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Research Article

Uncommon Mutations in EGFR Exon 7 in Patients with Non-Small Cell Lung Cancer (NSCLC): Clinical and Pathological Characteristics of Four Cases

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Abstract:

The most common cause for hepatocellular carcinoma (HCC) is cirrhosis. Furthermore, cirrhosis is a risk factor for cholangiocarcinoma (CC). Detection of HCC and CC can be challenging in both radiologic imaging and during surgical resection, especially in patients with an underlying parenchymal liver disease such as cirrhosis. Therefore, radioactive seed-guided resection of these tumors, analogously to breast cancer, could be an interesting approach. We present two cases of cirrhotic patients in whom this method of tumor labeling was used.

The first case was a patient suffering from suspected HCC. Although the targeted lesions had been verified by intraoperative ultrasound before non-anatomical resection, histological examination of the specimen showed no tumor. Three months later, tumor progression was seen on liver imaging. Therefore, the patient underwent interventional labeling of the tumor with a radioactive seed followed by open resection. Complete removal of a combined HCC-CC of the liver in segment VII was achieved.

In the second patient, seed-guided resection was recommended due to underlying cirrhosis. Furthermore, the two lesions were rather small and the localization were surgically difficult to reach. Both lesions were pre-labelled with help of TACE and Lipiodol the day before. Subsequently, two radioactive seeds were placed in the lesions, and resection was performed successfully.

This report emphasizes the difficulties, which surgeons and radiologists may face in tumor entities that are difficult to identify both macroscopically, by palpation and intraoperative imaging techniques. It also highlights the successful adaption of a procedure commonly used for breast cancer surgery for liver surgery.

Key words: radioactive seed-guided resection; cholangiocellular carcinoma; combined cholangio-hepatocellular carcinoma

1.Introduction

Exons 18 to 21 of the Epidermal Growth Factor Receptor (EGFR) gene are the most frequently mutated regions in NSCLC. These mutations, including point mutations, small insertions/deletions, and gene rearrangements, affect the intracellular region of the EGFR protein, resulting in abnormally phosphorylated tyrosine residues [1].

Clinical trials have demonstrated superior clinical responses to tyrosine kinase inhibitors (TKIs) in NSCLC patients with specific EGFR mutations such as 19-Del, L858R, T790M, 20-Ins, G719X, S768I, and L861Q [2]. However, infrequent EGFR mutations present diagnostic and therapeutic challenges due to their varied responses to standard TKI treatment.

Among these uncommon mutations are those found in exon 7 of EGFR, which are scarcely documented in the literature. In 2018, L. Dai et al. [3] reported the c.866C>T (p. A289V) mutation, involving the extracellular region of EGFR's exon 7. This mutation has yet to be included in major international databases (Oncokb, Uncommon EGFR, and Clinvar). [4]

Previous studies suggest that this point mutation may affect EGFR's normal function and could be a potential therapeutic target for TKI treatment. However, it has only been described in glioblastoma cell lines and rarely in NSCLC cases, with no evidence of TKI treatment effects in NSCLC with the c.866C>T mutation.

This study presents the first report of four NSCLC cases with potentially pathogenic exon 7 EGFR mutations in our healthcare area.

Objective

To describe the clinical, pathological, and molecular characteristics of patients in our case series and to report previously undocumented mutations in exon 7 of EGFR that may be relevant to clinical practice.

Methodology

This descriptive analysis covers clinical, pathological, molecular characteristics, and treatment responses in four NSCLC patients diagnosed between December 2023 and February 2024 with uncommon exon 7 EGFR mutations.

Mutations were detected using Next-Generation Sequencing (NGS) by the Pathological Anatomy and Genetics Services at Hospital Clínico Universitario Lozano Blesa, Zaragoza, (Spain).

- Test: Oncomine Precision Assay, on the Genexus platform
- Technique: Automated DNA and RNA extraction using the Genexus Purification System

Therapeutic decisions were made individually by a multidisciplinary Molecular Committee following the ESMO-ESCAT scale recommendations [5] to assess the therapeutic actionability of the variants found.

Results

Our sample included four NSCLC patients (three men and one woman, aged 74-82, mean age 78). All patients had been exposed to tobacco smoke (three former smokers, one active smoker), with three ECOG 0 and one ECOG 2.

Histologically, there were three adenocarcinomas and one squamous cell carcinoma. Two patients had high PD-L1 expression (95% and 80%), one had 2% expression, and one was not analyzed.

Molecular analysis revealed three potentially pathogenic variants:

- NM_005228.3; c.866C>T, p.A289V (VAF 12%)
- NM_005228.3; c.866C>A, p.A289D (VAF 3%)
- NM_005228.5; c.866C>A, p.A289D (VAF 9.3%)

Additionally, two variants of uncertain significance were identified in one patient:

- NM_005228.5; c.857G>T, p.S286I (VAF 13%)
- NM_005228.5; c.858C>A, p.S286R (VAF 7%)

Despite being diagnosed in the same geographical area and timeframe, the patients had no familial relationship.

One patient with the c.866C>A, p.A289D mutation in EGFR exon 7 (male, 82 years, PD-L1 2%) received third-generation TKI treatment (osimertinib 80 mg/day) per ESMO-ESCAT scale recommendations (evidence level IB). Disease progression occurred after three treatment cycles. Two patients received platinum-based chemo-radiotherapy; one died from cardiogenic shock due to acute myocardial infarction before response evaluation, and the other is awaiting reevaluation. One patient relocated to their native country, so their treatment outcome is unknown.

Conclusions

This series describes three potentially pathogenic variants in the c.866 region of EGFR exon 7 for the first time. The clinical and pathological characteristics of our patients differ from those typically associated with common EGFR mutations (e.g., women, young age, non-smokers, absent PD-L1 expression). The only patient treated with a TKI showed early disease progression, suggesting these exon 7 mutations may not be EGFR inhibition-dependent.

The implementation of NGS in clinical practice will allow us to further understand the molecular profiles of our patients, expanding our knowledge of these uncommon EGFR mutations and their responses to standard TKI treatments.

References

1. Melosky B, Kambartel K, Häntschel M, Bennetts M, Nickens DJ, Brinkmann J, et al. *Worldwide prevalence of epidermal growth factor receptor mutations in non small cell lung cáncer: a metaanalysis*. Mol Diagn Ther. 2022;26(1):7-18. doi: 10.1007/s40291-021-00563-1
2. Chen, D., Zhang, L., Huang, J., & Liu, B. (2019). Identification of rare EGFR mutations and their clinical significance in lung adenocarcinoma. *OncoTargets and Therapy*, 12, 1085-1092. doi: 10.2147/OTT.S192201
3. L. Dai, X. Su, L. Lu. Non-Small Cell Lung Cancer with rare exon 7 p.A289V mutation in the EGFR gene responds to Icotinib treatment. Medicine (Baltimore). 2018. doi: 10.1097/MD.0000000000013809.
4. (Oncokb www.oncokb.org. Uncommon EGFR www.uncommonegfrmutations.com. Clinvar www.ncbi.nlm.nih.gov/clinvar/).
5. Chakravarty, D., Dienstmann, R., Jezdic S., Gonzalez-Perez A., et al A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Annals of Oncology, 2018; 29 (9) 1895-1902. doi.org/10.1093/annonc/mdy263

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