

## Combined Large Cell Neuroendocrine Carcinoma of the Lung

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### Abstract

We report the case of a 74 year old man, non-smoker who presented with a 3 months history of weight loss and nausea. Apart from an irregular pulse, clinical examination was normal. Blood biochemistry revealed an elevated alkaline phosphatase with hypercalcemia. CXR showed right lower lobe pleural thickening. CT Thorax/Abdomen/Pelvis followed by a PET scan revealed 4.2 cm right lower lobe mass with FDG avid pleural, extra pleural, pancreatic and osseous lesions. Interestingly CT core biopsy of the right lower lobe showed an unusual histopathology: non-small cell carcinoma with acinar growth pattern consistent with adenocarcinoma and cells showing neuroendocrine features with pleomorphism CD56 positivity and chromogranin positivity in solid area. These features were suggestive of a combined large cell neuroendocrine carcinoma of the lung.

### Case Report

This 74 year old man presented to the emergency department with a 3 months history of weight loss and nausea. He lost 2 stones in weight over this period of time with a significant loss of his appetite. He also complained of generalised body ache mostly around his shoulders and back. His past medical history included hypertension and atrial fibrillation for which he was on a calcium channel blocker and warfarin respectively. He had no significant family history and no known drug allergy. He lived with his wife and was a non-smoker. He used to be a heavy drinker but had been abstinent over the last two years. His mobility had decreased significantly and required assistance for his daily activities. His vitals were normal. Apart from an irregular pulse, there were no positive findings on general examination.

His haematology and biochemistry laboratory blood reports were as follows: Hb 12.1 (13-18), WCC-7.3 (411), PLT – 249 (150-450), ESR-24, Na – 138 (135-145), K-3.8 (3.5-5.0), creatinine-38 (62-106), urea 2.3 (2-7), protein 57 (65-85), albumin 33 (35-50), bilirubin-5 (0-17), alkaline phosphate-167 (40-130), Gamma GT-106 (0-60), Alkaline phosphatase-167 (40-130), corrected calcium-2.71 (2.15-2.55), phosphate 1.25 (0.8-1.4), CRP-14. Urine Dipstick showed 4 + ketones, 1 + protein, no leucocyte, no nitrate. ECG showed atrial fibrillation with a rate of 72 beats per minute.

His CXR (Figure 1) was reported as follows: “The heart size is normal. There is unfolding of the thoracic aorta. There is a hiatus hernia. The lungs show chronic changes, with some pleural fluid/thickening at the right base”

Subsequently because of his clinical presentation, a CT thorax/abdomen/Pelvis was done. It showed a subpleural mass like opacification in the right lower lobe (Figure 2) with two illdefined low-attenuation areas within the pancreatic body and tail, which given the presence of extensive peritoneal nodularity and pulmonary nodules were concerning for underlying malignancy.

After being discussed at the lung cancer multidisciplinary meeting, a PET scan and a CT core biopsy of the right lower lobe were organized. PET scan (Figure 3) showed a 4.2 cm right lower lobe mass with FDG avid pleural, extra pleural, pancreatic and osseous lesions.

A CT core biopsy of the right lower lobe showed an unusual histopathology: non-small cell carcinoma with acinar growth pattern consistent with adenocarcinoma and cells showing neuroendocrine features with pleomorphism CD56 positivity and chromogranin

positivity in solid area. These features were consistent with a combined large cell neuroendocrine carcinoma of the lung (Figures 4-8).

His Eastern Cooperative Oncology Group performance status was 4. After explaining the diagnosis, prognosis, pros and cons of treatment plan, patient refused treatment. Patient’s autonomy was respected and was referred to palliative team for continuation of care. Differential diagnosis includes primary lung carcinoma, metastatic carcinoma, or benign tumor. Therefore histopathological analysis is required for a definitive diagnosis [1-7].

### Discussion

Combined LCNEC is categorized as LCNEC with components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma, and/or spindle cell carcinoma according to the WHO classification

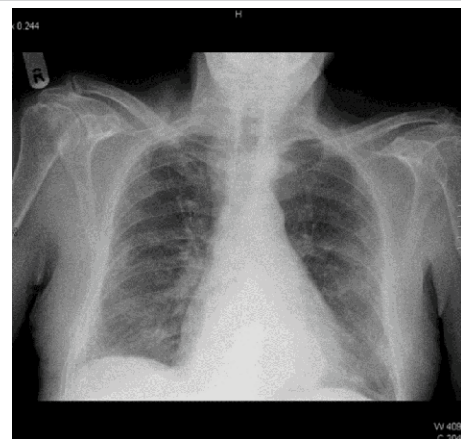


Figure 1: CXR showing right sided pleural thickening.

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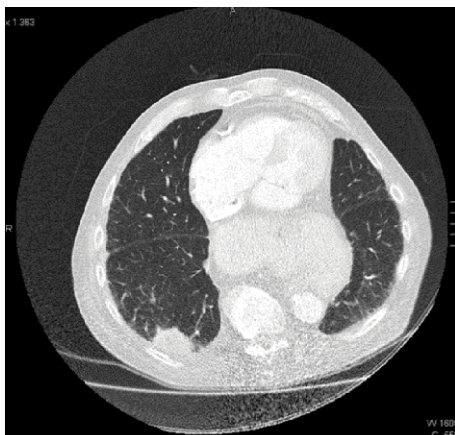


Figure 2: CT thorax showing subpleural mass in the right lower lobe.

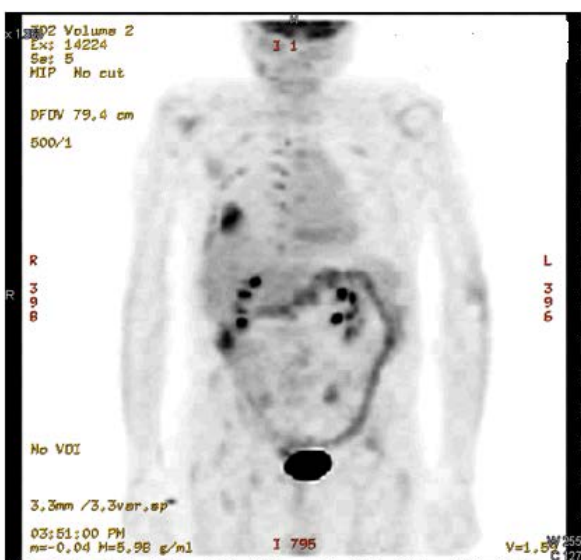


Figure 3: PET scan showing 4.2 cm right lower lobe mass with FDG avid pleural, extra pleural, pancreatic and osseous lesions.

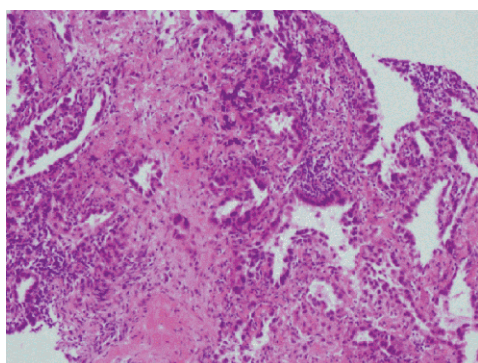


Figure 4: Non small cell carcinoma with acinar growth pattern consistent with adenocarcinoma.

grade neuroendocrine pulmonary tumor, small cell lung carcinoma (SCLC), with two exceptions: primary LCNECs tend to be located peripherally (as in our case) rather than centrally and presentation of LCNECs with early stage (I-II) disease is more common than for SCLC (approximately 25 percent versus less than 5 percent). Thus, patients with LCNEC more commonly undergo resection. Further, because LCNEC can be a difficult diagnosis based on needle aspirate

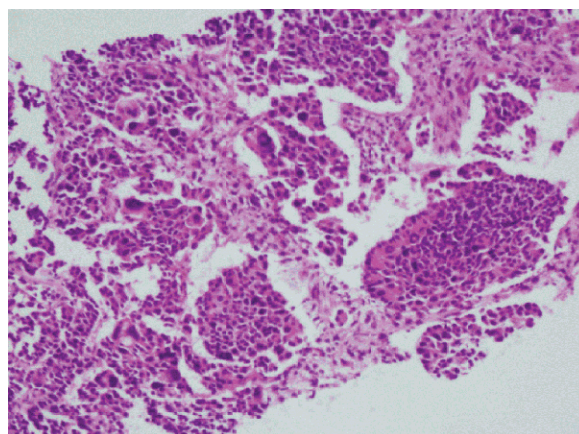


Figure 5: Non small cell carcinoma with solid and packeted growth pattern.

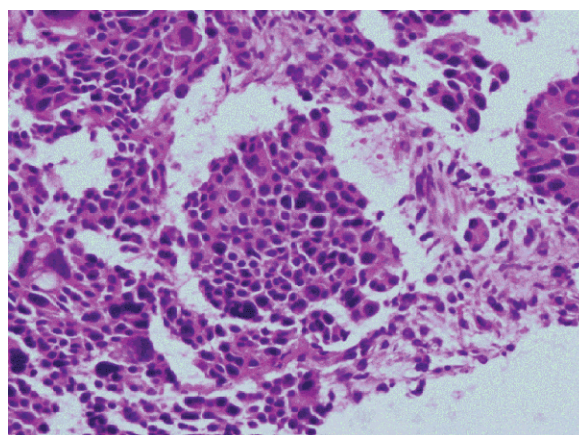


Figure 6: Cells show neuroendocrine features with pleomorphism.

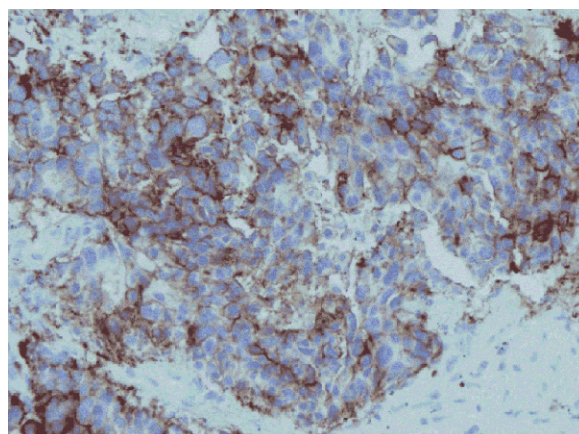


Figure 7: CD56 positivity in solid area.

[8]. In total, 10.6% of LCNECs are classified as combined LCNEC, and components of combined LCNEC are adenocarcinoma (33.3%), squamous carcinoma (53.3%), and others (13.3%). The natural history and clinical presentation of LCNEC appear similar to the other high

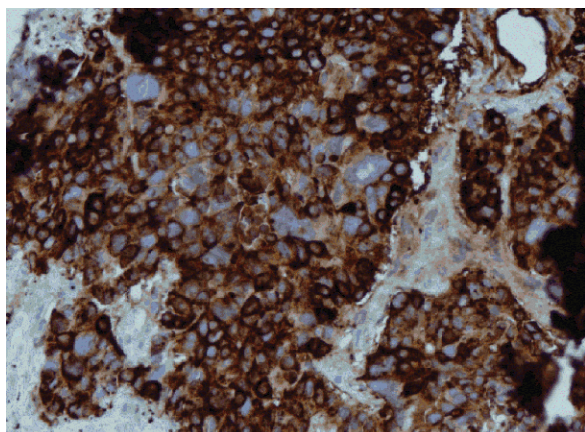


Figure 8: Chromogranin positivity in solid area.

or small biopsy, the diagnosis is frequently made post-resection. Immunohistochemical analysis is crucial for diagnosing LCNEC. LCNEC occasionally resembles the other variants of large cell carcinoma. Neuroendocrine markers are important in getting a good differential diagnosis. Regarding LCNEC, TTF-1, 34 $\beta$ E12 (cytokeratin 1.5.10.14), chromogranin A, synaptophysin, and NCAM, are expressed in 40.9%, 2.2%, 68.5%, 84.2%, and 91.2% of tumors, respectively [9,10].

Combined LCNEC has no standard therapy. Combination therapy for LCNEC may now be appropriate in patients with combined LCNEC. Because it has a poor prognosis, surgery alone is not sufficient. Sakaria and colleagues reported that the response rate of LCNEC to platinum-based neoadjuvant chemotherapy was 68%. In addition, univariate analysis revealed that platinum + etoposide chemotherapy improved the overall survival (OS) of patients with advanced-stage, completely resected LCNEC [11]. On the other hand, in a recent multicentre phase II study of cisplatin- etoposide, Le Treut and colleagues demonstrated that the outcomes of advanced LCNEC treated with cisplatin-etoposide doublet were poor similar to those of patients with advanced small cell lung carcinoma [12].

### Learning Point

- Preoperative diagnosis of combined LCNEC is very difficult
- Immunohistochemical analysis is important for diagnosing LCNEC.
- There is no standard therapy for combined LCNEC

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