CEA (161 ng/ml), much higher than those in our case. However, in the above case there was also ectopic secretion of VIP and consecutive diarrhea. Cisplatin-Etoposide chemotherapy induced transient CT reduction and clinical improvement, as was achieved in our case.[12] Monsieur I et al presented the case of a 58-year old man, a smoker, with NSCLC (poorly differentiated adenocarcinoma) with neuroendocrine differentiation and multiple paraneoplastic syndromes. In this patient, ectopic Cushing syndrome, elevated CT levels, SIADH, tylosis, hypertrophic pulmonary osteoarthropathy and erythema anulare were observed.[14] Interestingly, this patient had a euthyroid diffuse goiter, but, since the antiTPO antibody was not determined, we do not know if the patient had Hashimoto thyroiditis.

Epidemiological data suggest that LCNEC is a rare tumor and that it occurs significantly more commonly in men (80-90%), most frequently in the 7th decade and almost always in patients with a history of smoking (95-100% of patients).[28,29] In our case the patient was a 47-year old women, which is unusual for

this type of lung cancer, but she was a smoker. The location and size of the tumor at presentation were typical for LCNEC, a type of tumor that is characterized by poor prognosis. This high-grade cancer has 5-year survival rates of 13-47%, i.e. almost the same as SCLC.[29] Elevated CEA levels can be detected in 50% of patients with LCNEC, while NSE was observed in 12.4% of these patients.[29] Elevated NSE and CYFRA 21-1 levels are associated with poor outcome.[30]

The treatment options for neuroendocrine tumors are surgical resection of tumor mass and/or therapy with cytotoxic drugs, inhibitors of angiogenesis, somatostatin analogs and receptor targeted radiotherapy.[31] Surgical therapy is the treatment of choice when it is applicable.[32] Adjuvant pre- and postoperative chemotherapy was associated with better outcome in patients with stage I LCNEC.[33] Moreover, Rossi et al demonstrated that adjuvant platinum-etoposide based chemotherapy can be very effective and significantly improves survival in stage I, II and III LCNEC patients.[34] On the other hand, chemotherapy is usually associated with significant side effects and the median time to progression is mostly shorter than 18 months.[35]

Therapy with long-acting somatostatin analog (octreotide LAR) provides relief of symptoms and stabilization of tumor growth in patients with functionally active and inactive midgut neuroendocrine tumors.[31,36] In patients with LCNEC, adjuvant therapy with octreotide alone or with radiotherapy demonstrated significant efficacy when preoperative indium In-111 pentetreotide scintigraphy was positive.[37] Radiolabeled somatostatin analogs therapy, named peptide receptor radionuclide therapy (PRRT), was associated with significant tumor response rate and progression-free survival and was very safe compared to other treatment modalities in patients with foregut and midgut neuroendocrine cancers. Treatment with ^{177}Lu-octreotate resulted in tumor reduction in 46% of patients, stable disease was observed in 35% of patients and the median time to progression was 40 months.[38] The better the tumor uptake on somatostatin receptor scintigraphy with ^{111}In-DTPA^{0} octreotide, the better the results that can be expected using PRRT. Furthermore, an additional treatment cycle can be safely administered when disease becomes active again. The results of additional therapy are less effective than with initial treatment.[39] Our patient exhibited an excellent response to chemotherapy with cisplatin-etoposide. However, the effect of PRRT therapy could not be observed since the patient died due to pneumonia soon after the first cycle was administered. Therapy with tyrosine kinase inhibitors (TKI) such as vandetanib is not available in our country.

Increased incidence of thyroid, breast, gastric and colorectal cancer was observed in patients with Hashimoto thyroiditis.[40-44] Larson et al demonstrated that P-Akt, Akt 1 and Akt2 components of the PI3K pathway were highly expressed in Hashimoto thyroiditis (HT), HT-associated thyroid cancer and thyroid cancer alone. Previously, increased PI3K activity was observed in colon, thyroid and ovarian cancers. We did not find any report suggesting an association between chronic thyroiditis and/or thyroid function and lung carcinoma, nor increased PI3K activity in lung carcinoma.

In conclusion, we herein report a female patient who clinically presented with goiter, cervical lymphadenopathy and elevated CT levels. Careful examination demonstrated that the patient had LCNEC with ectopic CT secretion. Interesting points of this case are the following: a) that it concerned a young woman with LCNEC (this type of tumor is usually diagnosed in 60-70 year old men), b) that ectopic CT secretion is usually seen in patients with other types of lung cancer (SCLC and carcinoids), c) that it raises the question as to whether there is a possible association between thyroid disease and lung cancer.

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