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Case Report

Misleading wheeze in a case of atypical large cell neuroendocrine carcinoma of lung - A deadly variety

Jeevanandham Anandan[1]*, **Zeenathalam Nadaf**[1], **Sneha Leo**[2]

[1]*Dept. of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, India*
[2]*Chettinaud Medical college, Chennai, Tamil Nadu, India*

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ABSTRACT

Neuroendocrine tumors are neoplasms arising from cells of endocrine and nervous system containing special secretory granules with biogenic amines and polypeptide hormones. One of the varieties that occurs commonly in the lung is large cell neuro endocrine carcinoma. The replicative potential of these neuroendocrine malignancies is so rapid that the patients usually present with metastatic disease. We describe a case of 29-year-old-male presented with nocturnal wheeze which led on to a misdiagnosis of bronchial asthma and finally found to be LCNEC with endobronchial obstruction. They are usually peripherally located lesions, mostly in the upper lung zones of an elderly male smoker. But he had a hilar mass with right lower lobe collapse due to endobronchial obstruction. Hence careful examination of wheeze whether unilateral or bilateral, monophonic or polyphonic, random or fixed, inspiratory or expiratory or biphasic may help in early identification of the endobronchial lesions.

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1. Introduction

The most common site for neuroendocrine malignancies is the gastrointestinal tract whereas the large cell neuroendocrine carcinoma (LCNEC) variety occurs most commonly in the lungs. LCNEC is one of the rare varieties of lung cancer which is now recognized as a distinct entity in the World Health Organization classification of lung malignancies by Travis et al. Incidence. It is approximately 3% among surgically resected specimens of lung cancer.[1] LCNECs have faster rate of progression and poor survival rate only next to that of small cell lung cancer. They are peripherally located lesions, mostly in the upper lung zones of an elderly male smoker. Endobronchial obstructions are rare in a LCNEC, if present, may result in production of wheeze which may be misleading especially in young individuals with normal radiology. Hereby we describe a patient who presented with nocturnal wheeze and normal roentgenography and hence suspected to have bronchial asthma, finally diagnosed as LCNEC.

2. Case Details

A 29-year-old male construction worker who was a current smoker (3 cigarettes/7days for 9 years - smoking index of 4.5 and pack years of 0.22) and occasional alcoholic presented with complaints of breathlessness for one month, insidious in onset initially MMRC grade - 1 worsened to MMRC grade – 2 over 1 week. He had wheeze which was more during the night. There wasn't orthopnea or paroxysmal nocturnal dyspnea. No hemoptysis, chest pain 28 or fever. He had no loss of weight or appetite. There wasn't leg swelling, facial puffiness. On examination, he had pulse rate - 88/min, BP -110/80mmHg, respiratory rate -22/min and SpO2-95% in room air. On chest auscultation he had bilateral vesicular

* *Corresponding author*.
E-mail address: jeevanand114@gmail.com (J. Anandan).

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breath sounds with biphasic wheeze, predominantly in right hemithorax. His chest X-ray (Figure 1a) showed normal lung parenchyma. Taking into account his young age, worsening breathlessness and wheeze for a week, and normal chest X-ray, clinical diagnosis of bronchial asthma exacerbation was made and started on bronchodilators. He was advised to follow up for spirometry after a month. Within few weeks, he presented to the Department of Emergency medicine with complaints of hemoptysis for 3 days, frank blood, 5ml/episode (multiple episodes), not associated with clots. There was no hematemesis, malena, epistaxis, hematochezia or gum bleeding. Chest X-ray was suggestive of right lower lobe collapse. Contrast enhanced computed tomography (CECT) of the thorax showed right hilar mass with endobronchial obstruction with right lower lobe bronchus cut off (Figure 1b) and right lower lobe collapse. Bronchoscopy revealed a right main bronchus fleshy endobronchial lesion that was bleeding on touch and extended into the lower trachea. Biopsy done from endobronchial lesion was reported as having tumor cells arranged in sheets and the individual Cells (pleural) had moderate amount of eosinophilic cytoplasm, hyperchromatic nuclei, inconspicuous nucleoli, moderate nuclear pleomorphism and areas of necrosis. On immunohistochemistry, the tumor cells were positive for synaptophysin, cluster of differentiation (CD)-56 molecule and negative for p63 and Napsin-A. Ki-67 labelling index was 50%. Hence the diagnosis of large cell neuroendocrine carcinoma was made and chemotherapy was initiated. Inspite of this, repeat chest X-ray after a month in April, 2021 showed complete collapse of right lung (Figure 1c). Positron emission tomography-computed tomography (PET-CT) was reported as primary lesion involving the right main bronchus (Figure 1 d) with collapse of the entire right lung and multiple mediastinal lymph nodal metastasis involving peripancreatic and retroperitoneal lymph nodes with multiple liver, adrenal, renal, brain, pleural deposits and subcutaneous nodular metastatic deposits in the bilateral arms (Figure 1e). Patient was not affordable for airway stenting and hence started on palliative chemotherapy. Despite chemotherapy, 8 months later, he ended up in emergency medicine department where his X-ray (Figure 1f) showed furthermore narrowing of trachea and left main bronchus where he succumbed to the disease due to respiratory failure.

3. Discussion

LCNECs are rare and distinct subtype of high-grade neuroendocrine malignancy which are biologically and morphologically heterogenous. The most common site is upper lobes of lungs and it arises more peripherally.[2] In our case it was a central mass with endobronchial obstruction. LCNEC has a more frequent occurrence in an elderly male who is a heavy smoker, but this patient was a 29-year-old with very low smoking index. The patients often present with cough (most common), hemoptysis or post obstructive pneumonia,[3] whereas our patient had breathlessness and wheeze as predominant symptoms. According to the American Thoracic Society guidelines, wheeze is defined as a high-pitched continuous sound with a dominant frequency of 400Hz or more. Airflow induced oscillation of bronchial walls produces wheeze which can be explained by Bernoulli's phenomenon. Production of wheeze occurs only in the first five to seven generations of bronchi as speed of airflow is too low to reach the critical flutter velocity in smaller airways. It can be monophonic (a single musical note starting and ending at different times) as in a local pathology like foreign body (or) polyphonic (multiple notes starting and ending at the same time) as in dynamic compression of the airways. In this case, since the obstruction was more proximal involving trachea, he had biphasic wheeze intensified over right hemithorax. Hence a careful scrutiny of wheeze, its laterality (unilateral or bilateral) and phase identification {monophonic (fixed or random) or polyphonic} would be lifesaving as well as cost effective for early diagnosis and helps to differentiate a benign condition like bronchial asthma from a deadly malignant endobronchial obstruction.

Computed tomography (CT) findings in a case of LCNEC are mass lesion with well-defined borders, lobulated margins and peripheral location whereas this patient had a non-lobulated mass located in the right hilum with complete right lower lobe endobronchial obstruction and partial endotracheal obstruction. The characteristic features in a CT are used to estimate the survival and prognosis in a case of LCNEC. TNM stage >1, non-lobulated margins, maximum standard uptake value (SUV max) in PET-CT more than 12.9 and diameter of more than 5.6cm are associated with poor prognosis.[4] CT thorax in this patient revealed a tumor in right hilum of size 6.3 × 4.8 cm in the greatest dimension with a smooth margin and was stage IV-C(TNM stage) which all pointed towards poor prognosis except for SUV max of 3.35.

Microscopic diagnosis of LCNEC is difficult in small biopsy samples due to crush artifacts, hence surgical resection shouldn't be delayed when there is a suspicion of neuroendocrine malignancy.[5] Tumor cells are typically larger than three times the diameter of resting lymphocytes with prominent nucleoli and eosinophilic cytoplasm which were consistent with our patient. Within a span of two months, an absolutely normal lung had collapsed completely, which explains the rapidity of progression due to high mitotic activity of LCNEC. LCNEC is the only neuroendocrine malignancy that requires at least one neuroendocrine marker by immunohistochemical stain or electron microscopy for diagnosis.[6,7] The most sensitive (92-98%) marker is NCAM/CD-56 but has low specificity. CgA is the most specific (70%) marker but has low

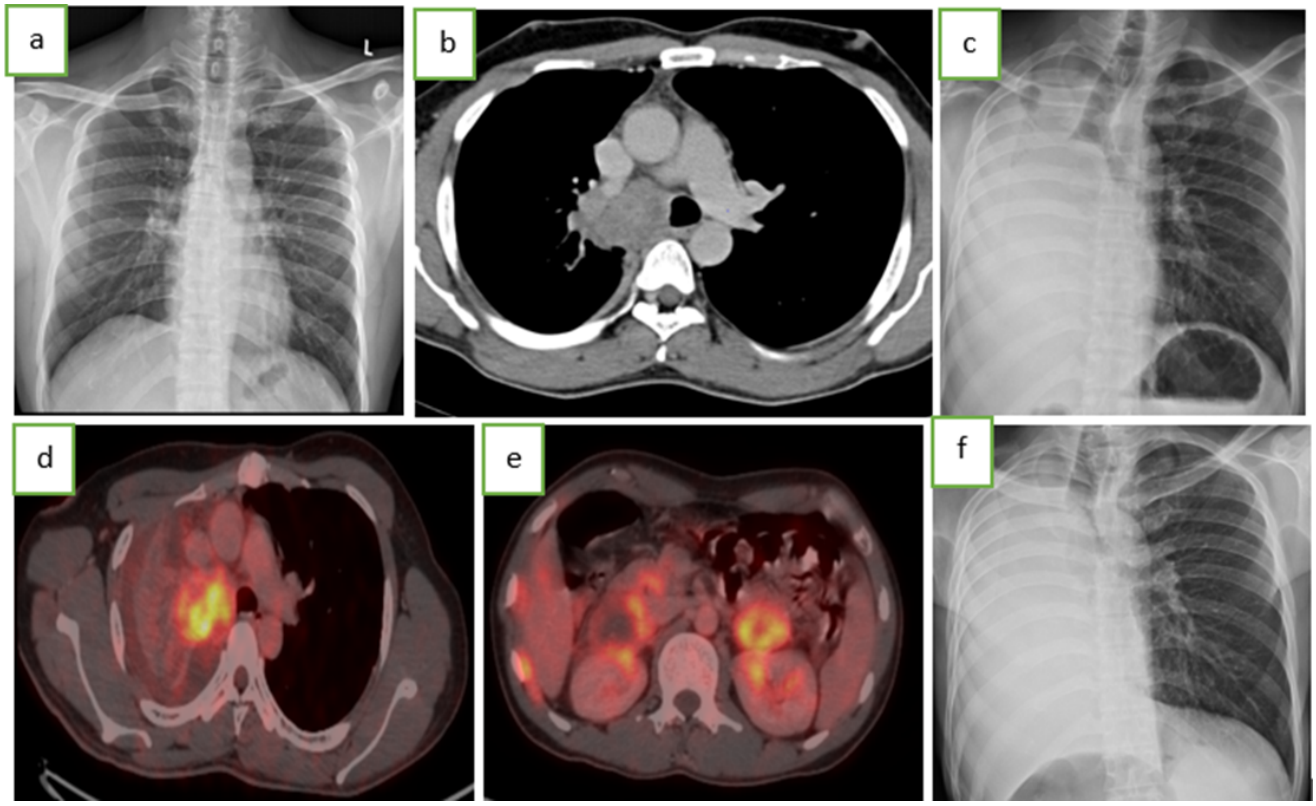

Figure 1: **a:** Chest X-ray posteroanterior view with normal lung zones in the month of February; **b**: A heterogeneously enhancing mass in the right hilum and right main bronchus; **c:** Complete right lung collapse in the month of April; **d**: PET-CT image shows the uptake of primary lesion involving the right main bronchus; **e**: PET-CT image shows multiple liver, adrenal and renal uptake suggestive of metastasis; **f:** Even after 8 months of chemotherapy, chest X-ray showed furthermore narrowing of trachea and left main bronchus in the month of December.

sensitivity. Synaptophysin has sensitivity of 87% but less specific.[6,7] The tumor cells in this case were positive for CD 56 and synaptophysin and negative for Napsin-A and p63 which confirmed the diagnosis of LCNEC. George et al. conducted transcriptome and genomic analysis comparing genomic alteration of LCNEC with other lung malignancies. Two types of mutations were identified. Type-1 mutation included TP53 and RB1 genes while type 2 mutation had STK11 and KEAP1 genes whose roles are well known in targeted therapy.[8] Programmed death ligand-1 and tumor mutational burden are the predictors of response to immunotherapy.[9,10] Stenting and mutational analysis were not done due to economical concerns.

Treatment of LCNEC depends on the stage. For early stages upto III-A, surgery remains the cornerstone for curing the disease.[1] For locally advanced unresectable tumors (stages III-B and III-C) chemo-radiotherapy (Platinum+etoposide) showed much benefits.[1] For other metastatic diseases, palliative chemo-radiotherapy may be advocated. This patient was started on palliative chemotherapy. In spite of this, after 6 months, he ended up in emergency medicine department where his chest X-ray showed complete right lung collapse with furthermore narrowing of left main bronchus and resultant respiratory failure. Unfortunately, we couldn't prolong his life and had expired on the same day of admission in emergency. Informed consent was obtained from the patient prior publication.

4. Conclusion

With this we would like to conclude that a large cell neuroendocrine cancer can present as a centrally located mass with endobronchial obstruction, resulting in wheeze in a young male even with very low smoking index which can be readily fatal where early diagnosis and treatment can prolong the survival. Suspicion of endobronchial obstruction even before the development of overt symptoms and signs like collapse and post obstructive pneumonitis is mandatory, especially in a suspected case of malignancy where time is considered platinum in terms of curative intent. Thus, in patients exhibiting unilateral wheeze or whose wheezing does not improve with bronchodilators, it is imperative to do a complete examination for signs of malignancy, deploy appropriate imaging, and carry

out a bronchoscopic evaluation for the early detection of endobronchial lesions even if no lesions are revealed in radiological images.

5. Clinical Practice Points

1. Large cell neuroendocrine cancer can present as a centrally located mass with endobronchial obstruction, resulting in wheeze in a young male even with very low smoking index which can be readily fatal where early diagnosis and treatment can prolong the survival.
2. Suspicion of endobronchial obstruction even before the development of overt symptoms and signs like collapse and post obstructive pneumonitis is mandatory, especially in a suspected case of malignancy where time is considered platinum in terms of curative intent.
3. Therefore, it is crucial to conduct a thorough examination for indications of malignancies, use appropriate imaging, and perform a bronchoscopic evaluation for the early diagnosis of endobronchial lesions in patients with unilateral wheeze or in whom wheeze is not improving with bronchodilators.

6. Sources and Funding

None.

7. Conflict of Interest

None.

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None.

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Author biography

Jeevanandham Anandan, Senior Resident https://orcid.org/0000-0002-1856-2664

Zeenathalam Nadaf, Junior Resident https://orcid.org/0009-0002-2781-3450

Sneha Leo, Assistant Professor

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