INTRODUCTION
Large cell neuroendocrine carcinoma (LCNC) is rare lung cancer accounting for 15% of neuroendocrine tumors and 3% of all lung cancers. Although in 1981, carcinoid tumors, small cell lung carcinoma and large cell carcinoma were classified separately; but in 2015 World Health Organization classification, they were grouped together as neuroendocrine tumors. A small percentage of LCNC, which is called combined LCNC, is histologically heterogeneous and can be seen in combinations with other lung cancer types such as adenocarcinoma or squamous cell carcinoma of lung cancers.

We present a case of combined LCNC with adenocarcinoma in a male heavy smoker.

CASE REPORT
A 66-year man was found to have a lesion in his right lung on a chest radiograph before the preoperative evaluation for prostate surgery. He had no symptoms of pulmonary disease like cough, dyspnea or chest pain. Computed tomography (CT) revealed an irregular mass measuring 3.5 × 3.4 cm located in the right lower lobe (Figure 1). Distant metastases were not seen. On positron emission tomography/computed tomography (PET/CT) examination, the maximum standardized uptake value (SUVmax) of the mass was 6.8; posterior the main lesion, there were two satellite nodules measuring 4 and 5 mm with SUVmax of 1.9. There was no mediastinal lymph node positivity on PET/CT.

Fiberoptic bronchoscopy showed no endobronchial lesion. CT core biopsy of the right lower lobe showed lepidic pattern of atypical epithelial cell proliferation and suspected adenocarcinoma. Right lower lobectomy was performed with mediastinal lymph node dissection via mini thoracotomy. The tumor was diagnosed as combined LCNC with adenocarcinoma. The patient was discharged on the seventh postoperative day and sent to the oncology clinic for chemotherapy. There has been no recurrence for eight months after surgery.

analysis of main tumor showed staining for nuclear TTF-1 and membranous CK7 (+). The peripheral part of the tumor showed neuroendocrine tumor morphology. The satellite nodules revealed CK7 (+), synaptophysin (+), chromogranin-A, CD56, TTF-1, CDX2(-). The immunohistomorphology of the tumors were compatible with LCNC and atypical carcinoid tumor; and in a tumoral nodule, there was a transition state from lepidic pattern adenocarcinoma to neuroendocrine morphology (Figures 2 A-F). All lymph nodes were negative pathologically. The diagnosis of tumor was thought as combined LCNC with adenocarcinoma, lymphatic invasion (-), vascular invasion (+), and p-T3N0M0 stage IIB. The patient was discharged in stable condition on the seventh postoperative day and sent to the oncology clinic for chemotherapy. Eight months after surgery, there was no recurrence of tumor.

**DISCUSSION**

Although large cell neuroendocrine carcinoma (LCNC) is seen rarely, it has very malignant potential and is highly aggressive tumor. It is seen approximately for 2-3% of all lung cancers. LCNC is diagnosed more frequently in smokers, male gender, and older age.\(^1,4,5\) This was the clinical profile of the present case.

LCNC was classified as a subtype of large cell carcinomas in 2004 World Health Organization (WHO) classification,\(^6\) now they are no longer classified under large cell carcinoma, but in a group of neuroendocrine tumors neoplasms with Small Cell Lung Cancer (SCLC), carcinoid tumors, and others in 2015 WHO classification.\(^3\)

Combined LCNC of lung is a LCNC with an additional non-small cell carcinoma histological component of any proportion. In total, 10.6% of LCNCs are grouped as combined LCNC. The non-small cell carcinoma component may include any of the following, adenocarcinoma (33.3%), squamous cell carcinoma (53.3%), spindle cell carcinoma and giant cell carcinoma (13.3%).\(^7\)

The clinical presentation of combined LCNC is very different. These tumors present as peripheral tumors in contrast to carcinoid tumors or SCLC that are located centrally. The clinical symptoms change from no symptoms to paraneoplastic syndromes. Generally, most of the patients, as in our patient, are less likely to present with characteristic symptoms of lung cancer such as cough, dyspnea, hemoptysis or post obstructive pneumonia.\(^8\)

There is difficulty in diagnosis of combined LCNC preoperatively, the accurate diagnosis requires careful examination of the pathologic specimen. Neuroendocrine differentiation must be performed microscopically by mitotic rate and presence or absence of necrosis. In our case, in the peripheral part of the tumor, there was necrosis in large areas and mitotic rate was >11/10 high-power fields (hpf) for LCNC and 2-10/10 hpf for atypical carcinoid tumor. The central part of the tumor was compatible with dominant lepidic pattern adenocarcinoma. Confirmatory immunohistochemical staining should be performed with neuroendocrine markers such as chromogranin, synaptophysin, neuron-specific enolase, and CD56 for absolute diagnosis of LCNC. In difficult cases, the determination of neuroendocrine differentiation should be needed in ultrastructurally using electron microscopy. LCNC tumors show biological behaviors of small cell lung carcinomas and high-grade neuroendocrine tumors. Genetic differences between small cell and large cell neuroendocrine carcinoma exist but many characteristics are shared, such as the PI3K/AKT/mTOR pathway, despite their distinct morphologic appearances.\(^5\)

Combined LCNs and LCNCs have poor prognosis. Most of the LCNCs are diagnosed postoperatively, there is no any significant treatment modality for this disease. Some authors proposed the surgical therapy and others proposed multimodal therapy such as surgical, chemotherapy and radiotherapy. Because of the rarity of these cases, the understanding of tumor behavior goes on very slowly. We need more cases to understand these tumors and to evaluate treatment regimens such as molecular-based therapy methods.\(^9,10\)

**Disclosure:** This manuscript has been accepted as a poster and will be presented in National Congress of Turkish Thoracic Surgery Society, 4-7 May 2017, Antalya, Turkey.

**REFERENCES**


---