Complex Germline K757N Mutation in Non-Small-Cell Lung Cancer: A Case Report

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Abstract
Epidermal growth factor receptor (EGFR) mutations are usually oncogenic drivers of lung tumor development and progression. While common sensitizing mutations respond well to targeted therapy, the relevance of germline EGFR mutations is less clear. We describe a 65-year-old, previously healthy, male diagnosed with non-small-cell lung cancer. Familial history for lung cancer is negative. Targeted next-generation sequencing on the tumor biopsy sample revealed an atypical EGFR K757N mutation at 50% allele frequency and genetic review of a previously acquired gastric sample confirms the mutation as a germline change. He received standard first-line chemoimmunotherapy with carboplatin, pemetrexed, and pembrolizumab, and after 8 months therapy continues, with stable disease, to receive maintenance pemetrexed and pembrolizumab. To our knowledge, this is the first report of an atypical, germline K757N EGFR mutation. While the clinical relevance of this mutation is unclear, standard reporting of the allelic frequency of novel, atypical mutations can detect potential germline changes.
Introduction

Activating mutations of the epidermal growth factor receptor (EGFR) represent the first clinically approved subtype of non-small-cell lung cancer (NSCLC) patients for targeted therapy. Corresponding tyrosine kinases inhibitor (TKI) treatment options act to inhibit the constitutive activation of signaling pathways downstream to EGFR that promote cancer cell growth, survival, and chemotherapy resistance [1, 2]. Classical mutations, representing 85–90% of EGFR mutations, are either an L858R point substitution in exon 21 or an exon 19 deletion, and typically respond to TKI therapy. The remaining approximately 15% of mutations are divided into EGFR exon 20 insertion mutations, and then a disparate group termed “uncommon” or “atypical” mutations, that often have poorer response rates to classic TKI therapy [3]. A proportion of “uncommon mutations” occur in the situation of “compound” mutations where >1 EGFR mutations are discovered. Compound mutations may include common + common mutations, uncommon + common, uncommon + uncommon, or any mutation plus de novo T790M mutation. While the majority of EGFR mutations arise spontaneously, 1% of diagnosed lung cancers exist as germline mutations suggesting a potential inherited familial predisposition to lung cancer [4]. In this study, we report an otherwise healthy patient with NSCLC harboring a complex exon 19 K757 germline EGFR mutation. While the K757 mutation has previously been reported, we report its incidence as an isolated germline mutant for the first time.

Case Report/Case Presentation

A 65-year-old male first presented to his family physician with a 1-year history of a cough and a few months of progressive dyspnea and weight loss. He had no history of tobacco exposure, and no significant past medical history aside from an uncomplicated cholecystectomy. Immediate family history reports no known incidence of cancer in parents or children. He did not have any siblings. He was hospitalized with progressive dyspnea, and severe acute respiratory syndrome coronavirus 2 infection was consistently ruled out over the course of his hospital stay. A chest X-ray revealed a large right-sided pleural effusion, with subsequent computed tomography scan of the thorax, abdomen/pelvis confirming the presence of the pleural effusion and additional multiple lung nodules, extensive upper retroperitoneal lymphadenopathy, and small volume ascites (Fig. 1). PET scan and bone scan both reported the presence of an isotope avid solitary sclerotic lesion in the T7 vertebral body suggestive of a bone metastasis. MRI brain confirmed no intracranial disease.

A thoracoscopy, right pleural biopsy, and PleurX catheter insertion was performed for diagnostic purposes and to manage symptoms. Pleural biopsy confirmed stage IV primary lung adenocarcinoma. Corresponding biomarker tests were negative for ALK1 and ROS rearrangement by immunohistochemistry and showed moderate PDL1 expression (1–49% by immunohistochemistry). Targeted next-generation sequencing (NGS) revealed the absence of KRAS and BRAF mutations but was positive for an exon 19 missense mutation where a lysine residue was substituted with asparagine at position 757 (K757N) at 49% allele frequency (Fig. 2). Further analysis by circulating tumor DNA NGS (Canexia Health) detected the same EGFR K757N mutation at 49.1% allele frequency. No other EGFR variants were detected. The high allelic frequency suggested a germline mutation. To confirm this suspicion, an archived gastric biopsy sample taken 2 years previously, in 2019, was also analyzed by NGS and the same K757 mutation was found at the same allelic frequency (50%). Participation in the Ontario-wide Cancer TArgeted Nucleic acid Evaluation (OCTANE) study also failed to demonstrate any other driver mutations or rearrangements (fusions). Given that
complex EGFR mutations and germline variants are unlikely to respond to TKI therapy, the healthcare team elected to instead initiate standard first-line chemoimmunotherapy with carboplatin, pemetrexed, and pembrolizumab.

The patient tolerated the chemoimmunotherapy regimen well without significant side effects; however, after his third cycle, he developed significant chest wall suspected to be related to malignant seeding of his PleurX tract. His lung had not re-expanded despite ongoing PleurX drainage, so the catheter was removed and he underwent 5 fractions of palliative radiotherapy to the right hemithorax. Given his borderline performance status, the fourth cycle of platinum therapy was omitted and he started on maintenance pemetrexed and pembrolizumab. His performance status improved, and restaging imaging has showed ongoing disease stability/minor response. At the time of writing, he remains in stable condition and has received 7 cycles of maintenance therapy.

**Discussion/Conclusion**

Screening for mutations has become the cornerstone of modern NSCLC diagnosis and treatment. The presence of a driver mutation such as EGFR allows for the deployment of effective targeted therapies that drastically improve prognoses compared to classic chemotherapy regimens [5]. Unfortunately, not all mutations to EGFR effectively respond to TKI therapy, which are classified as rare or complex mutations, and typically have more ambiguous treatment plans. In the case of our K757N mutation, there are only several mentions of this variant in the literature to date, none of which directly link the mutation to any clinical significance. A retrospective mutational testing study from Australia reported that the K757N mutation was only found in 2/514 (0.4%) patients reviewed with a confirmed EGFR mutation [6].
There have been only 2 cases reported in the literature which include outcomes with TKI therapy for patients with a K757N mutation. In both cases, K757N was found in combination with the classical EGFR sensitizing mutation L858R. In the case report by Wu et al. [7], the patient had a transient, stable response to TKI therapy with gefitinib for 8.8 months before progression. The other reported case also received gefitinib for 12.4 months before progression [8]. At this point of disease progression, another common resistance mutation T790M (threonine to methionine at position 790) of exon 20 was detected, the most commonly reported and well recognized resistance mechanism to 1st and 2nd generation TKIs when used against the common EGFR mutations [9]. Taken together, these data suggest that the clinical significance of K757N may be influenced by co-mutations (or indeed the K575N mutation influences efficacy of treatments for more common mutations), and that the clinical role of an isolated K757 mutation remains unknown, if at all relevant to TKI therapy responsiveness.

Of additional interest, the K757N mutation in EGFR has never been reported as a germline variant. No other study of K757N in lung cancer reports its allelic frequency, so it is unknown whether these cases also represented germline variants. This mutation has been detected in one study as a somatic change, with a patient having emergence of the K757N mutation after initial treatment [10]. The establishment of a novel germline EGFR K757N mutation would raise the question whether individuals harboring this mutation could be predisposed to an increased chance of developing NSCLC with TKI-resistant features. Among others, the T790M variant is an example of a mutation associated with germline inheritance, resulting in potentially increased cancer susceptibility [11, 12]. This relationship between germline EGFR mutations and increased lung cancer susceptibility are being explored in the ongoing INHERIT EGFR trial (NCT01754025). While the results will primarily be focused on the T790M mutation, exploration of this same relationship for patients with the K757N variant may also prove significant.

In our case, since both parents of our patient were cancer-free well into their 90s, the isolated germline K757N mutation was maybe less likely to be a driver mutation. As such, we chose to proceed with a carboplatin/pemetrexed/pembrolizumab chemoimmunotherapy regimen based on the KEYNOTE-189 clinical trial. If the atypical K757N mutation had been a somatic change, we would have offered a second- or third-generation TKI (e.g., afatinib, omisertinib) based upon evidence of TKI responsiveness in other atypical EGFR mutations [13–15]. As a final consideration, the generation of a patient-derived xenograft model could prove instrumental in screening approved EGFR targeted therapies for therapeutic efficacy against this atypical K757N mutation.

Taken together, we report for the first time to our knowledge, a germline occurrence of the atypical K757N EGFR mutation. Upon recognition of a 50% allelic frequency and cross-referencing with a previously obtained biopsy sample, we determined this K757N was of germline origin, and therefore, had potential genetic significance. While it remains to be seen what role this germline mutation has in the tumor development and therapy resistance in this respective patient, this case highlights the importance of allele frequency reporting when encountering novel, atypical mutations. The uncovering of these germline mutations could inform novel biomarkers to dictate treatment regimens or direct familial genetic and cancer screening.

Acknowledgment

Figure 2 was created with Biorender.ca with permission for publication, licensed to Boaz Wong.
Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and the need for approval was waived by the Ottawa Health Science Network Research Ethics Board (OHSN-REB).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Boaz Wong was responsible for conceptualization of the project, data curation, methodology, resource management, project administration, visualization of data, writing of the original draft, and review and editing. Dr. Sara Moore was responsible for conceptualization of the project, data curation, methodology, resource management, visualization of data, and review and editing. Dr. Paul Wheatley-Price was responsible for conceptualization of the project, methodology, project administration, resource management, supervision, and review and editing.

Data Availability Statement

Data will be made available upon request to the lead author (boaz.wong@uottawa.ca). These data are only available upon request, given the inclusion of sensitive patient data and data transfer agreements may be required.

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