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A First Reported Combination of Exon 18 Missense (G719X) Mutation and Exon 20 Insertion Mutation (Exon20ins) Of Epithelial Growth Factor Receptor in A Patient with Non-Small Cell Lung Carcinoma

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Abstract

The majority of non-small cell lung cancer (NSCLC) associated with epidermal growth factor receptor (EGFR) mutations involve exon 19 deletion mutations and exon 21-point mutation L858R (arginine for leucine substitution at amino acid 858). G719X point mutation (substitutions of the glycine at position 719 to other residues) in exon 18 and insertion in exon 20 are less commonly detected. However, the combination of the latter two mutations has never been reported. We report the first case of metastatic NSCLC with EGFR mutation harboring both exon 18 missense point mutation (G719X) and exon 20 insertion (exon20Ins).

Keywords: stage IV lung cancer, combined mutations, complex mutations, point mutations, tyrosine kinase inhibitors.

Introduction

Lung cancer is the primary cause of cancer mortality worldwide. NSCLC accounts for around 85% of lung cancer population [1]. In 2004, the discovery of activating mutations of EGFR revolutionized the treatment approach to this subgroup of patients with NSCLC [2]. Those mutations prevail differently among NSCLC patient population based on ethnicity; they occupy around 40-60% in Asians and 10-20% in Caucasian patients [3].

EGFR is a member of the tyrosine kinase (TK) family and comprises 4 domains where the TK domain is cytoplasmic. The binding of EGFR to its ligand causes autophosphorylation of the TK resulting in cellular proliferation. Mutations at exons 18 to 21 coding the TK domain cause auto activation of the kinase [2]. The classical EGFR mutations are in-frame deletions in exon 19 and point mutation (L858R) at exon 21 and are commonly found in non-smoker females with a histology of adenocarcinoma on lung tissue biopsy. Those mutations reduce the kinase affinity for Adenosine Triphosphate (ATP) rendering the tumor sensitive to first and second generation of tyrosine kinase inhibitors (TKIs) which bind to the ATP site thus preventing phosphorylation [2].

Furthermore, uncommon mutations were also detected, with exon20Ins being the most prevalent accounting for up to 10% of all EGFR mutations and are linked to never-smoked females and Asian ethnicity. Over 100 exon20Ins have been sequenced and reported [2]. Most of those mutations activate the kinase by forming a wedge at the end of the C-helix with variable response to TKIs depending on the location of insertion with the majority displaying resistance [2,4].

Exon 18 point-mutations account for 3-5% of all EGFR mutations where G719X is the most common [5]. Those mutations are associated with smoking history and have no sex predilection [2]. In contrast to exon20Ins, exon 18 point-mutations are susceptible to afatinib, a second generation TKI [5].

These two rare mutations generally have a poor clinical prognosis [4]. Various EGFR combination mutations have been reported in the literature, however, herein we report the first case that harbors the combination of exon 18 point mutation (G719X) and exon 20 insertion mutation of EGFR in a newly diagnosed case of NSCLC where palliative treatment of afatinib was started.

History

A 56-year-old non-smoker patient was recently diagnosed with stage IV left lung adeno-squamous carcinoma involving the hilum, extending to the anterior mediastinum with mediastinal and infra-carinal lymph nodes enlargement. Abdominal and pelvic CT showed a left hepatic lobe nodule lesion, a heterogeneous mass of the left adrenal gland, and diffuse osteoblastic bone lesions. Non-small cell lung adeno-squamous carcinoma with PDL1 60% was confirmed by immunohistochemistry of pelvic core biopsy. Genetic testing obtained from histological samples was performed in the molecular diagnostics laboratory at the American University of Beirut Medical Center, using the Cobas EGFR mutation test v2 technique (by a real time PCR test), revealed G719X mutation of EGFR at exon 18 and an insertion mutation at exon 20. The exons 19 and 21 are wild type.

The exon 20 Insertion mutations detected by this machine are limited to: 2307_2308insGCCAGCGTG, 2319_2320insCAC, and 2310_2311insGGT.

A palliative treatment with afatinib in combination with zoledronic acid was administered to the patient.

The patient passed away after 2 months of afatinib initiation.

Discussion

The prevalence of harboring an EGFR mutation in patients with NSCLC is variable among different ethnic groups and countries worldwide [6,7]. It can reach up to 53.6% in Eastern Asian countries such as Japan and down to 14.1% in Europe [7]. In a multicentered study performed in different countries of the Middle East by Jazieh et al., [8] the prevalence of EGFR mutations in adenocarcinoma attained 36.5%. In Lebanon, two studies evaluated EGFR prevalence in NSCLC: one multicentric by Arafat Tfayli et al. [9] with a value of 15.6% and the other single-centered by Samah Naderi et al. [6] with a finding of 11.9%. Those values approximate the prevalence in Europe (14.1%) and Caucasian and African American ethnicities (17.4% and 17.2%, respectively) [7].

Rare EGFR mutations are encountered in approximately 15% of all EGFR-mutant NSCLC [10]. Exon20Ins mutation is the most common and constitutes up to 10% of all mutated EGFR population [2]. In the previously mentioned studies in Lebanon, only one case was reported to have exon20Ins mutation [9]. It is usually associated with female sex, old age (>55 years), Asian ethnicity, never-smoked status, and adenocarcinoma cancer type on histology [10]. Besides that, this mutation is associated with poorer prognosis and treatment outcomes compared with other EGFR mutations [5]. Patients with this mutation have a progression free survival (PFS) interval between 1.4 to 3 months and an overall survival (OS) range between 4.8 to 16.8 months [10].

Moreover, exon 18 mutations are described as the rarest and account for 3-4%, with G719X point mutation being the commonest one detected and carries a shorter median PFS compared to classical mutations [2]. In a study by M. Beau-Faller et al. among the French population [11], 29 patients out of 1047 (2.7%) harbored this mutation.

Various EGFR combination mutations were reported in the literature. According to Chao-Hua Chiu et al., [12] the commonest combination mutation was G719 X in exon18 and S768I in exon 20, with combination of G719X and L861Q of exon 21 being the second frequent combination. However, no study reported a combination involving G719X point mutation in exon 18 and an exon20Ins mutation as the patient in our case.

Generally, NSCLC with classical EGFR mutations in exon 19 and 21 exhibited marked response to TKI treatment. G719X point mutation in exon 18 demonstrated variable degrees of EGFR-TKI sensitivity compared to that of classical mutations with a response rate reaching 77.8% to afatinib. On the contrary, afatinib administration to patients harboring exon20Ins demonstrated the lowest efficacy among those with rare EGFR mutations [7]. Yet, the study performed by Chao-Hua Chiu et al. [12] showed that patients with NSCLC harboring uncommon complex mutations solely had a significantly longer progression free survival as compared to those with single rare mutation. In a case report by Watanabe M. et al., [13] afatinib administration demonstrated a good and progression free response for 12 months in a patient with advanced NSCLC harboring complex exon 18 G719X plus exon 20 S768I mutations. Different studies demonstrated the superiority of second-generation EGFR-TKIs over first generation in patients harboring uncommon EGFR mutations [7].

Our case is the first to report a NSCLC harboring EGFR combination mutation in exon 18 (G719X) and insertion mutation in exon 20, with a very aggressive pattern where bone, liver and lymph nodes metastasis were identified. Due to the rarity of occurrence of complex exon 18 and exon 20 EGFR mutations, and since the literature is scarce in studies and reports that tackle the management of such cases, and since exon 20 mutations exhibit variable response to TKIs due to the heterogeneity of mutation location and type, and as a previous multicentered observational study demonstrated partial response or stabilized disease in patients with complex exon 18 and exon 20 EGFR mutations with the majority having stage IIIB-IV and receiving Second-line EGFR-TKI [11], and considering that each mutation alone carries a poor prognosis with poor response to classical TKIs, afatinib was the most suitable choice to be prescribed to our patient.

Though it is rare to encounter such mutations, it is of immense importance to report such cases and perform extensive trials and experiments to optimize management in patients harboring them to improve their quality of life.

Conclusion

Our case is the 1st to report a NSCLC harboring EGFR combination mutation in exon 18 (G719X) and insertion

mutation in exon 20, with a very aggressive pattern where bone, liver and lymph nodes metastasis were identified, and the patient was started on afatinib considering that each mutation alone carries a poor prognosis with poor response to classical TKIs.

Considering the rarity of such mutations and the deficiency of literature tackling their management, it is high recommended to sequence exon20Ins mutations, report cases harboring them alone or in combination with other mutations and perform observational studies and trials regarding patient prognosis and response to different treatment lines. This will assist physicians in understanding the behavior of such mutations and provide better patient care.

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