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Case Report

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Primary (*De Novo*) EGFR T790M Mutation and High PD-L1 Expression in A Smoker with Metastatic Lung Adenocarcinoma: A Case Report and Literature Review

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Abstract

Primary Epidermal Growth Factor Mutation (EGFR) T790M mutation with concurrent high PD-L1 expression is uncommon in Non-Small Cell Lung Cancer (NSCLC). Due to the rare occurrence of primary EGFR T790M mutation and high programmed cell death-ligand 1 (PD-L1) expression, the disease course, treatment and prognosis of such patients has not yet been clearly elucidated. Here we report a case of an Asian male patient with primary EGFR T790M mutated metastatic non-small cell lung cancer with concurrent high PD-L1 expression, which was not responsive to EGFR T790M Tyrosine Kinase Inhibitor (TKI) Osimertinib and a review of literature.

Case Presentation: A 81 year- old man, smoker was diagnosed with a right upper lobe lung mass and large right pleural effusion. Biopsy of the lung mass was consistent with lung adenocarcinoma, EGFR T790M mutated with high PD-L1 expression. He was treated with Osimertinib, however he did not respond and developed clinical and radiographic progression of disease. Due to poor performance status, immunotherapy could not be initiated. We recommended hospice.

Conclusion: Our patient with primary EGFR T790M mutated lung adenocarcinoma with high PD-L1 expression, failed to respond to EGFR T790M TKI, Osimertinib. Further research is needed to determine if immunotherapy combined with TKI may be a better treatment option for such patients.

Keywords: Immunotherapy; Osimertinib; Primary EGFR T790 Mutation

Background

Epidermal Growth Factor Gene (EGFR) mutations are found in advanced Non-Small Cell Lung Cancer (NSCLC) in about 30-50% of patients in East Asia and in 10-15% in Western countries [1]. EGFR mutations, predominantly exon 19 deletion and point mutation in exon 21 (L858R), comprise up to 86% of somatic mutations found in Non-Small Cell Lung Cancer (NSCLC) and confer sensitivity to EGFR Tyrosine Kinase Inhibitors (TKI). However, despite the initial response to EGFR TKIs, all patients will eventually develop resistance. Acquisition of a second mutation at exon 20 in the EGFR gene, T790M, is the most common mechanism of acquired resistance to EGFR TKI in more than 50% of EGFR mutant lung cancers [2]. This involves a threonine to methionine substitution, which causes steric interference with the binding of EGFR TKIs to the ATP binding site [3]. Most of these cases are acquired resistance through somatic mutations.

Pre-treatment somatic T790M mutations are rare and have been described in case reports. Also, a small number of germline EGFR T790M have been reported, and are estimated to occur in

1% of non-small cell lung cancer cases. These *de novo* mutations confer primary resistance to the first generation TKIs like Erlotinib and Gefitinib. Osimertinib, a third generation TKI, is approved for treatment of patients with metastatic EGFR, T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. Programmed death 1 (PD-1) is a co-inhibitory receptor expressed on the membrane of activated T and B cells, which plays a crucial role in tumor immune escape. PD-L1 is the major ligand for PD-1 and is expressed in a variety of cancers. Approximately 23 to 28% of patients with advanced NSCLC have a high level of PD-L1 expression [4]. PD-L1 inhibitor, Pembrolizumab has been approved for the first line use in metastatic NSCLC whose tumors express PD-L1 as determined by an FDA approved test (tumor proportion score ≥ 50%) with no EGFR or ALK genomic tumor aberrations and no prior systemic chemotherapy. There are no clear guidelines for the treatment of patients with *de novo*, pre-treatment T790M mutation with concurrent high PD-L1 expression. It is unclear if third generation TKI, immunotherapy or both should be used as first line in such patients.

Case Report

A 81 year old man, with past medical history of atrial fibrillation on rivaroxaban, stroke, hypothyroidism and sixty pack years smoking history, presented with cough. Computed Tomography (CT) scan of chest showed a lung mass in the right upper lobe. He declined tissue biopsy and further work up at that time. Ten months later he presented to the emergency department with progressive shortness of breath and weight loss of 10 pounds over the last three months. Laboratory tests were significant for anemia with hemoglobin of 10 gm/dl, thrombocytopenia (platelet count-121,000/µl) and coagulopathy (Partial thromboplastin time: 46.8 seconds, International normalized ratio: 3.6). CT scan of chest showed a dense mass-like opacity in the posterior right upper lobe and large right pleural effusion with mediastinal and right hilar adenopathy. Right chest tube was placed. Chemical pleurodesis could not be done due to increased output from the chest tube. So, patient underwent right tunneled catheter placement and biopsy of the lung mass by interventional radiology. His shortness of breath improved and he was discharged. He was readmitted with hemoptysis a few weeks later. Rivaraxoban was held. His hemoptysis resolved without further intervention and he was discharged in a few days. CT scan during this admission again showed a 2.7 cm x 2.8 cm right upper lobe mass (Figure 1).

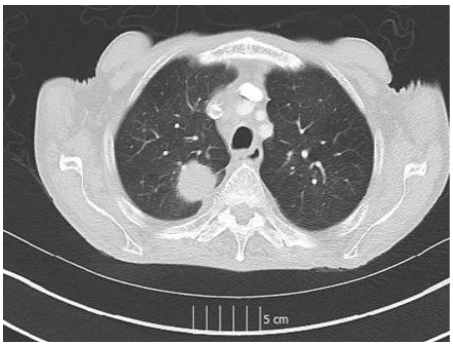

Figure 1: Pretreatment CT scan.

3.5 mm right upper lobe nodule, mediastinal and hilar lymphadenopathy. MRI brain and bone scan did not show any metastases. There was no reported family history of lung cancer.

The lung mass biopsy was consistent with lung adenocarcinoma, EGFR T790M mutated with 50% PD-L1 expression. We started him on targeted therapy with Osimertinib 80mg daily. He tolerated Osimertinib well with mild pancytopenia and skin rash. However, he did not respond to treatment and developed progressively worsening shortness of breath. He became wheelchair bound and was oxygen dependent. CT scan done after two months of Osimertinib therapy showed increase in size of lung mass, increasing bilateral pleural effusions (Figure 2).

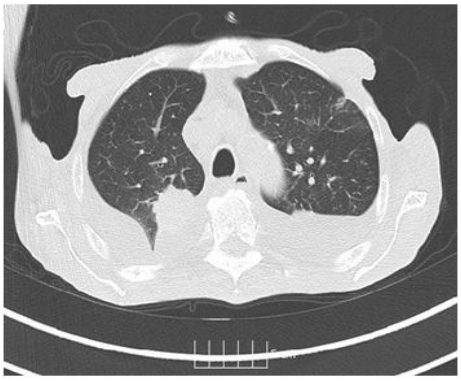

Figure 2: CT scan showing disease progression on Osimertinib.

increased size of mediastinal and paratracheal lymphadenopathy, anasarca and ascites. Due to disease progression, we discontinued Osimertinib. Due to his poor performance status, we could not initiate immunotherapy with Pembrolizumab and recommended hospice (Figure 1,2).

Discussion

Occurrence of somatic T790M mutations in patients who never receive EGFR TKIs is rare and can occasionally be found in tumors with primary TKI resistance [5]. Germline EGFR T790M mutations have been reported commonly in Caucasian females who are never smokers and are found to occur most commonly with EGFR L858R mutation [6,7]. Our male patient, who was a smoker, had a primary *de novo* EGFR T790M mutation with concurrent high PD-L1 expression. He had no family history of lung cancer. We think our patient most likely had a primary somatic T790M mutation. Studies in mice suggest that the T790M change may potentiate oncogenic activity, either by itself or in association with activating EGFR mutations, for example exon 19 deletion and L858R point mutation. Mice expressing the EGFR T790M transgene alone usually develop tumors with longer latency than animals expressing EGFR L858R+T790M [8]. Our patient with primary T790M mutation had a relatively late onset of lung cancer at the age of 80 years.

On the other hand, presence of activating EGFR mutations like EGFR L858R with primary *de novo* EGFR T790M mutations (somatic or germline) leads to an earlier onset of malignancy [9] with rapid progression and reduced overall survival [10,11]. Disease course of patients with primary *de novo* T790M with concurrent high PD-L1 expression like our patient has not been fully studied. Preclinical studies have shown the germline T790M mutation to be a weak oncogene that often requires a secondary mutation to potentiate cancer development [6]. Our patient who declined further workup initially, presented at 10 months with disease progression, suggesting that such patients may have a slower course of progression. Osimertinib (AZD9291, Tagrisso™), an oral, third-generation EGFR TKI, has been designed to target the EGFR T790M mutation, while sparing wild-type EGFR. It shows 200-fold selectivity for T790M/L858R protein over wild-type EGFR [12]. Osimertinib was granted accelerated approval by the US Food and Drug Administration (FDA) in November 2015 for patients with metastatic EGFR T790M-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. For patients with EGFR T790M mutated NSCLC, Osimertinib demonstrated clinically superior efficacy over Pemetrexed plus a platinum agent with a 70% reduction in the risk of disease progression, according to the results of the AURA3 study [13]. The objective response rate for Osimertinib in patients with T790M-positive non-small-cell lung cancer was 61%; the median duration of progression-free survival was 9.6 months.

The role of immunotherapy in EGFR TKIs resistant patients has not been elucidated [14,15], demonstrated that the activation of EGFR pathway increases PD-L1 expression [16]. Demonstrated that the level of PD-L1 in EGFR-mutant NSCLC cell lines was significantly higher than that in EGFR-wild type cell lines and the expression of PD-L1 was the highest in resistant cells with EGFR-T790M mutation. This finding is consistent with our patient who had an elevated PD-L1 expression of 50%. Akbay, et al. stated that in EGFR mutant NSCLC, EGFR TKIs reduced PD-L1 expression. He also showed that blocking the PD-1 pathway in EGFR mutant tumors resulted in tumor reduction and significantly increased overall survival. He concluded that combination of PD-1 blockade with EGFR TKIs may be a promising therapeutic option in such patients. Due to rare occurrence of pre-treatment primary T790M mutations (both somatic and germline), studies have not been conducted with third generation EGFR TKIs like Osimertinib, alone or in combination with immunotherapy in this patient population. Our patient did not respond to treatment with osimertinib. There are no clear guidelines if TKI inhibitor or immunotherapy or both should be used as first line in tumors harboring both, *de novo* T790M mutation and increased PD-L1 expression.

Ongoing trials are assessing EGFR TKIs in combination with immune checkpoints inhibitors in patients who progressed on prior EGFR TKI. A phase I study is evaluating the combination of Afatinib with Pembrolizumab in patients with EGFR-mutant NSCLC progressing after a prior EGFR TKI (NCT02364609). A phase III trial is evaluating the combination of the PD-L1 inhibitor MEDI4736 with AZD9291 compared to AZD9291 alone in patients with T790M-positive NSCLC following a prior EGFR TKI (NCT02454933) Data from these studies with use of immunotherapy with or without EFGR TKI in patients with acquired resistance to the first line EGFR TKI can be extrapolated to patients like our patient. Further studies will be needed to study disease course and response to treatment, in tumors with *de novo* T790M mutation concurrent high PD-L1 expression.

Conclusion

In conclusion, the presence of *de novo* T790M mutation with concurrent high PD-L1 expression in patients with NSCLC is rare and may predispose to lung adenocarcinoma. It may be associated with a late age of onset, slower disease progression and poor response to the third generation TKI. Further studies will be needed to determine if these patients should be treated with immunotherapy or a combination of a third generation TKI and immunotherapy.

References

1. Anita Midha, Simon Dearden, Rose McCormack (2015) EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res 5: 2892-2911.

2. Stewart EL, Tan SZ, Liu G, Tsao MS (2015) Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations-a review. Transl Lung Cancer Res 4: 67-81.

3. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, et al. (2008) The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci USA 105: 2070-2075.

4. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, et al. (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 375:1823-1833.

5. Prudkin L, Tang X, Wistuba II (2009) Germ-Line and Somatic Presentations of the EGFR T790M Mutation in Lung Cancer. J Thorac Oncol 4: 139-141.

6. Gazdar A, Robinson L, Oliver D, Xing C, Travis WD, et al. (2014) Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. J Thorac Oncol 9: 456-463.

7. Yu HA, Arcila ME, Harlan Fleischut M, Stadler Z, Ladanyi M, et al. (2014) Germline EGFR T790M mutation found in multiple members of a familial cohort. J Thorac Oncol 9: 554-558.

8. Regales L1, Balak MN, Gong Y, Politi K, Sawai A, et al. (2007) Development of New Mouse Lung Tumor Models Expressing EGFR T790M Mutants Associated with Clinical Resistance to Kinase Inhibitors 2: e810.

9. Lou Y, Pecot CV, Tran HT, DeVito VJ, Tang XM, et al. (2016) Case Report: Germline Mutation of T790M and Dual/Multiple EGFR Mutations in Patients with Lung Adenocarcinoma. Clin Lung Cancer 17: e5-11.

10. Gregory J. Riely, Helena Alexandra Yu, Maria E. Arcila, Matthew David Hellmann, Marc Ladanyi, et al. Response to erlotinib and prognosis for patients with *de novo* epidermal growth factor receptor (EGFR) T790M mutations.

11. Li H, Hu H, Wang R, Pan Y, Wang L, et al. (2014) Primary concomitant EGFR T790M mutation predicted worse prognosis in non-small cell lung cancer patients. Onco Targets Ther 7: 513-524.

12. Soejima K, Yasuda H, Hirano T (2017) Osimertinib for EGFR T790M mutation-positive non-small cell lung cancer. Expert Rev Clin Pharmacol 10: 31-38.

13. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, et al. (2017) Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 376: 629-640

14. D'Incecco A, Andreozzi M, Ludovini V, Rossi E, Capodanno A, et al. (2015) PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer 112: 95-102.

15. Akbay EA, Koyama S, Carretero J, Altabef A, Tchaicha JH, et al. (2013) Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov 3: 1355-1363.

16. Chen N, Fang W, Zhan J, Hong S, Tang Y, et al. (2015) Upregulation of PD-L1 by EGFR Activation Mediates the Immune Escape in EGFR-Driven NSCLC: Implication for Optional Immune Targeted Therapy for NSCLC Patients with EGFR Mutation. J Thorac Oncol 10: 910-923.