Literature Publishers

Clinical Images and Case Reports Journal

Case Report | Vol 2 Iss 3

Crizotinib Re-Challenge Overcomes Multiple Resistant Clones in cMET(+) NSCLC Patient

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Received: May 28, 2020; **Accepted:** June 10, 2020; **Published:** July 04, 2020

Abstract

Objectives: Non-Small Cell Lung Carcinomas (NSCLC) presents mesenchymal-epithelial transition factor exon 14 skipping (METex14) mutation in 0.6-7 % of patients. Crizotinib is a Tyrosine Kinase Inhibitor (TKI) that has been approved for the treatment of ALK-rearranged tumors and demonstrated clinical activity in MET(+) NSCLC. Acquired point mutations in the MET gene have been described as mechanisms of resistance to crizotinib.

Materials and Methods: For the evaluation of the MET clones we have used cell-free DNA (cfDNA) NGS test (Guardant360).

Results: In this report, we present a 66-year-old previously healthy non-smoking male who was diagnosed with metastatic adenocarcinoma of the lung with METex14 mutation, PDL-1 expression more than 50 %. The patient developed multiple secondary c-MET resistant clones and responded to re-exposure to crizotinib therapy.

Conclusion: According to this case we suggest that clonal evolution is not necessarily a synonymous with resistant to previous lines (beyond the recent one). Similar phenomenon was previously reported in an ALK fusion case with respond to crizotinib re-exposure, by Shaw et al. The eradication of the emerging clones by crizotinib, as presented in this case, may support this assumption and suggest cautious re-exposure to previous lines in case of emerging resistant. Hypothetically, if this is not the case, we may suggest that crizotinib has changed the microenvironment in a way allowing eradication of the different clones by the activated immune system, however we do not have any support for this assumption.

Keywords: Targeted therapy; Non-small cell lung carcinoma (NSCLC); c-MET Acquired resistance; Crizotinib

Introduction

Non-Small Cell Lung Carcinomas (NSCLC) presents mesenchymal-epithelial transition factor exon 14 skipping (METex14) mutation in 0.6-7 % of patients [1,2]. Crizotinib is a Tyrosine Kinase Inhibitor (TKI) that has been approved for the treatment of ALK-rearranged tumors [3] and demonstrated clinical activity in MET(+) NSCLC [4,5]. Acquired point mutations in the MET gene have been described as mechanisms of resistance to crizotinib [6,7].

In this report, we present a patient with METex14 skip mutation who developed multiple secondary c-MET resistant clones and responded to re-exposure to crizotinib therapy.

Case Report

A 66-year-old previously healthy non-smoking male diagnosed with metastatic adenocarcinoma of the lung with METex14 mutation, PDL-1 expression more than 50 % (Figure 1A). ALK, ROS1 and EGFR were not detected. The patient was treated by crizotinib (250 mg BID) with a complete metabolic response as demonstrated by PET-CT at 4 months. A year after initiation of treatment, he had systemic progression (liver, bone) and a targeted cell-free DNA (cfDNA) NGS test (Guardant360) revealed the METex14 (c.2888-5_2905 deletion) driver mutation and a TP53 mutation, plus a MET D1228H resistance mutation (Figure 1B).

Upon his refusal for chemotherapy and his PDL1>50 %, 2nd line therapy with pembrolizumab was initiated for 25 cycles. After 15 months of Immune Checkpoint Inhibitor (ICI) therapy with a very slow progression (Figure 1C-1D), repeated cfDNA NGS revealed multiple new c-MET clones with numerous secondary point mutations in the cMET gene (Figure 1E). Due-to patient's continuous refusal for chemotherapy, crizotinib was re-challenged with unexpected clearance of the MET resistance clones on repeated cfDNA testing (Figure 1F-1G). Unfortunately, three months later, upon brain disease progression, the patient died.

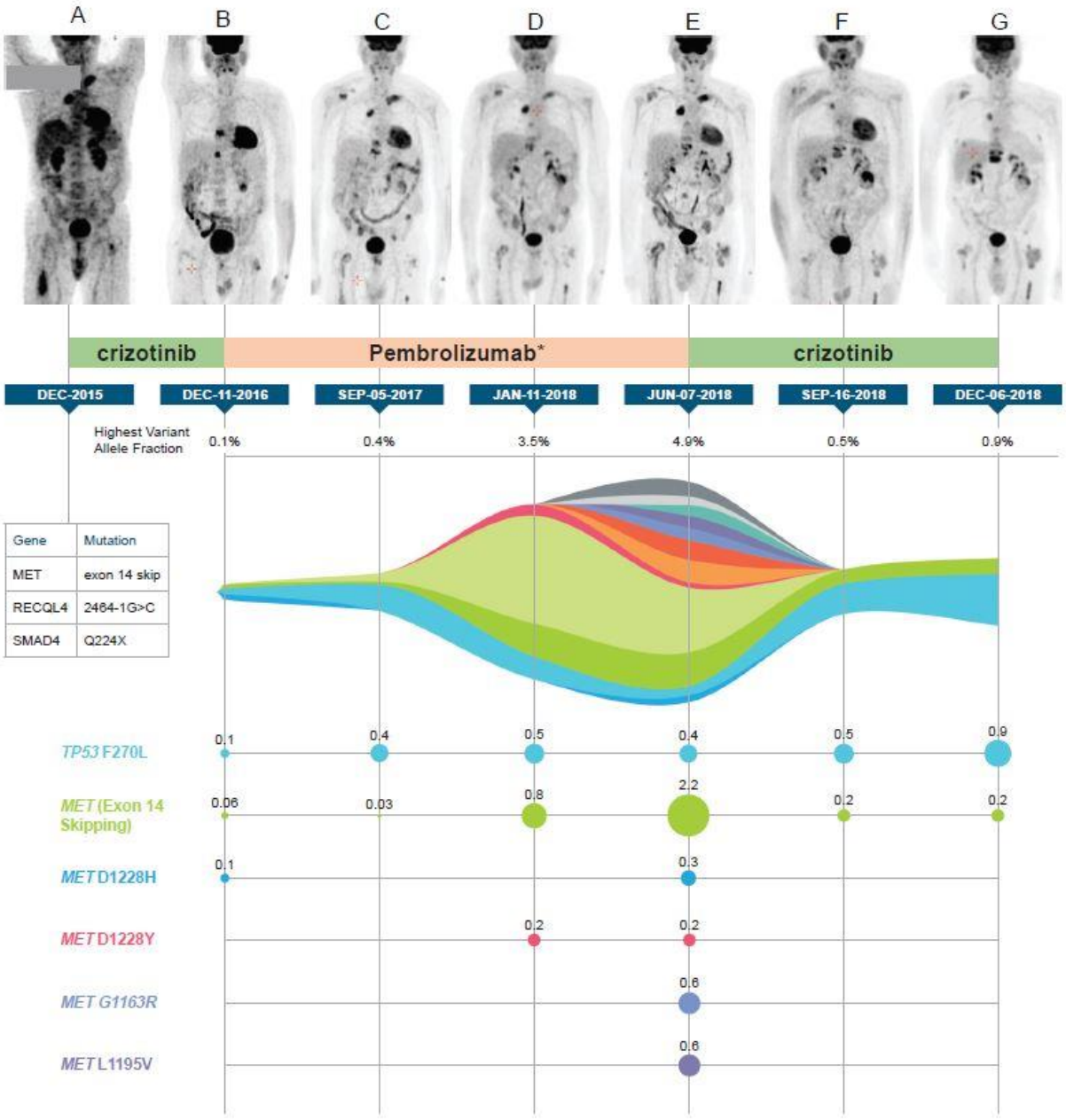

Figure 1: Positron Emission Tomography-Computed Tomography scan (PET-CT) and cfDNA (GUARDANT^{360}). The table below annotates the variant allele fraction (% cf-DNA) detected in the samples, listed in descending order. *Three cycles of ipilimumab were given along with pembrolizumab between 6-9/2017.

Discussion and Conclusion

In recent years c-MET alterations have been well designated in NSCLC and constitute a signaling pathway susceptible for targeted therapies. Crizotinib is a tyrosine kinase inhibitor with proven antitumoral activity in NSCLC harboring MET amplifications and METex14 skip mutation [4]. Second and third MET TKIs are on clinical trials [8,9].

In our reported case we described a year-long complete metabolic response to crizotinib as demonstrated by PET-CT in a patient with NSCLC harboring METex14 skipping mutation, until progression with co-occurring MET D1228H which is a known acquired crizotinib resistance mutation. After a 15-month period of stable to slowly progressive disease on ICI, and because those clones were crizotinib-naive, we speculated we may see some activity for crizotinib in spite of previous reports [10]. Resistant point mutations in MET pathways are recognized [11]. As the multiple MET clones in this case have emerged under pembrolizumab therapy, we speculate that it reflects the natural history of clonal evolution, rather than resistant to MET TKI. That might suggest that clonal evolution is not necessarily a synonymous with resistant to previous lines (beyond the recent one). Similar phenomenon was previously reported in an ALK fusion case with respond to crizotinib re-exposure, by Shaw et al. [12]. The eradication of the emerging clones by crizotinib, as presented in this case, may support this assumption and suggest cautious re-exposure to previous lines in case of emerging resistant. Hypothetically, if this is not the case, we may suggest that crizotinib has changed the microenvironment in a way allowing eradication of the different clones by the activated immune system, however we do not have any support for this assumption.

Acknowledgements

Walid Shalata* and Roni Gillis* has contributed equally to this work.

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