MedCrave
Step into the World of Research

Journal of Cancer Prevention & Current Research

Case Report

Open Access

CrossMark

Case of inherited epidermal growth factor receptor (EGFR) in non-small cell lung carcinoma (NSCLC) in a 37-year-old male

Abstract

Lung adenocarcinoma is a lung malignancy most known for its prevalence among non-smokers compared to the other non-small cell and small cell lung cancers. There is a genetic component involving a gene mutation of the epidermal growth factor receptor which depending on the type of mutation can be responsive to tyrosine kinase inhibitor therapy. However, there are rare mutations that cause resistance to first line treatment and require further genetic analysis on the type of gene mutation. We present a young 37-year-old non-smoking male patient who developed an inherited lung adenocarcinoma. His genetic screening indicated he had a germline T790M mutation in his EGFR which is particularly uncommon. He was fortunately responsive to third-line treatment therapy. With this particular diagnosis, routine screening has no benefit, but it is important for family members to be screened as this particular malignancy was inherited.

Keywords: EGFR, NSCLC, TKI, T790M gene mutation

Volume 12 Issue 4 - 2021

Joseph R Malhis,[1] S Blake O'Brien,[1] Rikhav Vasanwala,[1] Kerry J Williams-Wuch[2]

[1]PGY-3 Internal Medicine Resident, University of Arkansas for Medical Sciences Northwest Regional Campus, USA

[2]Department of Hematology & Oncology, VA Medical Center, USA

Correspondence: Joseph R Malhis, PGY-3 Internal Medicine Resident, University of Arkansas for Medical Sciences Northwest Regional Campus, Fayetteville, AR, USA, Tel 9493440845, Email ymalis@gmail.com

Received: July 20, 2021 | **Published:** August 13, 2021

Background

Lung cancer is one of the most diagnosed malignancies and the leading cause of death worldwide. In the United States, over 150,000 deaths occur annually; the 5-year survival rate is 16% due to late diagnosis and non-resectable tumors.[1] There are two major groups of lung cancer: Small Cell Lung Cancer (SCLC) and Non-small Cell Lung Cancer (NSCLC). NSCLC makes up the majority of lung cancer at 75%.[2] NSCLC is categorized into three subtypes: squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma.[3] Smoke exposure has been a dominant risk factor but risk will vary in different ethnicities and genders.[4] Statistics indicate that they are highest among men and especially in the Micronesian/Polynesian, Eastern Asian and Eastern European population. Additionally, 10-25% of lung cancers occur in those who never smoke.[3] There are cases of those who may have smoke exposure or other environmental risk factors. These include exposure to carcinogenic chemicals, ionizing radiation, asbestos and alcohol consumption.[3] There are also familial risk factors and genetics play a role in acquiring NSCLC. Familial clustering of cancer is seen when the same type of cancer is presented in two or more first degree relatives. This can be seen with shared environments, inherited mutations and high penetrance genes.[5] Genome wide association studies (GWAS) have been used to detect common alleles for inherited malignancies.[5]

In 2004, it was found that lung adenocarcinoma has been associated with a somatic gene mutation in the epidermal growth factor (EGFR).[4] This was seen in 10% of Western patients and over 40% of East Asian patients.[1] This is a gain of function of mutation involving the tyrosine kinase domain and it is mostly seen in female patients of East Asian ancestry with little to no tobacco exposure.[6] An example is the EGFR T790M mutation which is associated with inherited lung cancer syndrome. Sanger sequencing has correlated this with familial clustering and this mutation is seen in non-smokers. This mutation can induce oncogenic production in mouse models, but it is rather weak unless it has a second activating mutation.[5] This germline mutation is seen in 1% of NSCLC and the median age of diagnosis is 40 with histology being adenocarcinoma.[5]

A normal function of EGFR with tyrosine kinase is to initiate signal transduction in multiple pathways which will vary depending on the pathway but it may be cell proliferation or cell maintenance via apoptosis.[2] Any gain of function mutation may promote unregulated cell growth and proliferation. With EGFR gene mutations, the exon 19 deletion and L858R point mutation are the classical examples and predictors of response to tyrosine kinase inhibitor therapy. When two or three mutations in one tumor is seen with combination of for example ex19del-ex20ins with the T790M, the frequency is at 1.7% Overall, the frequency of having two-three gene mutations in EGFR is 0.33% so it is especially rare.[7] There are other mutations rarer in the exon 18-25 that tend to reflect poor prognosis.[8] About 10% of non-small cell lung cancers respond well with tyrosine kinase inhibitors (TKIs) that target EGFR.[9] Sanger sequencing and real-time PCR have been used for EGFR genotyping but have been limited in its use since it cannot detect rare and novel mutations.[10] There were landmark trials in 2004 that showed response to first generation TKIs like gefitinib and erlotinib which increased survival improvement but not overall survival benefit.[2]

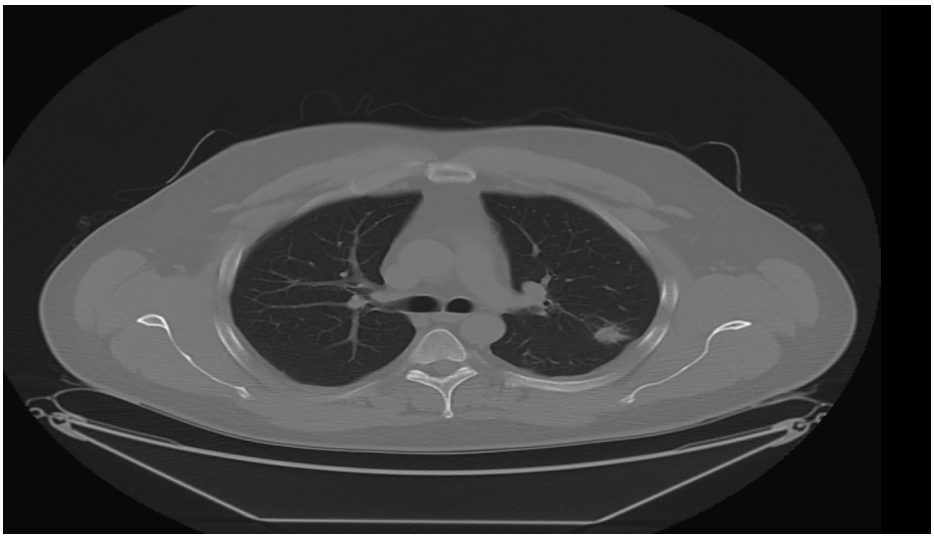
However, not all EGFR mutations are susceptible to TKI therapy. EGFR mutations in exons 18, 19 and 21 may respond well to gefitinib and erlotinib, it does not last and some patients may relapse within the year.[1] Outside of the classical mutations involving the exon 19 deletion or L858R mutation, the inframe base pair insertion in exon 20 has de novo resistance to current therapy. There has been a low response rate to erlotinib and gefitinib[11] with this mutation. There is a second generation EGFR inhibitor afatinib which has been qualified to be used as first-line therapy but had minimal response.[11] However, there are individual cases reported with a patient with exon 18 deletion and exon 20 insertion who had a very good response to afatinib.[12]

Due to the resistance of these therapies, there is a third-generation inhibitor that targets the T790M secondary mutation which has

been the reason for such resistance. Of the relapse seen in patients treated with the first generation inhibitors, 50% had the T790M gene mutation. It decreases affinity to the gefitinib in L858R mutations.[1] The T790M-selective irreversible inhibitors rociletinib and osimertinib, especially the latter, have shown significant benefit compared to the first generation medications.[11]

Case report

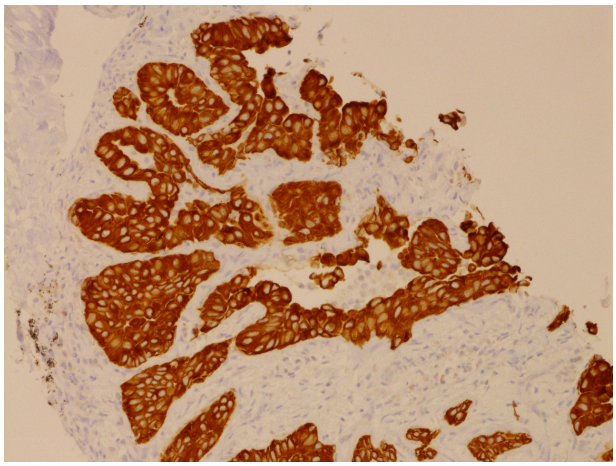
A healthy 37 year old male with no previous tobacco history or occupational exposure had an incidental finding of a left upper lobe lung nodule a couple of years prior in September 2018 when he had an abdominal computed tomography scan performed for a urinary tract infection (hematuria). The size of the nodule was 11mm. He had a follow-up CT in May 2019 which showed a slight increase to 13mm. There were multiple nodules noted but the one in the left upper lobe continued to increase in size and repeat CT in November 2019 showed an increase to 2cm with spiculations and almost certainly malignant neoplastic disease in appearance. The 4 and 5mm nodules in his right lung were stable and benign.



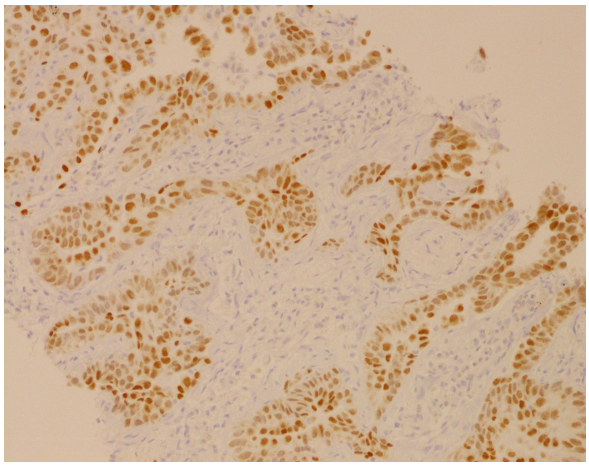
CT Chest with lung nodule found in left upper lobe November 2019.

He was asymptomatic at the initial visit, denying any shortness of breath, chest pain, fevers, chills, weight loss, or focal neurological deficits. He does have a significant family history of lung cancer in his grandfather, who was also a smoker, and his grandmother, who was a non-smoker and was diagnosed at age 50. His past medical history includes chronic PTSD and depression for which he takes diazepam and sertraline. He has never smoked and does not consume a significant amount of alcohol. He works in a chicken feed plant and states it is a very dusty environment.

CT guided biopsy was performed and pathology showed well-differentiated adenocarcinoma consistent with lung primary. The left upper lobe mass showed lung parenchyma with infiltrating atypical cells with increased nuclear to cytoplasmic ratio, nuclear hyperchromasia and markedly irregular nuclear contours. Focal gland formation in fibrous stroma with cells having bubbly cytoplasm suggestive of adenocarcinoma. Immunohistochemical staining Pan CK (AE1/AE3/PCK26), TTF1 and CK 7 are strongly positive. CK20, CDX-2, p63 and CK5 and CK6 were negative.

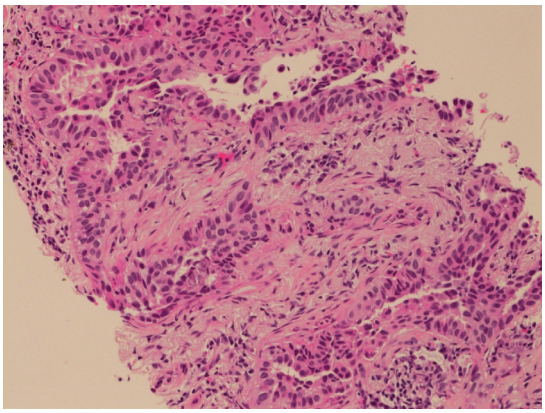


CK7 at 200x

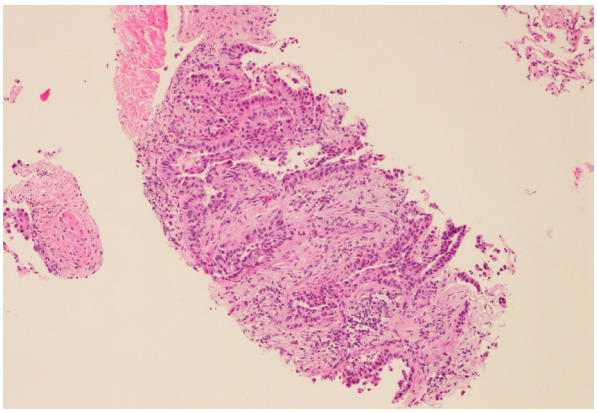


TTF1 at 200x

Citation: Malhis JR, O'Brien SB, Williams-Wuch KJ. Case of inherited epidermal growth factor receptor (EGFR) in non-small cell lung carcinoma (NSCLC) in a 37-year-old male. *J Cancer Prev Curr Res.* 2021;12(4):133–136. DOI: 10.15406/jcpcr.2021.12.00466



H&E staining at 200x

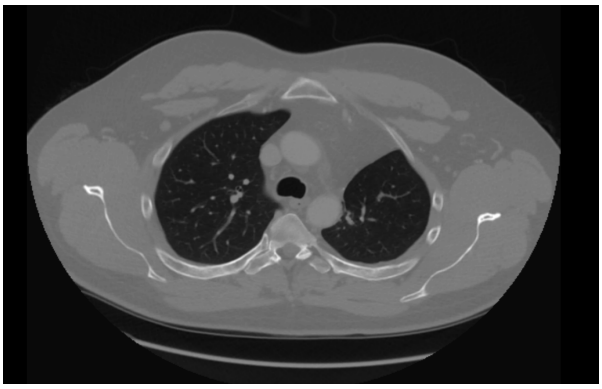


H&E staining at 100x

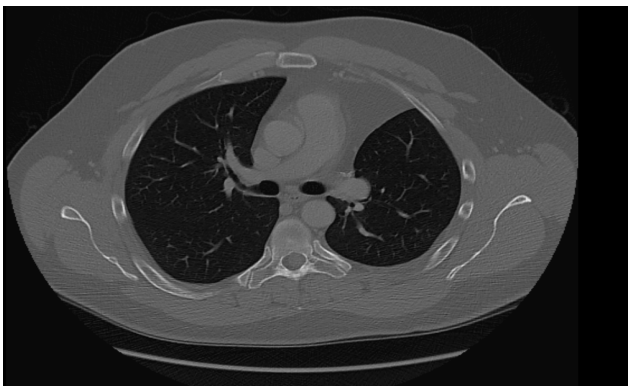
In January 2020, he had a PET scan which showed 1.9x1.4cm mildly spiculated nodule in the posterior left upper lobe with SUV of 12.8 with esophageal uptake with SUV of 6.0 likely inflammatory. He was referred to thoracic surgery and had left lobectomy in February 2020. The pathology after the removal showed this was a T1, N1, Stage IIB lung adenocarcinoma, well-differentiated with negative margins, 1 peribronchial lymph node positive.

By March 2020, he was started on adjuvant cisplatin and Almita (premextred) for which he had 4 cycles. In August 2020, his mutational analysis indicated EGFR exon 19+, EGFR exon 20 T790M positive NSCLC adenocarcinoma. In addition, the analysis confirmed that he not only had an EGFR mutation, since the mutation was present in his serum and saliva, it indicated that the mutation was germline. The geneticist explained to him that there is a 50% chance his siblings and children may also have this mutation.

He tolerated chemotherapy well. By May 2020, CT scan of his thorax, abdomen and pelvis found 4 new nodules left lower lobe of his lung and by June, he was started on 80-mg osimertinib daily for the metastasis. Repeat PET CT in August 2020 indicated an excellent response. He continues to follow up and is doing well.



Repeat CT Chest February 2021



Repeat CT Chest June 2021

Discussion

Since this patient did not have obvious risk factors, smoking being the most common, he would not have gotten a low dose CT screening to rule out lung cancer. Also, those screenings typically begin at age 55 and this patient was in his mid-30s at diagnosis. His mother had lung cancer in her 50s and it is not known which type but it can be assumed adenocarcinoma as she too was a non-smoker. But with her father being a smoker, she may have had significant exposure.

His initial imaging that found any suspicion of this malignancy was incidental as he did not have significant symptoms related to it. So, how do we prevent these from occurring? Should we have genetic screenings like BRCA testing in patients with family histories of breast cancer? This gene is not common and to implement this on a wider scale would not be very beneficial in the long term and costly. Fortunately, this patient did well with treatment and did not have significant problems. But with relevant family history and clinical findings, this can be implemented on case by case.

Is there a clinical correlation with diagnosis and age? If that were the case, maybe screenings at a certain age with known family history would be beneficial. He was diagnosed over a decade ago when his mother was diagnosed. There have been studies in order to develop guidelines for cases like this. According to Lindeman et al, they developed a 37-item guideline with 15 recommendations for testing EGFR mutations and ALK fusions for those with advanced stage adenocarcinoma regardless of sex, race, smoking history or other clinical markers.[13] In addition, EGFR mutations are excellent biomarkers to predict how well patients with NSCLC will respond to targeted therapy.[10] As seen with this patient, there are rare mutations that are missed unless full sequencing is performed.

Citation: Malhis JR, O'Brien SB, Williams-Wuch KJ. Case of inherited epidermal growth factor receptor (EGFR) in non-small cell lung carcinoma (NSCLC) in a 37-year-old male. *J Cancer Prev Curr Res.* 2021;12(4):133–136. DOI: 10.15406/jcpcr.2021.12.00466

Environmental factors also play a role although for this case, it was mostly genetic. However, he worked at a chicken feed plant that was very dusty according to him and it is not known if he has been exposed to anything. Among certain toxin exposure, there have been cases of asbestos and radiation exposure inducing lung adenocarcinoma. Chicken feed processing plants will have incidences of mycotoxin exposure including aflatoxin. Although aflatoxin exposure is notorious with liver cancer, there are incidences of lung cancer as well due to inhalation. There is a risk of developing lung adenocarcinoma via a different pathway than the EGFR mutation. AFB1 can cause oxidative damage to DNA, inducing tumorigenesis and it can also affect the insulin receptor substrate and Src kinase which, when upregulated, can induce more cell migration.[14] However, there is not enough data to truly clinically correlate and this was predominantly induced by genetic components from the EGFR mutation from what we surmised.

His family history was the most relevant part of this case and it brings the question of making genetic screening more regulatory in the future when it comes to most ailments. However, screening for the general population has no proven benefit as it is so rare. Patients potentially with these mutations should have routine germline genotyping to identify carriers.[5] This patient did visit a geneticist who recommended that his siblings and children be tested due to the strong genetic connection related to his cancer. If they proceed with screening and are known to be at risk or at least a carrier of this gene, this can greatly affect their lives. This is an important discussion for the whole family to be involved when making this decision.[15]

Acknowledgments

None.

Conflicts of interest

The authors declare there is no conflict of interests regarding the publication of this paper.

References

1. Greulich H. The genomics of lung adenocarcinoma: opportunities for targeted therapies. *Genes Cancer*. 2010;1(12):1200–1210.
2. Bethune G, Bethune D, Ridgway N, et al. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. *J Thorac Dis*. 2010;2(1):48–51.
3. de Alencar VTL, Formiga MN, de Lima VCC. Inherited lung cancer: a review. *Ecancermedicalscience*. 2020;14:1008.
4. Cheng YI, Gan YC, Liu D, et al. Potential genetic modifiers for somatic EGFR mutation in lung cancer: a meta-analysis and literature review. *BMC Cancer*. 2019;19(1):1068.
5. de Alencar VTL, Formiga MN, de Lima VCC. Inherited lung cancer: a review. *Ecancermedicalscience*. 2020;14:1008.
6. Gazdar A, Robinson L, Oliver D, et al. Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. *J Thorac Oncol*. 2014;9(4):456–463.
7. Olmechuk EP, Kit OI, Petrusenik NA, et al. Multiple Mutations in the EGFR gene in patients diagnosed with Lung Cancer. *Journal of Clinical Oncology*. 37(15 suppl):e20542.
8. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol*. 2020;61:167–179.
9. Bell D, Gore I, Okimoto R. et al. Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet.* 2005;37(12):1315–1316.
10. Sousa AC, Silveira C, Janeiro A, et al. Detection of rare and novel EGFR mutations in NSCLC patients: Implications for treatment-decision. *Lung Cancer*. 2020;139:35–40.
11. Vyse S, Huang PH. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Sig Transduct Target Ther*. 2019;4(5).
12. Ikeuchi T, Tokuyasu H, Ishikawa S. Successful Treatment of Lung Adenocarcinoma with Epidermal Growth Factor Receptor Compound Mutations Involving Exon 19 Deletion and Exon 20 Insertion by Afatinib. *Intern Med*. 2019;58(1):101–104.
13. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol*. 8(7):823–859.
14. Marchese S, Polo A, Ariano A, et al. Aflatoxin B1 and M1: Biological Properties and Their Involvement in Cancer Development. *Toxins (Basel)*. 2018;10(6):214.
15. Non-Small Cell Lung Cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®); 2020.