Pulmonary Large Cell Neuro-Endocrine Carcinoma with ALK-EML-4 Fusion with Good Response to ALK Inhibitors

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Summary

Large cell neuroendocrine carcinoma (LCNEC) is a rare but aggressive cancer with very poor outcome. Lung and gastrointestinal tract are the primary sites for majority of cases. Hereby, we are presenting a case report discussing the importance of understanding the molecular biology and use of targeted therapeutics to improve survival in such unusual entity.

Keywords: LCNEC, ALK fusion, ALK inhibitors, Alectinib, Lorlatinib.

Introduction

Lung cancer is the second most common cancer worldwide and is most common cause of cancer related deaths. There are various common types of lung cancer such as small cell carcinoma and non-small cell variants including squamous cell carcinoma, adenocarcinoma and other rare variants such as oat cell carcinoma, large cell carcinoma, carcinoid tumor and large cell neuro endocrine carcinoma.[1]

Large cell neuro-endocrine carcinoma [LCNEC] of lung is a rare entity and LCNEC with ALK-EML4 fusion is even rarer. ALK fusion is seen in adenocarcinoma of lung patients. ALK-EML-4 fusion is seen in about 2% to 5% of non-small cell lung cancer patients. In studies using SEER data, age adjusted incidence of pulmonary LCNEC is 0.3 per 100,000 with a rise by 0.011 people per 100,000 per year from 2004-2015. It is even rarer in other variants such as large cell neuro endocrine tumors with less than 10 cases reported in literature.[2-10]

Here, we present a case report of metastatic ALK-EML-4 fusion positive large cell neuro endocrine carcinoma of lung.

Case Report

A 44 year old male resident of Ahmedabad, non-smoker presented with dry cough, intermittent fever and significant weight loss for 3 months. On examination there was a right supra clavicular (SCF) node and on chest x-ray there was widening of mediastinum and mild pleural effusion. CT chest revealed a large conglomerated lymph nodal mass involving right lower para tracheal and pre-vascular region and multiple pleural based nodules. Excision biopsy from right supra clavicular node was done which showed possibility of medullary carcinoma of thyroid. Immunohistochemistry revealed possibility of medullary carcinoma or large cell neuro endocrine carcinoma. Serum calcitonin was normal and thyroid imaging showed no lesion involving thyroid and was diagnosed as large cell neuro endocrine carcinoma of lung with pleural and lymph nodal metastasis.

Whole body PET-CT showed right lung upper lobe mass lesion with multiple nodular pleural lesions involving right pleura, mediastinal and right supra clavicular nodal metastasis and liver metastasis. Patient received 3 cycles of chemotherapy (carboplatin plus etoposide) and was re-evaluated with whole body PET-CT which showed regression in size of pleural nodules and mediastinal nodules but new appearance of bone metastasis in skull and vertebrae and clinically patient was worsening with continued weight loss.

Patient presented to us (The Gujarat Cancer & Research Institute, Ahmedabad.) with ECOG-3 performance status and weight on presentation was 30 kgs. Patient had continuous projectile vomiting which was investigated with MRI brain which revealed multiple cerebral and cerebellar metastasis. Patient received whole brain radiotherapy of 30 GY in 10 fractions. Biopsy sample from right supra clavicular node was sent for Next Generation Sequencing (NGS) which revealed EML4-ALK fusion and other variants

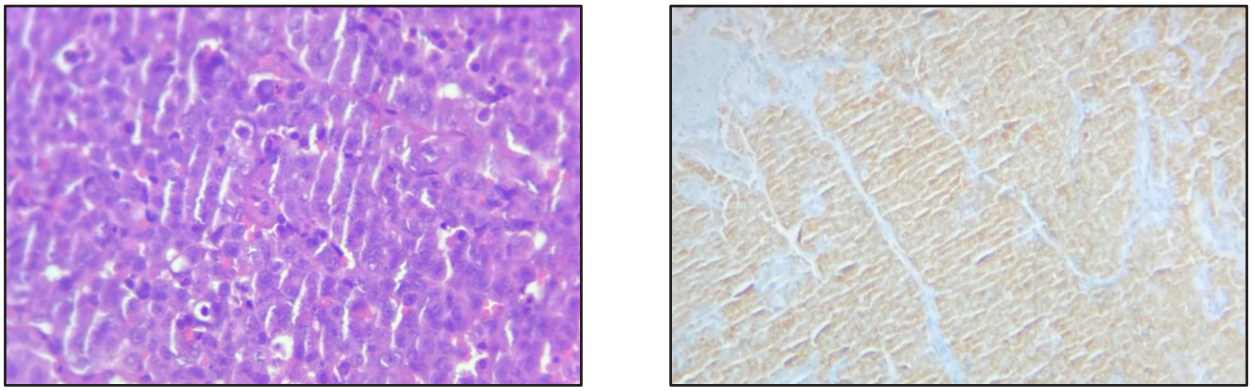

Figure 1: Showing SCF Node Histology on Microscopy and ALK Fusion by Immunohistochemistry

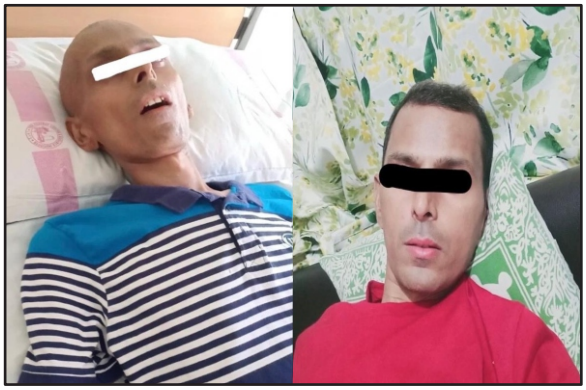

Figure 2: Comparision of Pre Treatment PET CT with Post 4 Months of ALK Inhibitor Therapy

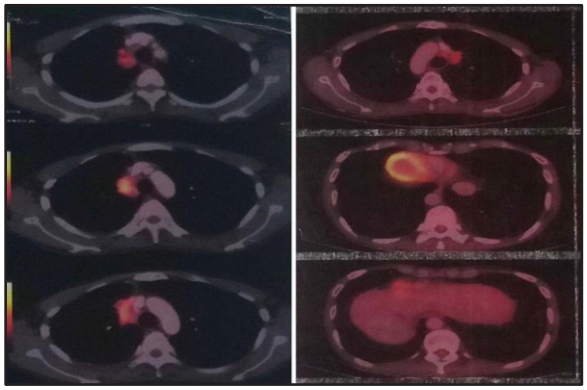

Figure 3: Showing Pre Treatment and Post Treatment General Condition of Patient after 4 Months of ALK 4 Inhibitor Therapy

of unknown significance such as ATR and PTEN mutation. ALK fusion was confirmed by IHC as shown in Figure 1, patient was started on second generation ALK inhibitor, alectinib 600mg BD plus denosumab for bone metastasis.

Results

Patient tolerated Alectinib well and was clinically responding with decrease in cough and increasing weight. After 4 months of therapy patient's weight increased to 35 kgs as shown in Figure 3 with complete resolution of symptoms like cough and fever, patient's performance status improved to ECOG 1 and he started attending his office. Whole body PET-CT revealed significant reduction in size and metabolic uptake of pleural and lymph nodal lesions as shown in Figure 2. Alectinib and Denosumab was continued for 5 more months. Patient's weight increased to 45 kgs with ECOG PS-1.

Re-evaluation PET CT revealed ametabolic sclerotic bone lesions, increase in size and uptake of mediastinal lymph nodal lesion with re appearance of mild pleural effusion suggestive of progression. MRI brain revealed new brain lesions for which patient received whole brain re-irradiation (20 Gray in 10 fractions).

Patient was started on 3rd generation ALK inhibitor, Lorlatinib 100 mg once daily. Patient received Lorlatinib for 3 months. Two months of Lorlatinib therapy improved patient's general condition but after 3rd month of therapy patient presented to emergency with poor performance status and severe weight loss and was managed symptomatically. Patient eventually expired after 15 days of inpatient care.

Discussion

LCNEC is a rare lung cancer which is treated with surgery and adjuvant chemotherapy if patient presents in early stage. For metastatic disease platinum based chemotherapy is the chemotherapy of choice. It is treated similar to the small cell carcinoma due its similarity with small cell carcinoma of lung.[11-12]

But large cell carcinoma of lung rarely harbour ALK fusion and other mutations which may be targeted using targeted therapies. This also shows the importance of molecular testing in such rare cases. Our patients NGS has also revealed other variant mutations of unknown significance such as ATR, PTEN (tumor suppressor genes).

Previously it has been reported that ALK positive LCNEC is not responsive to crizotinib[5] as

expected but our patient had responded well to alectinib similar to a case reported from Japan.[13] The good response to ALK inhibitor-alectinib is mostly due to the fact that the patient was a young, non-smoker and had better cancer biology unlike other patients.

Conclusion

Pulmonary LCNEC is a rare, aggressive entity with dismal prognosis. Patient must be evaluated thoroughly with all available investigations including next generation sequencing. Particularly in non-smoking patients ALK by IHC can also be done in patients with limited resources.

ALK-EML4 fusion positive pulmonary LCNEC do respond to alectinib/lorlatinib and should always be considered before starting chemotherapy due to better quality of life and ease of administration with targeted therapy.

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