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Case Report

Complex paradigm of *MET* exon14 mutation: A skip beyond *EGFR* in lung adenocarcinoma

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Abstract

Lung cancer is a leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for 80–85% of cases. It is characterized by diverse histological subtypes and distinct molecular drivers, each with specific therapeutic implications. These include mutations in *EGFR*(15–30%), *KRAS*(25–30%), *BRAF*(1–2%), *HER2*(2–3%), and *MET*(3–4%), as well as gene rearrangements in *ALK*(5–7%), *ROS1*(1–2%), *RET*(1–2%), and *NTRK*(~1%). Lately, *MET* alterations, particularly, *MET* exon 14(*MET*ex14) skipping mutation occurring in approximately 3% of NSCLC cases, has emerged as a clinically actionable target. Other alterations of *MET*, such as point mutations, amplifications, alternative splicing events, can mimic *MET*ex14 skipping by leading to constitutive activation of *MET* signaling. These alterations confer resistance to *EGFR* inhibitors or influence treatment responses, necessitating targeted NGS panels to guide personalized therapeutic strategies in NSCLC. We present a case of a 71-year-old male, treated for rectal adenocarcinoma, now diagnosed with primary lung adenocarcinoma. Molecular testing with targeted NGS panel covering key lung cancer genes for various genomic alterations (SNVs, InDels, CNVs, and Fusions) was considered. On sequencing analysis, a tier I pathogenic variant in *MET* c.3028 G>C; p.Asp1010His was detected with a VAF of 35%. No other co-mutations were noted. The patient was started on radiation for painful bone metastasis, however succumbed to the widespread disease. The identification of the *MET*ex14 mutation underscores the significance of targeted therapy, particularly with *MET* inhibitors such as Capmatinib and Tepotinib, which have demonstrated promising efficacy. This report emphasizes the necessity of targeted multi-gene NGS panels for precision medicine in NSCLC.

Keywords: Non-small cell lung carcinoma, Molecular alterations, *MET* alteration, *MET* exon 14 skipping mutation

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1. Introduction

Lung cancer is a frequently diagnosed cancer, with an estimated 2.2 million new cases annually.[1] NSCLC accounts for approximately 80–85% of all cases, encompassing adenocarcinoma (47.9%) and squamous cell carcinoma (23.2%) as per SEER database.[2] Majority of these are diagnosed at advanced stages, where traditional treatment modalities, such as chemotherapy and radiotherapy, have limited effectiveness and tolerance.

Advancements in molecular diagnostics have uncovered a diverse spectrum of oncogenic driver alterations in NSCLC, revolutionizing diagnostic precision and targeted therapeutic strategies. Common alterations include mutations in *EGFR*, *KRAS*, *BRAF*, *HER2*, and *MET*, followed by gene rearrangements in *ALK*, *ROS1*, *RET*, and *NTRK*. The frequency of these alterations, particularly *EGFR*, varies significantly by region (10–15% in Western versus 25–30% in Southeast Asian population).[3] In a large Indian cohort of 5,219 NSCLC patients, 80.6% had at least one genomic alteration, with *EGFR* mutations in 34.1% followed by *TP53*(37%), *KRAS* (13.3%), *ALK* rearrangements(8.8%) and *MET* alterations(2.9%).[4] Various other alterations such as InDels, Single Nucleotide Variants (SNVs), Copy Number Variants (CNVs) and gene rearrangements are reported with variable incidence across lung tumors.[3]

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METex14 skipping mutations, though less common, have emerged as relevant molecular drivers and clinically actionable targets. These activating mutations prevent normal degradation of the *MET* receptor, resulting in aberrant pathway activation contributing to tumour progression. Beyond exon 14 skipping, other *MET* alterations, such as amplifications, point mutations, and fusions also contribute significantly to oncogenesis, disease progression, and therapy resistance, underscoring the need for advanced molecular techniques for precise detection and timely patient management.[4] In this rapidly evolving era of molecular diagnostics, Next Generation Sequencing (NGS) plays a key role in identifying such alterations and rarely necessitates orthogonal techniques such as fragment length analysis for cross verification.

In NSCLC, the *METex14* alterations are most frequently associated with pulmonary sarcomatoid carcinoma (~13%), followed by adeno-squamous carcinoma (~6%) and adenocarcinoma (~2%).[5]

The approval of *MET* tyrosine kinase inhibitors (TKIs) such as Capmatinib (FDA, 2020; GEOMETRY mono-1 trial) and Tepotinib (FDA, 2021; VISION trial) has significantly improved survival of patients with *MET*-altered NSCLC, with an observed median overall survival reported between 12–19 months in treated patients.[6,7]

2. Case Report

A 71-year-old male, known smoker, presented with a history of cough and progressive breathlessness over the past few weeks. He was treated for rectal adenocarcinoma two years ago.CECT scan of the chest revealed a large, irregular mass measuring 7.8 × 5.5 cm in the left upper lobe, with areas of necrosis, suggestive of a primary lung malignancy (**Figure 1**). Metastatic workup showed brain and skeletal Metastases.A CT-guided biopsy of the lung mass was performed and the sample was sent for histopathological evaluation.

2.1. Pathology findings

Histopathological examination showed an invasive carcinoma with tumour cells arranged in lepidic predominant pattern and ill-formed glands. The neoplastic cells exhibited moderate anisonucleosis with prominent nucleoli and cytoplasmic vacuolation (**Figure 2**) A diagnosis of well-differentiated adenocarcinoma with lepidic predominant growth pattern was established. On Immunohistochemistry (IHC), the tumour cells were immunoreactive for CK7 and TTF-1, thus confirming the diagnosis of primary lung adenocarcinoma (**Figure 2**), in a patient who was treated for carcinoma rectum in the past.

2.2. Molecular analysis

Molecular analysis was performed at an outisde centre on NGS platform (Illumina, Inc. San Diego, California) with a lab developed multi-gene panel covering key lung cancer genes. Various genomic alterations like SNVs, InDels, CNVs, and gene fusions. FFPE tissue block with 40% tumour content was used as starting material. Nucleic acid extraction and subsequently, library preparation was performed using a custom hybrid capture kit. The QC passed libraries were sequenced to a minimum depth of 250X on sequencing platform. The variants were annotated using our in-house annotation pipeline and genomic alterations were prioritized, classified, and reported based on AMP/ASCO/CAP guidelines.

Sequencing analysis revealed a variant in *MET* c.3028 G>C; p.Asp1010His, with a variant allele frequency (VAF) of 36% (**Figure 3**), which is a tier I pathogenic variant of clinical significance. No co-mutations or concurrent mutations were noted. In view of rarity of this variant, sample was cross verified on fragment length analysis, which showed a mutant peak at 101bp, thus confirming a *MET*ex14 skipping alteration. (**Figure 4**)

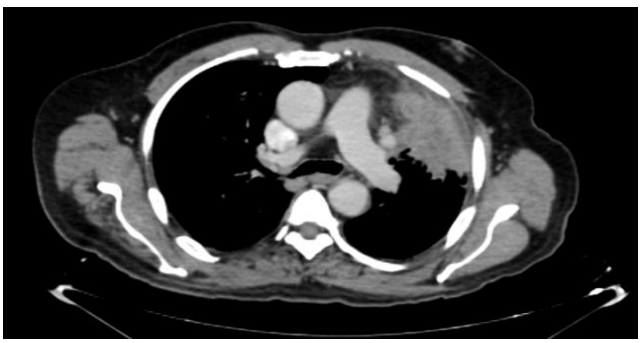

Figure 1: CECT Thorax: Apical lung mass in the left upper lobe with contralateral pulmonary lesions.

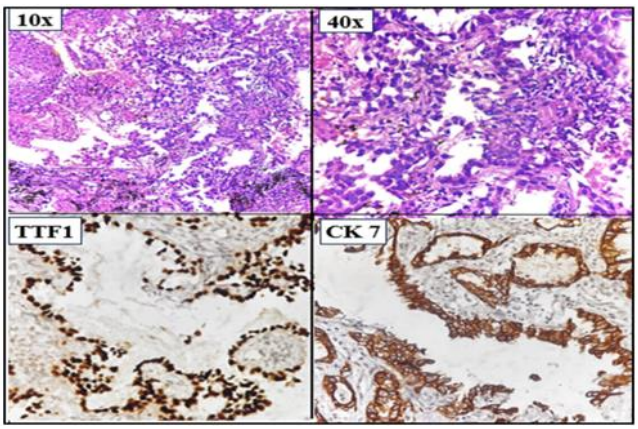

Figure 2: H&E(20X & 40X): Tumour cells in lepidic predominant pattern with moderate anisonucleosis with vacuolated cytoplasm. **IHC:** Tumour cells diffusely positive for TTF1 and CK7

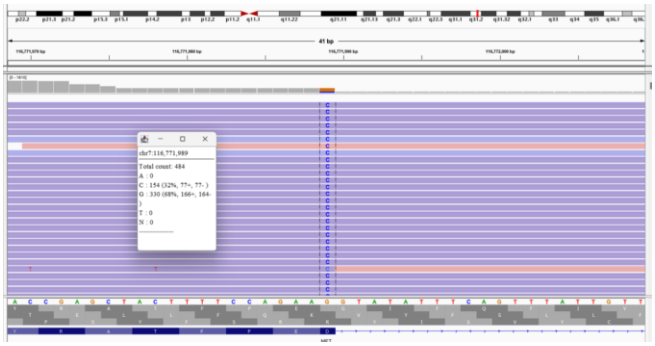

Figure 3: Integrated genomic viewer showing G>C change at c.3028of *MET* gene.

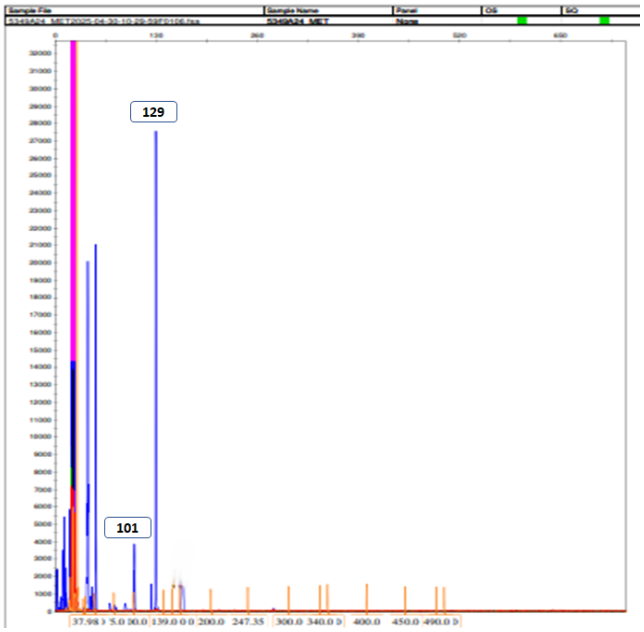

Figure 4: Fragment length analysis showing two peaks, wild type peak at 129bp and a mutant peak at 101bp, thus confirming a *MET*ex14 skipping mutation.

The identified *MET* exon 14 skipping mutation rendered the patient suitable for treatment with *MET* TKIs, such as Capmatinib or Tepotinib. In view of bone pain, the patient received palliative radiotherapy; however, he succumbed to disease due to widespread metastasis, before the initiation of TKIs.

3. Discussion

MET gene, located on chromosome 7q31, encodes hepatocyte growth factor receptor (HGFR), a tyrosine kinase involved in cellular growth, survival and motility.[8]

As an oncogenic driver, *MET* is frequently altered in papillary renal cell carcinoma (4–5%) and gastric cancers (1–3%).[3] In NSCLC, *MET* alterations occur through several mechanisms, including exon 14 skipping mutations that prevent normal receptor degradation, amplifications that lead to overexpression, point mutations affecting splice sites or kinase activity, and rare fusions.[5] These alterations mimic *METex14* by activating downstream oncogenic pathways like *PI3K/AKT*, *RAS/MAPK*, and *STAT3*, promoting tumor progression and therapy resistance. Detection of such alterations is optimally achieved through NGS, using a targeted panel, which identifies a variety of *MET* alterations, including complex and cryptic ones, which may be otherwise missed by limited assays.[9]

Common co-mutations in *MET*-altered NSCLC, such as *TP53*, *STK11*, *KEAP1*, *KRAS*, and *SMARCA4*, can negatively influence response to *MET* inhibitors. *MET* amplification is a known mechanism of acquired resistance to *EGFR* TKIs, particularly Osimertinib, observed in 10–15% of resistant cases.[10] Therapeutic targets for combined *MET* and *EGFR* blockade is under investigation as a potential strategy.[9]

The variant, c.3028 G>C; p.Asp1010His, observed in our case is an extremely rare *MET* variant, which has not been reported in commonly accessed public databases such as ClinVar, COSMIC or OncoKB, though a few entries exist in clinical genomic repositories such as Franklin by Genoox.[11] Yuan L et al, in their study of 2,296 NSCLC cases, identified *MET* exon 14 mutation in 44 (1.9%) patients, six of which harboured the p.Asp1010His variant. This is so far the largest data on this variant, however, lacks the variant specific clinical relevance in terms of survival and prognosis.[12]

The knowledge of orthogonal molecular platforms for the cross-verification of such rare variants is crucial. This rarity also underscores the importance of expanding and utilizing population-specific and real-world clinical databases. Registries and shared databases help track regional mutation patterns and support personalized treatment decisions. Additionally, techniques like liquid biopsy may aid in early detection of such alterations, particularly in cases where tissue access is limited.

4. Conclusion

Targetable molecular alterations in NSCLC are rapidly evolving, consisting of well-established and potential alterations. Broad targeted NGS panel is crucial for identifying various *MET* alterations, thus enabling personalized therapy, in an otherwise aggressive case. Rare and novel variants highlight the importance of cataloguing population-specific mutations. Ongoing advances in sequencing technology and bio-informatics pipelines with multi-omics integration will enhance our understanding of tumor biology and reveal new therapeutic targets.

5. Source of Funding

None.

6. Conflict of Interest

None.

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