A Novel EGFR Germline Mutation in Lung Adenocarcinoma: Case Report and Literature Review

Parth Sharma,[1] Himil Mahadevia,[1] Sreekanth Donepudi,[2] Lara Kujtan,[3] Beth Gustafson,[4] Ben Ponvilawan,[1] Ammar Al-Obaidi,[3] Janakiraman Subramanian,[5] Dhruv Bansal[2]

Clinical Practice Points

- While most molecular testing focuses on somatic alterations in patients with non-small cell lung cancer, evidence is growing regarding the presence of germline lung cancer mutations. The most common lung cancer germline mutation is EGFR T790M.
- Herein, we describe an EGFR germline mutation not previously reported outside of Asia, T725M.
- Identification of germline lung cancer mutations could help to identify new therapeutic targets. Furthermore, further characterization of these mutations can aid in the development of screening and surveillance guidelines for patients with hereditary lung cancer, which currently do not exist.

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Introduction

Lung cancer accounts for the majority of cancer-related deaths worldwide, with a 5-year survival rate of 10%-20%.[1] Non-small cell lung cancer (NSCLC) represents approximately 82% of all lung cancer cases.[2] Tobacco smoking remains the primary risk factor for lung cancer development.[3] Additional risk factors such as infectious diseases, occupational hazards, radon exposure, and genetic susceptibility are being increasingly recognized in never-smokers.[4] The role of genetic factors and familial predisposition in lung cancer was first described in 1963 by Tokuhata et al.[5] This observation paved the path for multiple studies analyzing the role of family history in lung cancer development. A pooled analysis performed by the International Lung Cancer Consortium revealed a 1.5-fold increase in the risk of lung cancer in first-degree relatives.[6] In addition, the prospective Nordic twin study estimated the heritability of lung cancer to be 18%.[7]

While specific germline mutations have been implicated in numerous malignancies, their association with lung cancer has only come to the forefront recently.[8-10] To date, the EGFR T790M mutation has been identified as the most common germline variant, with evidence emerging for germline mutations in other epidermal growth factor receptor (EGFR) variants as well as other oncogenes and tumor suppressor genes.[7,8,11]

Herein, we describe a case of a novel EGFR germline mutation, T725M, not previously described outside of Asia. Our case highlights the role of genomic profiling in the management of lung cancer and the prospects it holds as a surveillance tool for lung cancer.

Case Presentation

An 84-year-old Caucasian male, a former smoker with a history of smoking 50 pack-years and a medical history of chronic obstructive pulmonary disease and obstructive sleep apnea, initially presented for an incidental pulmonary nodule evaluation. The initial chest computed tomography (CT) scan revealed a 1.5 cm left lower lobe nodule. Subsequently, he underwent a positron emission tomography (PET)-CT scan followed by a CT-guided biopsy of the left lower lobe lesion, which was consistent with granuloma. A repeat CT chest performed nine months later revealed a 1.5 cm spiculated and lobulated right lower lobe lung lesion. He underwent

[1]Department of Internal Medicine, University of Missouri-Kansas City, Kansas City, MO
[2]Department of Hematology-Oncology, Saint Luke's Cancer Institute, Kansas City, MO
[3]Department of Hematology-Oncology, University of Missouri-Kansas City, Kansas City, MO
[4]Department of Pharmacology, Saint Luke's Cancer Institute, Kansas City, MO
[5]Department of Hematology-Oncology, Inova Schar Cancer Institute, Fairfax, VA

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Address for correspondence: Parth Sharma, Department of Internal Medicine, University of Missouri-Kansas City, Kansas City, MO
E-mail contact: parthduttsharma97@gmail.com

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Table 1 Prevalence of Pathogenic(P) or Likely Pathogenic (LP) Germline Variants in Lung Cancer

Studies of Pathogenic or Likely Pathogenic Germline Cancer Variants	Total Number of Participants (All Cancer Types)	Pathogenic or Likely Pathogenic Germline Variant Prevalence in Lung Cancer (%)
Mandelkar[30]	1040	2/2 cases
Liu[31]	1026	4.7
Samadder[27]	2984	14.7
Yap[28]	34642	5.8
Mukherjee[32]	5188	4.3
Sorscher[10]	7788	14.9

endobronchial ultrasound with biopsies of the right lower lobe lesion and of station 4L, 4R, 7, and 11R lymph nodes. Pathology results established the diagnosis of adenocarcinoma, papillary type, with immunohistochemistry (IHC) positive for CK7, TTF-1, and Napsin-A but negative for p40 and CK5/6. The patient was diagnosed with localized (stage IB) right lung adenocarcinoma. He underwent a right lower lobectomy with negative margins. Mediastinal lymph node dissection was performed and was negative for nodal involvement. Genomic analysis was not performed at this juncture.

He was subsequently followed with imaging surveillance, and no adjuvant therapy was administered. Subsequently, imaging performed two years after the initial resection revealed right-sided pleural effusion. Pleural fluid cytology revealed malignant cells consistent with metastatic lung adenocarcinoma. Further, staging workup with a PET-CT scan and brain magnetic resonance imaging (MRI) revealed no extrathoracic metastases. He underwent a pleural catheter placement for rapidly reaccumulating pleural effusion. Comprehensive next-generation sequencing (NGS) performed on the prior right lower lobectomy tumor sample revealed a somatic EGFR p.L858R mutation. Cell-free DNA (cfDNA) analysis at the time of tumor recurrence was notable for the presence of EGFR p.T725M mutation with a VAF of 49%, while EGFR p.L858R was not reported. EGFR p.T725M mutation was confirmed as a germline variant from tumor/normal-matched sequencing data. A concomitant germline ATM p.V1268fs mutation was observed in both the tumor and the liquid biopsy.

The patient commenced on osimertinib 80 mg once daily, a 3rd generation EGFR tyrosine kinase inhibitor. Successive imaging studies, with CT scans of the chest as well as abdomen and PET-CT, performed up to fifteen months after initiation of therapy, revealed a partial response with no further disease progression. He did not experience any recurrence of the pleural effusion. He experienced grade 1 creatinine elevation attributed to osimertinib but did not experience any other side effects. He passed sixteen months after the diagnosis of recurrence, and the cause of death was unknown.

Discussion

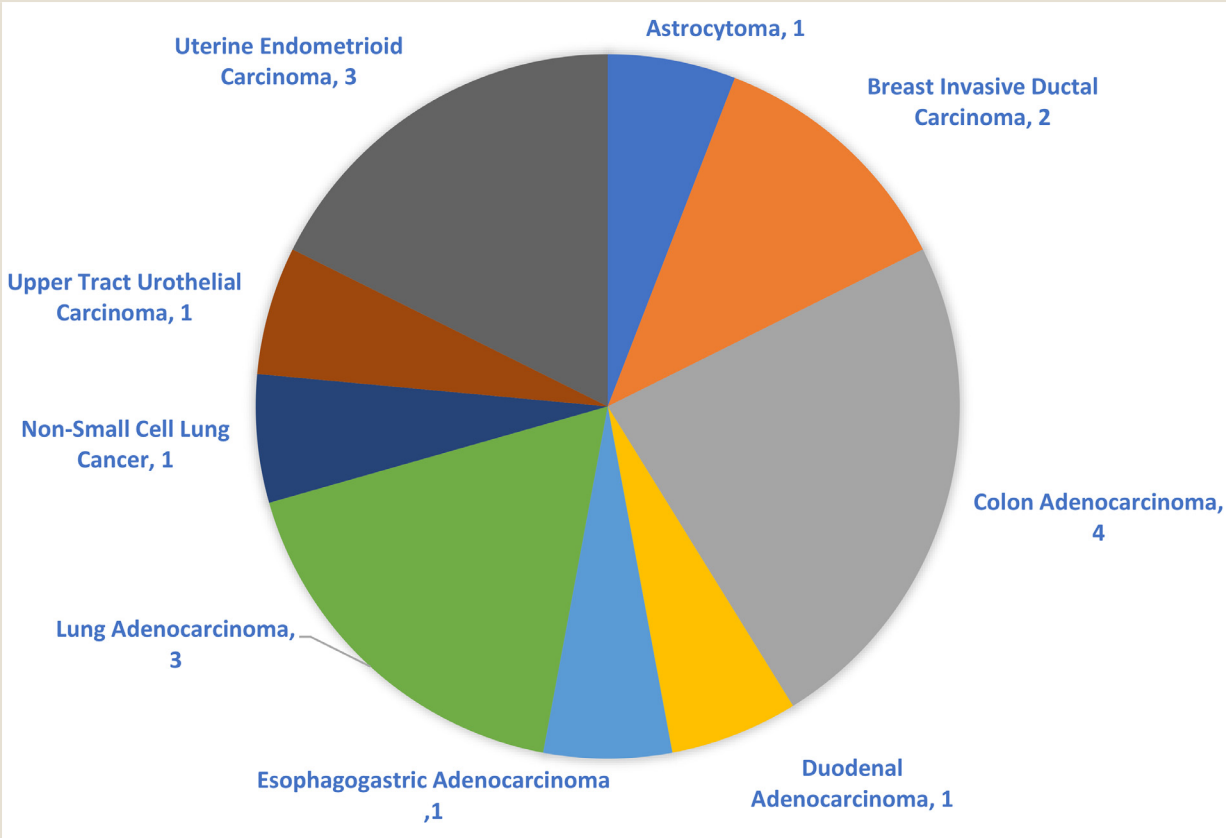
With multigene panel testing becoming the standard of care for patients with advanced NSCLC, tumor molecular profiling has become fundamental to lung cancer management.[12,13] The advent of molecular therapies targeting oncogenic driver mutations such as EGFR, ALK, and ROS1 has dramatically improved survival outcomes in patients with NSCLC.[14,15] EGFR tyrosine kinase somatic mutations are seen in about 10%-15% of individuals with lung adenocarcinoma in the United States. Rare or low-frequency EGFR mutations account for 15% of these mutations, some notorious for exhibiting resistance to 3rd generation EGFR tyrosine kinase inhibitors.[16]

Inherited risk for lung cancer was established with the discovery of germline mutations involving EGFR and ERBB2 genes.[17] Bell et al. first described germline transmission of EGFR T790M mutation in a family with multiple cases of NSCLC.[11] In the INHERIT study, a multicenter trial to prospectively evaluate the prevalence of germline EGFR T790M, 55% of germline EGFR pathogenic variant carriers were diagnosed with lung cancer.[18] Several other EGFR germline variants have been reported in lung cancer patients, including R776H,[19,20] R776G,[21] V769M,[22] V834L,[23] and V843I.[24] The prevalence of pathogenic and likely pathogenic germline variants in lung cancer patients ranges from 4.3%-14.9% (Table 1).

This novel germline EGFR p.T725M mutation was discovered incidentally in this individual with lung adenocarcinoma. We could not test his family members as he has no siblings or children; he does not recall his parents having malignancy. The EGFR T725M mutation has previously been described in the literature as an uncommon somatic mutation (Figure 1).[25] As per our review, this is the first description of this mutation as a germline finding in an individual with lung adenocarcinoma in the US population. A single case of this germline mutation was previously described in the Chinese population.[26] We also found a co-occurrence of EGFR L858R, a commonly occurring somatic mutation, which has been reported accompanying other EFGR germline variants as well.[23] It has been hypothesized that the germline mutations may be weakly oncogenic by themselves, and the presence of a concomitant somatic mutation appears to have a "second hit" effect and accelerated carcinogenesis. In the INHERIT trial, 95% of the lung cancer patients with a germline pathogenic variant had a somatic EGFR driver comutation.[18]

National Comprehensive Cancer Network (NCCN) guidelines recommend germline testing for various cancers, such as colorectal and breast cancer. The implementation of these guidelines has undoubtedly impacted the management of these cancers with the emergence of precision therapies and genetic counseling for the patients as well as their relatives. Since most multigene panels do not include germline testing, we are likely underestimating the prevalence of the inherited risk for lung cancer. Utilization of universal germline testing can increase the detection of clinically actionable germline variants over the guideline-based approach[27,28]. The

Figure 1 Number of EGFR T725M cases reported in AACR GENIE (classified according to cancer subtype).[33]



cost of genomic testing has steadily decreased over the years. Next-generation sequencing is associated with considerable cost savings in detecting molecular abnormalities in patients with newly diagnosed metastatic NSCLC.[29]

Conclusion

In conclusion, we describe the first case of lung adenocarcinoma harboring a germline EGFR T725M mutation in the US population. Although tobacco smoking remains the most important risk factor for the development of lung cancer, the role of genetic susceptibility is being increasingly recognized. With the advances in next-generation sequencing, limited germline testing would help establish the true prevalence of inherited lung cancer germline alterations. The data would help develop lung cancer screening guidelines for individuals with germline mutations and at-risk relatives.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Parth Sharma: Conceptualization, Writing – original draft, Methodology, Writing – review & editing. **Himil Mahadevia:** Methodology, Writing – review & editing. **Sreekanth Donepudi:** Writing – review & editing, Methodology. **Lara Kujtan:** Writing – review & editing, Methodology. **Beth Gustafson:** Writing – review & editing, Methodology. **Ben Ponvilawan:** Writing – review & editing. **Ammar Al-Obaidi:** Writing – review & editing. **Janakiraman Subramanian:** Writing – review & editing, Methodology. **Dhruv Bansal:** Conceptualization, Methodology, Writing – review & editing, Supervision.

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