A case of ACTH secreting large cell neuroendocrine carcinoma (LCNEC) of bronchus

Appalanaidu Sasapu, M D,1 Theepha Thayalakulasingam, M D,1 Arthur Zieske, M D,2 David Smith, M D,3 Fred Lopez, M D,1 and Brian Boulmay, M D1

1Department of Internal Medicine
2Department of Pathology
3Department of Radiology, Louisiana State University Health Sciences Center, New Orleans, LA

ABSTRACT

Bronchopulmonary neuroendocrine tumors account for only 20% of all lung carcinomas. These tumors are separated into four subtypes of low-grade (typical carcinoids), intermediate-grade (atypical carcinoids) and high-grade carcinomas which include large cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). LCNEC is a rare entity of aggressive cancer with poor prognosis. LCNEC is typically seen in older male with significant smoking history. We are presenting a young man with only five pack year smoking history and cushingoid features who was found to have LCNEC.

Keywords: Large cell neuroendocrine carcinoma, Ectopic ACTH Syndrome, Carcinoembryonic antigen, chromogranin, synaptophysin, Octreoscan, RTKs.

CASE PRESENTATION

A 27-year-old man with a five pack year history of cigarette smoking presented with complaints of five months of progressively worsening shortness of breath (SOB), cough and watery diarrhea. During this period, he was treated three times as outpatient for presumed pneumonia. His cough and SOB slightly improved with each pneumonia treatment, but symptoms continued to recur. He continued to have watery diarrhea 8–10 times per day over a 5 month period. Two months prior to admission, he was evaluated in the emergency department near his home for worsening diarrhea but was sent home without any interventions when his stool studies came back negative for infectious etiology. At presentation to our facility, the patient complained of worsening productive cough with greenish sputum and diarrhea associated with abdominal cramping and urgency. Additional review of systems was significant for subjective fevers, night sweats, hemoptysis and flushing episodes. He denied weight loss, nausea, vomiting, or chest pain. He denied history of incarceration or any known tuberculosis exposure. He had a history of 2 to 3 half pints per day of alcohol intake for 10 years, but he quit drinking 8 months prior to current admission. He denied IV drug abuse. He was living in a halfway home to recover from his substance abuse. Family history was significant for Head and neck cancer in his father and type 2 diabetes mellitus in his mother. He was not taking any medications at the time of admission.

Vital signs were significant for a blood pressure of 160/95, heart rate of 105, and a body mass index of 31. Physical exam was significant for a round face, abdominal obesity and disproportionate increase in the dorsocervical fat pad. On pulmonary exam, he had decreased breath sounds on the right lung base with rales in bilateral lung bases. On cardiac exam, there was an elevated heart rate of 105 bpm with normal rhythm and no murmurs, rubs or gallops. There was bilateral pitting pedal edema. On skin exam, he had a violaceous
rash on erythematous base over the upper chest and upper back. Laboratory analysis revealed WBC of $19.2 \times 10^3/\text{UL}$ (4.5–10 $\times 10^3/\text{UL}$), a hemoglobin of 12.5 (13.0–16.0 GM/DL), a hematocrit of 38% (39–46%), MCV of 91 FL (80–100 FL), and RDW of 16% (11.5–14.5%). Patient also had sodium of 143 mEq/L, fasting blood glucose of 115 mg/dl, and an HbA1c value of 6.5%. His chemistry showed potassium 2.6 mEq/L, serum bicarbonate 38 mg/dl, and normal renal function. Liver function tests were normal except for albumin of 2.6 mg/dl. His thyroid function testing was normal. Stool studies were normal. His cardiac work up was normal with an ejection fraction of $>55\%$. Chest radiograph showed right sided paratracheal and hilar opacities and pleural effusion (Figure 1). Patient's sputum culture grew methacillin resistant staphylococcus aureus (MRSA), but his blood and urine cultures were negative.

Additional testing was done to evaluate the cause of recurrent pneumonia and to further characterize the chest radiographic findings. Computed tomography (CT) scan of the chest showed a large relatively homogeneous mediastinal mass encasing the right main pulmonary artery and complete occlusion of the bronchus intermedius with complete consolidation of the right middle and lower lobes (Figure 1). Flexible bronchoscopy showed evidence of nodularity and tumor infiltration into the right distal bronchus intermedius resulting in near complete obstruction of the middle and lower lobe airways. This lesion was extremely friable and bled easily on contact.

Biopsy of the lesion showed dense infiltrate of large malignant cells expressing synaptophysin (SP11) and thyroid transcription factor 1 (TTF1), strongly and diffusely; neuron specific enolase (NSE), moderately and patchy; chromogranin A, pale and diffuse; and CD56 (NCAM), pale and patchy. The Ki-67 proliferation index was greater than 90% (Figure 2). Based on the nuclear size, the presence of nucleoli, the relative abundance of cytoplasm and the absence of significant molding in the better preserved areas of the specimen (Figure 3), he was diagnosed with large cell neuroendocrine carcinoma (LCNEC) primary to the lung. Metastatic work-up included a magnetic resonance imaging (MRI) of brain, CT scan of the abdomen/pelvis, and MRI of liver which revealed renal and numerous hepatic lesions consistent with metastasis (Figure 4). The hepatic lesions did not demonstrate the classic enhancement pattern of neuroendocrine tumors. Indium-111 penetrative scan (Octreoscan) showed faintly increased re-accumulation of radionucleotide in subcarinal, right paratracheal and right hilar regions, but no uptake in the liver. Pleural fluid analysis showed exudative type effusion and was negative for malignancy.

Based on the abnormal physical exam findings (skin rash, moon face, buffalo hump), the presence of metabolic alkalosis, hypokalemia, and hyperglycemia, hypercortisolism was suspected. Additional lab testing was undertaken which revealed random free cortisol of 2552 μg/dl (normal <16 μg/dL), 24-hour urine cortisol level of 6252 μg/24 h (0–5 μg/24 h), plasma adrenocorticotropic hormone (ACTH) of 265.3 pg/mL (7.2–63.3 pg/mL), renin <0.15 ng/mL/hr (0.15–2.33 ng/mL/hr), and aldosterone level <1.0 ng/dL (0.0–30 ng/dL). These lab findings were consistent with the diagnosis of Ectopic ACTH syndrome (EAS) secondary to metastatic LCNEC of bronchus. Neuroendocrine markers showed markedly elevated calcitonin of 6015 pg/ml (0–8.4 pg/mL) and carcinoembryonic antigen (CEA) of 211 ng/ml (0–5 ng/ml).

Figure 1. Admit chest radiograph (on far left) showing lobular right paratracheal and right hilar opacities, right hemithoracic volume loss and fluid accumulation. CT scan of the chest showed a large homogeneous mediastinal mass extending from the subcarinal space to the right hilum. There was eneasement of the right main pulmonary artery and complete occlusion of the bronchus intermedium with complete consolidation of the right middle and lower lobes along with a moderate sized pleural effusion and additional compression of the left atrium was noted.
There were mild elevations in chromogranin A at 8 ng/ml (1.5–5 ng/ml), neuron-specific enolase (NSE) at 16.2 ng/ml (<12.5 ng/ml). Other markers such as Vasoactive intestinal polypeptide (VIP), serotonin, 24-hr urine 5-HIAA, and neurokinin A were in normal limits.

Patient was started on palliative chemotherapy with etoposide and cisplatin. His diarrhea resolved in 2 weeks with chemotherapy, somatostatin, loperamide, and diphenoxylate/atropine. Patient was started on ketoconazole for his Cushing’s syndrome with remarkable improvement in his performance status. After 5 cycles of chemotherapy, his cortisol and ACTH levels dropped significantly to 18.7 mcg/dl and 65 pg/mL, respectively. His CEA level also decreased to 75 ng/ml. His serum calcitonin has dropped from 6015 pg/ml to 1679 pg/ml. Secondary hypertension was treated with combination of amlodipine, metoprolol, lisinopril, and spironolactone. Patient was sent home with close follow-up. To date, he has received six cycles of palliative chemotherapy and radiation.

DISCUSSION

Neuroendocrine tumors of the lung arise from Kulchitzky cells of the bronchial mucosa. Travis et al. were the first to propose the term pulmonary large cell neuroendocrine carcinoma (LCNEC) in 1991. Male predominance is reported in literature. Several authors reported the frequency of LCNEC to be 1.6–3.1% of total lung cancers.

Similar to other types of lung cancers, number of smokers in LCNEC cases was reported as 94%–98.6% and the incidence tied to a large pack year smoking history. Travis et al. proposed LCNEC as a fourth category of neuroendocrine tumors in addition to typical carcinoid, atypical carcinoid, and small cell lung carcinoma. In 1999, the World Health Organization (WHO) proposed a classification with histologic criteria for each subtype of LCNEC based on: (i) neuroendocrine morphologic features; (ii) mitotic rate; (iii) necrosis; (iv) cytologic features of a non-small cell lung carcinoma (NSCLC); (v) positive immuno-histochemical staining for one or more neuroendocrine markers.
Clinical presentation of LCNEC tumor depends on the type of neuroendocrine substance the tumor produces. For instance, less than 20% of all lung cancers secrete ACTH, most of which are small cell carcinomas (SCC) and rarely non-small cell lung carcinoma[58]. Sixty percent of all patients with neuroendocrine lung cancers present with cough, hemoptysis, and post-obstructive pneumonia[59]. However, patients have a wide variety of signs and symptoms ranging from asymptomatic nodule, chest pain, dyspnea, night sweats, nonspecific flu like symptoms, features of hypercortisolism, and carcinoid syndrome[60].

Although like all lung cancers, the diagnostic work-up begins with imaging such as chest radiography and CT of chest, the definite diagnosis of LCNEC can only be made by histology. As the prognosis depends on the tumor histology, it is very important to correctly identify LCNEC. Histologically, LCNEC has a cell size at least three times larger than small cell carcinoma (SCC), an organoid growth pattern with cellular palisading or rosette-like areas and patches of geographic necrosis[60]. Somatostatin receptors are also expressed by these neuroendocrine tumors. Octreoscan can also help with staging in these cases[60]. It is also important to test for paraneoplastic syndromes like EAS and carcinoid syndrome as neuroendocrine tumors can secrete various molecules. Biochemical tumor markers may be associated with neuroendocrine tumors (NETs). Calcitonin and gastrin are found to be the most commonly elevated tumor markers, regardless of tumor type, in all recent series[64].

SCLC and LCNEC show similar morphologic and genetic changes that differentiate them from carcinoid tumors and NSCLC[13,40]. Both SCLC and LCNEC show high labeling index by Ki67, loss of Rb (retinoblastoma gene expression) and p53 tumor-suppressor genes, increased bcl-2 levels, and common chromosomal imbalances and genetic alterations[12,28–33]. In contrast with NSCLC, SCLC and LCNEC do not show mutational changes of the k-ras-2 and c-raf-1 genes[13] and they frequently show over expression for NCAM/CD56[41–43]. In one study LCNEC
and SCLC showed similar complex abnormal patterns of 4q-, 5q-, 10q-, 13q- and, 15q-[56,61]. The authors postulated that these genotypic differences may explain the aggressive natures of LCNEC and SCLC.[7]

Even though there are numerous neuro-endocrine markers expressed in pulmonary neuroendocrine tumors, according to world health organization, chromogranin and synaptophysin are only reliable neuroendocrine markers and the neural cell adhesion molecule (NCAM) may be helpful in diagnosis of pulmonary neuroendocrine tumors. Neuron specific enolase (NSE) is not specific for neuroendocrine tumors. Other commonly elevated markers include serum CEA and pro-gastrin-releasing peptide[10,54]. Sturm and colleagues[11,26] reported that the specificity of thyroid transcription factor-1(TTF-1) for LCNEC was 100% and the specificity of 34betaE12 for basaloid carcinoma was 98.3%, indicating that these markers are useful to distinguish LCNEC from basaloid carcinoma. Unlike SCLC, LCNECs do not stain for high molecular weight cytokeratins 1, 5, 10, and 14[27,49].

Surgery is the mainstay of treatment whenever possible[52,59]. Due to the rare nature of this tumor, treatment for cancer is still largely undefined. As a result of high expression of the multidrug resistance gene (MDR1) in LCNEC, it has been suspected that LCNEC is resistant to conventional chemotherapy for NSCLC[2]. Hiroshima et al. postulated that chemotherapy might be as effective for LCNEC as for SCLC, because of their similarities in genetic profile[69]. In 2005, Rossi and colleagues[40] reported that adjuvant chemotherapy based on cisplatin and VP-16 was effective for patients with LCNEC. One study reported 50% response rate to cisplatin-based chemotherapy in LCNEC as similar to SCLC[47]. Iyoda and colleagues[49,53] performed a prospective study of adjuvant chemotherapy for patients with completely resected LCNECs. Their results showed that patients with adjuvant chemotherapy based on cisplatin and VP-16 after complete surgical resection had overall survival rate of 88.9% at 2 and 5 years. In advanced disease combination of chemotherapy and somatostatin-analogues may have beneficial effects[59]. External beam radiation is only effective for local control. There is no clear data on effectiveness of prophylactic cranial irradiation for LCNEC patients[60].

In lung cancer patients with Ectopic ACTH Syndrome (EAS), it is important to treat hypercortisolism ideally before cytotoxic chemotherapy is initiated to minimize the side effects of chemotherapy. The optimal therapy for Cushing’s syndrome caused by extra-adrenal tumors (EAS) is the surgical removal of the tumor. In patients who cannot tolerate surgery and when primary tumor is unresectable, adrenolytic medications (ketoconazole, metyrapone, etomidate) and bilateral laparoscopic adrenalectomy could be used to control hypercortisolaemia[62-66].

Several reports suggest that the prognosis of LCNEC is poor, with a variable overall 5-year survival rate ranging from 13% to 57%[10,29,50,51,54,58]. LCNEC had a significantly worse prognosis than stage-comparable conventional NSCLC[5,40]. A recent large retrospective study from Japan showed no prognostic difference between LCNEC and SCLC[2,11,57]. High-grade neuroendocrine histology uniformly indicates poor prognosis regardless of its histologic type[57]. In surgical specimens, LCNEC has high mitotic rates, frequent lymph node metastases, and advanced pathologic stages[10]. It has been suggested that CEA expression might be associated with a poor survival in neuroendocrine tumors[9]. Some authors reported that patients with LCNEC that express the c-kit protein had poor prognosis[15,17,39]. Along with tumor histology, degree of hypercortisolism also affects the prognosis in patients presenting with ectopic ACTH syndrome. A large retrospective study found that 14 of 840 (1.7%) SCLC patients had EAS, which was associated with a low response rate to chemotherapy and a worse overall survival likely due to the aggressive nature of the underlying disease[60].

There are several potential new targets for development of future therapies for LCNEC[53]. RTKs are key molecules in normal cellular differentiation and are commonly deregulated or mutated in human cancers. RTKs are studied as molecular targets for alternative therapies using selective inhibitors[20,23,24,34]. Some authors reported the c-kit protein, a tyrosine-kinase receptor, expressed in LCNEC might be useful as a novel target[14,16,19,39,43]. Several other molecules acting against KIT, PDGFR, and other RTKs are currently in preclinical studies[10,21,37,50]. Further studies are needed to investigate the use of gefitinib (EGFR inhibitor) and imatinib mesylate (c-kit receptor tyrosine kinase and bcr/abl inhibitor)[44]. CD56 is a very sensitive marker of neuroendocrine differentiation in high-grade neuroendocrine tumors. It might be useful as a target for newer therapies for LCNEC[46,49]. Filosso and colleagues[40] reported that octreotide was effective for patients with LCNEC. For the treatment of patients with the EAS secondary to malignancy, some authors suggested methylation of the POMC promoter in tumor cells as a novel target[63].

In conclusion, pulmonary large cell neuroendocrine carcinoma (LCNEC) is an aggressive type of lung cancer. It has poor prognosis than NSCLC. More randomized controlled
trials are needed in future to evaluate the current chemotherapy regimens for LCNEC. LCNEC is known to produce numerous neuro-endocrine markers. Like SCLC, LCNEC also produces endocrine peptides like ACTH and can cause ectopic Cushing's syndrome as seen in our patient.

REFERENCES


